ベルケイド注射用 3mg
に関する資料

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ヤンセンファーマ株式会社

目次

1.5 起原又は発見の経緯及び開発の経緯 2

1.5　起原又は発見の経緯及び開発の経緯

全身性免疫グロブリン軽鎖（AL）アミロイドーシスは異常形質細胞より産生されるモノクローナル免疫グロブリン（M 蛋白）の軽鎖（L 鎖）に由来するアミロイド蛋白が多臓器に沈着し，多様な臨床症状を示す，予後不良の疾患である。全身性 AL アミロイドーシスの病態は多発性骨髄腫（MM）と類似しているため，悪性形質細胞を標的とする薬物療法（抗形質細胞療法）が実施されている。海外では，シクロホスファミド水和物，ボルテゾミブ及びデキサメタゾンの併用（CyBorD）療法が全身性 AL アミロイドーシスの標準治療の 1 つとしてガイドラインで推奨され[1) 2) 3)]，日本でも CyBorD 療法の有用性がガイドライン等で報告されている[4) 5)]。しかしながら，CyBorD 療法も含めた抗形質細胞療法は，いずれも十分な臨床的エビデンスは得られていないため，国内外で全身性 AL アミロイドーシの適応を有する治療法は現時点でなく，新規薬剤開発の医療的必要性が高い。そこで，抗形質細胞療法の中で推奨，汎用されている CyBorD 療法にダラツムマブ（遺伝子組換え）（以下ダラツムマブ）を上乗せしたダラツムマブ，シクロホスファミド水和物，ボルテゾミブ及びデキサメタゾン（DCyBorD）療法を全身性 AL アミロイドーシス対する治療法として開発した。

ダラツムマブは，CD38 を特異的に認識する免疫グロブリン G1 kappa（IgG1κ）完全ヒト型モノクローナル抗体である。CD38 は MM，リンパ腫，白血病を含む造血器腫瘍において，高い発現を呈し，その他の様々な細胞や組織でも発現が確認されている細胞表面抗原蛋白質である。CD38 は正常組織にも発現するが，MM 細胞と比べ，その発現量ははるかに少ない。非臨床薬理試験の結果，ダラツムマブは MM 細胞を含むヒト細胞で発現している CD38 に特異的に結合し，CD38 を発現する腫瘍細胞の増殖を in vivo で強力に阻害することが示された。補体依存性細胞傷害（CDC）及び抗体依存性細胞傷害（ADCC）がダラツムマブの主要な作用機序である。

ダラツムマブ点滴静注製剤は，日本において，「多発性骨髄腫」を効能・効果として承認されている。しかしながら，infusion related reaction のリスクや，長時間の投与による患者及び医療従事者の負担を軽減するため，ダラツムマブとボルヒアルロニダーゼ アルファ（遺伝子組換え）（rHuPH20）を配合したダラツムマブ皮下注製剤の開発に着手し，2020 年 4 月に「多発性骨髄腫」を効能・効果として製造販売承認を申請した。

全身性 AL アミロイドーシスの病態生理は，MM と類似しており，全身性 AL アミロイドーシス患者の骨髄においても CD38 陽性形質細胞のモノクローナルな増殖が報告されている[6) 7)]。したがって，MM に治療効果が認められるダラツムマブが全身性 AL アミロイドーシスにも治療効果を有すると考え，皮下注製剤での開発に着手した。

シクロホスファミド水和物は，ナイトロジェンマスタード系の抗悪性腫瘍剤で，アルキル化剤に分類され，腫瘍細胞の DNA 合成を阻害し，抗腫瘍作用を示すことが認められている。現在，米国及び欧州を含む約 100 カ国で「悪性リンパ腫」，「多発性骨髄腫」，「進行性自己免疫疾患」等の適応で承認されている。日本では，「多発性骨髄腫」，「悪性リンパ腫」，「乳癌」，「慢性リンパ性白血病」，「慢性骨髄性白血病」，「咽頭癌」，「胃癌」，「膵癌」，「肝癌」，「結腸癌」等の悪性腫瘍，「全身性エリテマトーデス」，「全身性血管炎」等のリウマチ性疾患及びネフローゼ症候群に関する適応が承認されている[8) 9)]。

ボルテゾミブはユビキチン化によって制御を受ける多数の蛋白がプロテアソームで分解されるのを阻害し，それによって細胞増殖抑制及び抗腫瘍作用を示すプロテアソーム阻害剤である。ボルテゾミブは動物細胞に存在する 26S プロテアソームのキモトリプシン様活性を強力かつ可逆的に阻害することにより，多様ながん細胞に対し in vitro で細胞毒性を示し，更に in vivo の非臨床腫瘍モデルにおいて MM 等の腫瘍の増殖を抑制する。特に，Nuclear Factor-kappa-B（NF-κB）の活性化阻害，骨髄ストローマ細胞のインターロイキン 6（IL-6）産生を抑制することによる細胞増殖の抑制，サイクリン及びサイクリン依存性キナーゼを介する細胞周期の停止，直接的なアポトーシス誘導作用及び血管新生抑制作用等を介し，MM に対し治療効果を発揮する[10) 11) 12)]。ボルテゾミブは腫瘍細胞の細胞内シグナル伝達経路に作用するだけでなく，MM の病態に重要な腫瘍微小環境に対しても作用する。現在，米国及び欧州を含む約 110 の国と地域で「多発性骨髄腫」及び「マントル細胞リンパ腫」に関する適応で承認されており，日本では，「多発性骨髄腫」，「マントル細胞リンパ腫」及び「原発性マクログロブリン血症及びリンパ形質細胞リンパ腫」の適応が承認されている[13)]。

デキサメタゾンは，合成糖質コルチコステロイドであり，抗炎症作用，抗アレルギー作用，免疫抑制作用等の作用がある。世界中で内分泌疾患，リウマチ性疾患，膠原病，皮膚疾患，アレルギー性疾患，悪性腫瘍性疾患等に関連する適応で承認されている。日本では，「慢性副腎皮質機能不全」や「急性副腎皮質機能不全」等の内分泌疾患，「関節リウマチ」等のリウマチ性疾患，「エリテマトーデス」等の膠原病，「気管支喘息」，「喘息性気管支炎」等のアレルギー性疾患，「悪性リンパ腫（リンパ肉腫症，細網肉腫症，ホジキン病，皮膚細網症，菌状息肉症）」，「乳癌の再発転移」等の悪性腫瘍，「多発性骨髄腫」に対する他の抗悪性腫瘍剤との併用療法，抗悪性腫瘍剤（シスプラチン等）投与に伴う消化器症状（悪心・嘔吐）等，様々な疾患領域の適応で承認されている[14) 15)]。

未治療の全身性 AL アミロイドーシス患者を対象とした 54767414AMY3001 試験（以下 AMY3001 試験）において，主要評価項目の complete response（CR）率で統計学的に有意な改善が認められ，CyBorD 療法に対するダラツムマブの上乗せ効果が検証された。感度分析，補足的解析，部分集団解析，及び主な副次評価項目である主要な臓器機能低下－無増悪生存期間（MOD-PFS）の結果からも DCyBorD 療法の有効性が確認された。日本人集団でも，主要評価項目である CR 率で全体集団との一貫性が示され，主な副次評価項目である MOD-PFS も全体集団と同様の結果であり，日本人患者でも有効性が期待できると考えられた。

DCyBorD 療法の安全性については，原疾患である全身性 AL アミロイドーシスの合併症を考慮するとダラツムマブ，ボルテゾミブ，シクロホスファミド水和物及びデキサメタゾンの既知の安全性プロファイルを比較したときと大きな差はないと考えられた。また，DCyBorD 療法の安全性プロファイルに日本人集団と全体集団で明らかな違いはないと考えられた。

このように AMY3001 試験では，DCyBorD 療法の良好なベネフィット・リスクプロファイルが全体集団及び日本人集団のいずれでも認められた。

海外のガイドラインでは，再発した全身性 AL アミロイドーシス患者に対しては，初回治療レジメンでの再治療，又はこれまでに投与していない代替併用レジメンでの治療が選択肢となるた

め[1) 2) 3)]，未治療の全身性 AL アミロイドーシス患者で有効性が検証された治療レジメンは，再発した全身性 AL アミロイドーシス患者での治療選択肢の 1 つとなると考える。

以上より，ダラツムマブ皮下注製剤，ボルテゾミブ，シクロホスファミド水和物及びデキサメタゾンの各薬剤で，効能・効果に全身性 AL アミロイドーシスを追加することを目的とした製造販売承認申請を行うこととした。なお，ダラツムマブ皮下注製剤は，ボルテゾミブ，シクロホスファミド水和物及びデキサメタゾンの併用療法で，米国及び欧州でも 2020 年 9 月及び 11 月に AMY3001 試験成績を基に製造販売承認申請を行った。

起原又は発見の経緯及び開発の経緯については，平成 13 年 6 月 21 日付医薬審発第 899 号厚生労働省医薬局審査管理課長通知「新医薬品の製造又は輸入の承認申請に際し承認申請書に添付すべき資料の作成要領について」の別紙 2 の 5（1）項の記述をもとに，当該内容を主に第 2 部（5）に記載した（表 1.5-1）。また，本申請に関する臨床試験の開発経緯を表 1.5-2 に示す。

表 1.5-1 CTD1.5 項の内容の記載場所

CTD 1.5 項の内容	CTD 第 2 部の記載場所
起原又は発見の経緯	2.5.1　製品開発の根拠
全身性 AL アミロイドーシスの病態及び疫学	2.5.1.2.1　全身性 AL アミロイドーシス
全身性 AL アミロイドーシスの治療	2.5.1.2.2　全身性 AL アミロイドーシスの治療法
開発の経緯	2.5.1.3　臨床開発経緯
申請効能・効果に対する有用性	2.5.6　ベネフィットとリスクに関する結論

表 1.5-2 臨床試験の開発経緯

相	実施地域	対象	試験番号等	実施時期
III	国際共同	未治療の全身性 AL アミロイドーシス患者	54767414AMY3001（評価資料）	2017 年 10 月～継続中
Ib	海外	PI 及び IMiD を含む前治療を 2 ライン以上受けたことがある再発又は難治性の MM 患者	54767414MMY1004[a]（参考資料）	2015 年 10 月～継続中
I	国内	PI 及び IMiD を含む前治療を 2 ライン以上受けたことがある再発又は難治性の日本人 MM 患者	54767414MMY1008（参考資料）	2017 年 8 月～継続中

IMiD：免疫調節薬，PI：プロテアソーム阻害剤
a MMY1004 試験では Part 1，Part 2 及び Part 3 を設定したが，本申請までに結果が得られていない Part 3 については省略した。

参考文献

1） National Comprehensive Cancer Network. NCCN guidelines version 1.2020. Systemic light chain amyloidosis. 2019.

2） Wechalekar AD, Gillmore JD, Bird J, et al. Guidelines on the management of AL amyloidosis. Br J Haematol. 2015;168:186-206.

3） The Risk Adapted Approach to Management of Multiple Myeloma and Related Disorders [homepage on the Internet]. Mayo clinic; [update 2019 August]. Treatment Guidelines: Amyloidosis. Available from: https://static1.squarespace.com/static/5b44f08ac258b493a25098a3/t/5d7fd7bd27708631a437368f/156865939

4） 造血器腫瘍診療ガイドライン 2018 年補改訂［2020 年 4 月］一般社団法人 日本血液学会

5） Kikukawa Y, Yuki H, Hirata S, et al. Combined use of bortezomib, cyclophosphamide, and dexamethasone induces favorable hematological and organ responses in Japanese patients with amyloid light-chain amyloidosis: a single-institution retrospective study. Int J Hematol. 2015;101(2):133-9.

6） Matsuda M, Gono T, Shimojima Y, et al. Phenotypic analysis of plasma cells in bone marrow using flow cytometry in AL amyloidosis. Amyloid. 2003 Jun;10(2):110-6.

7） Shimojima Y, Matsuda M, Gono T, et al. Correlation between serum levels of free light chain and phenotype of plasma cells in bone marrow in primary AL amyloidosis. Amyloid. 2005 Mar;12(1):33-40.

8） 注射用シクロホスファミド水和物 注射用エンドキサン®100 mg/注射用エンドキサン®500mg インタビューフォーム 2013 年 4 月改訂 第 8 版

9） シクロホスファミド錠 エンドキサン®錠 50 mg/シクロホスファミド水和物散 経口用エンドキサン®原末 100 mg インタビューフォーム 2015 年 12 月改訂 第 16 版

10） Hideshima T, Richardson P, Chauhan D, et al. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Res. 2001 Apr 1;61(7):3071-6.

11） Koepp DM, Harper JW, Elledge SJ. How the cyclin became a cyclin: regulated proteolysis in the cell cycle. Cell.1999 May 14;97(4):431-4.

12） Sherr CJ. Cancer cell cycles. Science. 1996 Dec 6;274 (5293):1672-7.

13） ベルケイド®注射用 3 mg インタビューフォーム 2019 年 8 月 第 12 版

14） 副腎皮質ホルモン製剤 デカドロン®錠 0.5 mg/デカドロン®錠 4 mg/デカドロン®エリキシル 0.01%インタビューフォーム 2020 年 8 月改訂 第 13 版

15） 副腎皮質ホルモン製剤 デカドロン®注射液 1.65 mg/デカドロン®注射液 3.3 mg/デカドロン®注射液 6.6 mg インタビューフォーム 2020 年 8 月改訂 第 14 版

1.6 外国における使用状況等に関する資料

ボルテゾミブは，米国で開発を開始され，2003 年に「既治療の多発性骨髄腫」，2006 年に「既治療のマントル細胞リンパ腫」，2008 年に「未治療の多発性骨髄腫」，2012 年に新投与経路として皮下投与が承認され，2014 年には「未治療のマントル細胞リンパ腫」に対しても承認されている。その後，米国及び欧州を含む世界 110 以上の国と地域で「多発性骨髄腫」及び「マントル細胞リンパ腫」に対する適応で承認されている。本邦においては 2018 年 3 月に「原発性マクログロブリン血症及びリンパ形質細胞リンパ腫」に対する適応が承認されているが，外国において承認されている国はない。また、「全身性 AL アミロイドーシス」の適応取得を目的として承認申請している国もない。

外国の添付文書として，米国及び欧州の添付文書，並びに企業中核データシート（CCDS）を添付する。

VELCADE® (bortezomib) for Injection

Company Core Data Sheet

Core Safety Information

[redacted]

For Internal Use Only
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Highlighted language is optional

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以下、非公開のため1~61頁を省略

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

VELCADE® (bortezomib) for injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2003

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

Warnings and Precautions,
Thrombotic Microangiopathy (5.10) 04/2019

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

VELCADE is a proteasome inhibitor indicated for:

- treatment of adult patients with multiple myeloma (1.1)
- treatment of adult patients with mantle cell lymphoma (1.2)

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

- For subcutaneous or intravenous use only. Each route of administration has a different reconstituted concentration; Exercise caution when calculating the volume to be administered. (2.1, 2.10)
- The recommended starting dose of VELCADE is 1.3 mg/m^2 administered either as a 3 to 5 second bolus intravenous injection or subcutaneous injection. (2.2, 2.4, 2.6)
- Retreatment for multiple myeloma: May retreat starting at the last tolerated dose. (2.6)
- Hepatic Impairment: Use a lower starting dose for patients with moderate or severe hepatic impairment. (2.8)
- Dose must be individualized to prevent overdose. (2.10)

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

- For injection: Single-dose vial contains 3.5 mg of bortezomib as lyophilized powder for reconstitution and withdrawal of the appropriate individual patient dose. (3)

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

- Patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. (4)
- Contraindicated for intrathecal administration. (4)

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

- Peripheral Neuropathy: Manage with dose modification or discontinuation. (2.7) Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment. (2.7, 5.1)
- Hypotension: Use caution when treating patients taking antihypertensives, with a history of syncope, or with dehydration. (5.2)
- Cardiac Toxicity: Worsening of and development of cardiac failure has occurred. Closely monitor patients with existing heart disease or risk factors for heart disease. (5.3)
- Pulmonary Toxicity: Acute respiratory syndromes have occurred. Monitor closely for new or worsening symptoms and consider interrupting VELCADE therapy. (5.4)
- Posterior Reversible Encephalopathy Syndrome: Consider MRI imaging for onset of visual or neurological symptoms; discontinue VELCADE if suspected. (5.5)
- Gastrointestinal Toxicity: Nausea, diarrhea, constipation, and vomiting may require use of antiemetic and antidiarrheal medications or fluid replacement. (5.6)
- Thrombocytopenia and Neutropenia: Monitor complete blood counts regularly throughout treatment. (5.7)
- Tumor Lysis Syndrome: Closely monitor patients with high tumor burden. (5.8)
- Hepatic Toxicity: Monitor hepatic enzymes during treatment. Interrupt VELCADE therapy to assess reversibility. (5.9)
- Thrombotic Microangiopathy: Monitor for signs and symptoms. Discontinue VELCADE if suspected. (5.10)
- Embryo-fetal Toxicity: VELCADE can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to avoid pregnancy. (5.11)

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

Most commonly reported adverse reactions (incidence ≥20%) in clinical studies include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia. (6.1)

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

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

- Strong CYP3A4 Inhibitors: Closely monitor patients with concomitant use. (7.1)
- Strong CYP3A4 Inducers: Avoid concomitant use. (7.3)

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

Patients with diabetes may require close monitoring of blood glucose and adjustment of antidiabetic medication. (8.8)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Multiple Myeloma
- 1.2 Mantle Cell Lymphoma

2 DOSAGE AND ADMINISTRATION
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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma
VELCADE is indicated for the treatment of adult patients with multiple myeloma.

1.2 Mantle Cell Lymphoma
VELCADE is indicated for the treatment of adult patients with mantle cell lymphoma.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Guidelines
VELCADE is for intravenous or subcutaneous use only. Do not administer VELCADE by any other route.

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

The recommended starting dose of VELCADE is 1.3 mg/m^2. VELCADE is administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL *[see Dosage and Administration (2.10)].*

VELCADE retreatment may be considered for patients with multiple myeloma who had previously responded to treatment with VELCADE and who have relapsed at least six months after completing prior VELCADE treatment. Treatment may be started at the last tolerated dose *[see Dosage and Administration (2.6)]*.

When administered intravenously, administer VELCADE as a 3 to 5 second bolus intravenous injection.

2.2 Dosage in Previously Untreated Multiple Myeloma
VELCADE is administered in combination with oral melphalan and oral prednisone for 9, six-week treatment cycles as shown in Table 1. In Cycles 1 to 4, VELCADE is administered twice weekly (Days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5 to 9, VELCADE is administered once weekly (Days 1, 8, 22 and 29). At least 72 hours should elapse between consecutive doses of VELCADE.

Table 1: Dosage Regimen for Patients with Previously Untreated Multiple Myeloma

Twice Weekly VELCADE (Cycles 1 to 4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
VELCADE (1.3 mg/m^2)	Day 1	--	--	Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	rest period
Melphalan (9 mg/m^2) Prednisone (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period
Once Weekly VELCADE (Cycles 5 to 9 when used in combination with Melphalan and Prednisone)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
VELCADE (1.3 mg/m^2)	Day 1	--	--		Day 8		rest period	Day 22		Day 29		rest period
Melphalan (9 mg/m^2) Prednisone (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

2.3 Dose Modification Guidelines for VELCADE When Given in Combination with Melphalan and Prednisone

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

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

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

Toxicity	Dose modification or delay
Hematological toxicity during a cycle: If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle
If platelet count is not above 30 $\times$ 10^9/L or ANC is not above 0.75 x 10^9/L on a VELCADE dosing day (other than Day 1)	Withhold VELCADE dose
If several VELCADE doses in consecutive cycles are withheld due to toxicity	Reduce VELCADE dose by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)
Grade 3 or higher nonhematological toxicities	Withhold VELCADE therapy until symptoms of toxicity have resolved to Grade 1 or baseline. Then, VELCADE may be reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For VELCADE-related neuropathic pain and/or peripheral neuropathy, hold or modify VELCADE as outlined in Table 5.

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

Dose modifications guidelines for peripheral neuropathy are provided *[see Dosage and Administration (2.7)]*.

2.4 Dosage in Previously Untreated Mantle Cell Lymphoma

VELCADE (1.3 mg/m^2) is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin and oral prednisone (VcR-CAP) for 6, three week treatment cycles as shown in Table 3. VELCADE is administered first followed by rituximab. VELCADE is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten day rest period on Days 12 to 21. For patients with a response first documented at cycle 6, two additional VcR-CAP cycles are recommended. At least 72 hours should elapse between consecutive doses of VELCADE.

Table 3: Dosage Regimen for Patients with Previously Untreated Mantle Cell Lymphoma								
Twice Weekly VELCADE (6, Three-Week Cycles)*								
Week	**1**					**2**		**3**
VELCADE (1.3 mg/m^2)	Day 1	--	--	Day 4	--	Day 8	Day 11	rest period
Rituximab (375 mg/m^2) Cyclophosphamide (750 mg/m^2) Doxorubicin (50 mg/m^2)	Day 1	--	--			--	--	rest period
Prednisone (100 mg/m^2)	Day 1	Day 2	Day 3	Day 4	Day 5	--	--	rest period

* Dosing may continue for two more cycles (for a total of eight cycles) if response is first seen at Cycle 6.

2.5 Dose Modification Guidelines for VELCADE When Given in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone

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

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

Interrupt VELCADE treatment at the onset of any Grade 3 hematologic or nonhematological toxicities, excluding neuropathy *[see Table 5, Warnings and Precautions (5)]*. For dose adjustments, see Table 4 below.

Table 4: Dose Modifications on Days 4, 8, and 11 During Cycles of Combination VELCADE, Rituximab, Cyclophosphamide, Doxorubicin and Prednisone Therapy	
Toxicity	**Dose modification or delay**
Hematological toxicity	
• Grade 3 or higher neutropenia, or a platelet count not at or above 25 $\times$ 10^9/L	Withhold VELCADE therapy for up to 2 weeks until the patient has an ANC at or above 0.75 $\times$ 10^9/L and a platelet count at or above 25 $\times$ 10^9/L. • If, after VELCADE has been withheld, the toxicity does not resolve, discontinue VELCADE. • If toxicity resolves such that the patient has an ANC at or above 0.75 $\times$ 10^9/L and a platelet count at or above 25 $\times$ 10^9/L, VELCADE dose should be reduced by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)
Grade 3 or higher nonhematological toxicities	Withhold VELCADE therapy until symptoms of the toxicity have resolved to Grade 2 or better. Then, VELCADE may be reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For VELCADE-related neuropathic pain and/or peripheral neuropathy, hold or modify VELCADE as outlined in Table 5.

For information concerning rituximab, cyclophosphamide, doxorubicin and prednisone, see manufacturer's prescribing information.

2.6 Dosage and Dose Modifications for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

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

Patients with multiple myeloma who have previously responded to treatment with VELCADE (either alone or in combination) and who have relapsed at least six months after their prior VELCADE therapy may be started on VELCADE at the last tolerated dose. Retreated patients are administered VELCADE twice weekly (Days 1, 4, 8, and 11) every three weeks for a maximum of eight cycles. At least 72 hours should elapse between consecutive doses of VELCADE. VELCADE may be administered either as a single agent or in combination with dexamethasone *[see Clinical Studies (14.1)]*.

VELCADE therapy should be withheld at the onset of any Grade 3 nonhematological or Grade 4 hematological toxicities excluding neuropathy as discussed below *[see Warnings and Precautions (5)]*. Once the symptoms of the toxicity have resolved, VELCADE therapy may be

reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1 mg/m^2/dose; 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose).

For dose modifications guidelines for peripheral neuropathy see section 2.7.

2.7 Dose Modifications for Peripheral Neuropathy

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

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

For dose or schedule modification guidelines for patients who experience VELCADE-related neuropathic pain and/or peripheral neuropathy see Table 5.

Table 5: Recommended Dose Modification for VELCADE related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

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

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

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

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

2.8 Dosage in Patients with Hepatic Impairment

Do not adjust the starting dose for patients with mild hepatic impairment.

Start patients with moderate or severe hepatic impairment at a reduced dose of 0.7 mg/m^2 per injection during the first cycle, and consider subsequent dose escalation to 1 mg/m^2 or further dose reduction to 0.5 mg/m^2 based on patient tolerance *(see Table 6) [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Table 6: Recommended Starting Dose Modification for VELCADE in Patients with Hepatic Impairment			
	Bilirubin Level	**SGOT (AST) Levels**	**Modification of Starting Dose**
Mild	Less than or equal to 1x ULN	More than ULN	None
	More than 1x-1.5x ULN	Any	None
Moderate	More than 1.5x-3x ULN	Any	Reduce VELCADE to 0.7 mg/m^2 in the first cycle. Consider dose escalation to 1 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	More than 3x ULN	Any	

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

2.9 Administration Precautions

The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose *[see Dosage and Administration (2.10)]*.

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

If local injection site reactions occur following VELCADE administration subcutaneously, a less concentrated VELCADE solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously *[see Dosage and Administration (2.10)]*. Alternatively, consider use of the intravenous route of administration *[see Dosage and Administration (2.10)]*.

VELCADE is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

2.10 Reconstitution/Preparation for Intravenous and Subcutaneous Administration

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

Different volumes of 0.9% sodium chloride are used to reconstitute the product for the different routes of administration. The reconstituted concentration of bortezomib for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration of bortezomib for intravenous administration (1 mg/mL). **Because each route of administration has a different reconstituted concentration, use caution when calculating the volume to be administered** *[see Dosage and Administration (2.9)]*.

For each 3.5 mg single-dose vial of bortezomib reconstitute with the following volume of 0.9% sodium chloride based on route of administration *(Table 7)*:

Table 7: Reconstitution Volumes and Final Concentration for Intravenous and Subcutaneous Administration			
Route of Administration	**Bortezomib (mg/vial)**	**Diluent (0.9% Sodium Chloride)**	**Final Bortezomib Concentration (mg/mL)**
Intravenous	3.5 mg	3.5 mL	1 mg/mL
Subcutaneous	3.5 mg	1.4 mL	2.5 mg/mL

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

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

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

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

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

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

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

Stability

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

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

3 DOSAGE FORMS AND STRENGTHS

For injection: Each single-dose vial of VELCADE contains 3.5 mg of bortezomib as a sterile lyophilized white to off-white powder for reconstitution and withdrawal of the appropriate individual patient dose *[see Dosage and Administration (2.10)]*.

4 CONTRAINDICATIONS

VELCADE is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol. Reactions have included anaphylactic reactions *[see Adverse Reactions (6.1)]*.

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

5 WARNINGS AND PRECAUTIONS

5.1 Peripheral Neuropathy

VELCADE treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with preexisting symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥Grade 3) during treatment with VELCADE. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. In the Phase 3 relapsed multiple myeloma trial comparing VELCADE subcutaneous vs intravenous the incidence of Grade ≥2 peripheral neuropathy was 24% for subcutaneous and 39% for intravenous.

Grade ≥3 peripheral neuropathy occurred in 6% of patients in the subcutaneous treatment group, compared with 15% in the intravenous treatment group. Starting VELCADE subcutaneously may be considered for patients with preexisting or at high risk of peripheral neuropathy.

Patients experiencing new or worsening peripheral neuropathy during VELCADE therapy may require a decrease in the dose and/or a less dose-intense schedule *[see Dosage and Administration (2.7)]*. In the VELCADE vs dexamethasone Phase 3 relapsed multiple myeloma study, improvement in or resolution of peripheral neuropathy was reported in 48% of patients with ≥Grade 2 peripheral neuropathy following dose adjustment or interruption. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥Grade 3 peripheral neuropathy in the Phase 2 multiple myeloma studies *[see Adverse Reactions (6.1)]*. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

5.2 Hypotension

The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8%. These events are observed throughout therapy. Patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated may be at increased risk of hypotension. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics *[see Adverse Reactions (6.1)]*.

5.3 Cardiac Toxicity

Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have occurred during VELCADE therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be frequently monitored. In the relapsed multiple myeloma study of VELCADE vs dexamethasone, the incidence of any treatment-related cardiac disorder was 8% and 5% in the VELCADE and dexamethasone groups, respectively. The incidence of adverse reactions suggestive of heart failure (acute pulmonary edema, pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock) was ≤1% for each individual reaction in the VELCADE group. In the dexamethasone group the incidence was ≤1% for cardiac failure and congestive cardiac failure; there were no reported reactions of acute pulmonary edema, pulmonary edema, or cardiogenic shock. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

5.4 Pulmonary Toxicity

Acute Respiratory Distress Syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration have occurred in patients receiving VELCADE. Some of these events have been fatal.

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

There have been reports of pulmonary hypertension associated with VELCADE administration in the absence of left heart failure or significant pulmonary disease.

In the event of new or worsening cardiopulmonary symptoms, consider interrupting VELCADE until a prompt and comprehensive diagnostic evaluation is conducted.

5.5 Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior Reversible Encephalopathy Syndrome (PRES; formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS)) has occurred in patients receiving VELCADE. PRES is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache,

lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing PRES, discontinue VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing PRES is not known.

5.6 Gastrointestinal Toxicity

VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting *[see Adverse Reactions (6.1)]* sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement should be administered to prevent dehydration. Interrupt VELCADE for severe symptoms.

5.7 Thrombocytopenia/Neutropenia

VELCADE is associated with thrombocytopenia and neutropenia that follow a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remain consistent in the studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in the treatment regimens studied.

Monitor complete blood counts (CBC) frequently during treatment with VELCADE. Measure platelet counts prior to each dose of VELCADE. Adjust dose/schedule for thrombocytopenia *[see Tables 2 and 4, Dosage and Administration (2.6)]*. Gastrointestinal and intracerebral hemorrhage has occurred during thrombocytopenia in association with VELCADE. Support with transfusions and supportive care, according to published guidelines.

In the single-agent, relapsed multiple myeloma study of VELCADE vs dexamethasone, the mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia related to pretreatment platelet count is shown in Table 8. The incidence of bleeding (≥Grade 3) was 2% on the VELCADE arm and was <1% in the dexamethasone arm.

Table 8: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the Relapsed Multiple Myeloma Study of VELCADE vs Dexamethasone

Pretreatment Platelet Count*	Number of Patients (N=331)‡	Number (%) of Patients with Platelet Count <10,000/µL	Number (%) of Patients with Platelet Count 10,000 to 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 one patient

In the combination study of VELCADE with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP) in previously untreated mantle cell lymphoma patients, the incidence of thrombocytopenia (≥Grade 4) was 32% vs 1% for the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) arm as shown in Table 12. The incidence of bleeding events (≥Grade 3) was 1.7% in the VcR-CAP arm (four patients) and was 1.2% in the R-CHOP arm (three patients).

Platelet transfusions were given to 23% of the patients in the VcR-CAP arm and 3% of the patients in the R-CHOP arm.

The incidence of neutropenia (≥Grade 4) was 70% in the VcR-CAP arm and was 52% in the R-CHOP arm. The incidence of febrile neutropenia (≥Grade 4) was 5% in the VcR-CAP arm and was 6% in the

R-CHOP arm. Myeloid growth factor support was provided at a rate of 78% in the VcR-CAP arm and 61% in the R-CHOP arm.

5.8 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with VELCADE therapy. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

5.9 Hepatic Toxicity

Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia. Interrupt VELCADE therapy to assess reversibility. There is limited re-challenge information in these patients.

5.10 Thrombotic Microangiopathy

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

5.11 Embryo-fetal Toxicity

Based on the mechanism of action and findings in animals, VELCADE can cause fetal harm when administered to a pregnant woman. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area caused postimplantation loss and a decreased number of live fetuses *[see Use in Specific Populations (8.1)]*.

Females of reproductive potential should avoid becoming pregnant while being treated with VELCADE. Advise females of reproductive potential that they must use contraception during treatment with VELCADE and for seven months following treatment. Advise males with female sexual partners of reproductive potential that they must use contraception during treatment with VELCADE and for four months following treatment. If VELCADE is used during pregnancy or if the patient becomes pregnant during VELCADE treatment, the patient should be apprised of the potential risk to the fetus *[see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)].*

6 ADVERSE REACTIONS

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

- Peripheral Neuropathy *[see Warnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.2)]*
- Cardiac Toxicity *[see Warnings and Precautions (5.3)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.4)]*
- Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.5)]*
- Gastrointestinal Toxicity *[see Warnings and Precautions (5.6)]*
- Thrombocytopenia/Neutropenia *[see Warnings and Precautions (5.7)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.8)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.9)]*
- Thrombotic Microangiopathy *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Safety Experience

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

Summary of Clinical Trial in Patients with Previously Untreated Multiple Myeloma

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

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

Table 9: Most Commonly Reported Adverse Reactions (≥10% in the VELCADE, Melphalan and Prednisone arm) with Grades 3 and ≥4 Intensity in the Previously Untreated Multiple Myeloma Study

	VELCADE, Melphalan and Prednisone			Melphalan and Prednisone		
	(n=340)			(n=337)		
Body System	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Adverse Reaction	n (%)	3	≥4	n (%)	3	≥4
Blood and Lymphatic System Disorders						
Thrombocytopenia	164 (48)	60 (18)	57 (17)	140 (42)	48 (14)	39 (12)
Neutropenia	160 (47)	101 (30)	33 (10)	143 (42)	77 (23)	42 (12)
Anemia	109 (32)	41 (12)	4 (1)	156 (46)	61 (18)	18 (5)
Leukopenia	108 (32)	64 (19)	8 (2)	93 (28)	53 (16)	11 (3)
Lymphopenia	78 (23)	46 (14)	17 (5)	51 (15)	26 (8)	7 (2)
Gastrointestinal Disorders						
Nausea	134 (39)	10 (3)	0	70 (21)	1 (<1)	0
Diarrhea	119 (35)	19 (6)	2 (1)	20 (6)	1 (<1)	0
Vomiting	87 (26)	13 (4)	0	41 (12)	2 (1)	0
Constipation	77 (23)	2 (1)	0	14 (4)	0	0
Abdominal Pain Upper	34 (10)	1 (<1)	0	20 (6)	0	0
Nervous System Disorders						
Peripheral Neuropathy*	156 (46)	42 (12)	2 (1)	4 (1)	0	0
Neuralgia	117 (34)	27 (8)	2 (1)	1 (<1)	0	0
Paresthesia	42 (12)	6 (2)	0	4 (1)	0	0
General Disorders and Administration Site Conditions						
Fatigue	85 (25)	19 (6)	2 (1)	48 (14)	4 (1)	0
Asthenia	54 (16)	18 (5)	0	23 (7)	3 (1)	0
Pyrexia	53 (16)	4 (1)	0	19 (6)	1 (<1)	1 (<1)
Infections and Infestations						
Herpes Zoster	39 (11)	11 (3)	0	9 (3)	4 (1)	0
Metabolism and Nutrition Disorders						
Anorexia	64 (19)	6 (2)	0	19 (6)	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	38 (11)	2 (1)	0	7 (2)	0	0
Psychiatric Disorders						
Insomnia	35 (10)	1 (<1)	0	21 (6)	0	0

* Represents High Level Term Peripheral Neuropathies NEC

Relapsed Multiple Myeloma Randomized Study of VELCADE vs Dexamethasone

The safety data described below and in Table 10 reflect exposure to either VELCADE (n=331) or dexamethasone (n=332) in a study of patients with relapsed multiple myeloma. VELCADE was administered intravenously at doses of 1.3 mg/m^2 twice weekly for two out of three weeks (21 day cycle). After eight 21 day cycles patients continued therapy for three 35 day cycles on a weekly schedule. Duration of treatment was up to 11 cycles (nine months) with a median duration of six cycles (4.1 months). For inclusion in the trial, patients must have had measurable disease and one to three prior therapies. There was no upper age limit for entry. Creatinine clearance could be as low as 20 mL/min and bilirubin levels as high as 1.5 times the upper limit of normal. The overall

frequency of adverse reactions was similar in men and women, and in patients <65 and ≥65 years of age. Most patients were Caucasian *[see Clinical Studies (14.1)]*.

Among the 331 VELCADE-treated patients, the most commonly reported (>20%) adverse reactions overall were nausea (52%), diarrhea (52%), fatigue (39%), peripheral neuropathies (35%), thrombocytopenia (33%), constipation (30%), vomiting (29%), and anorexia (21%). The most commonly reported (>20%) adverse reaction reported among the 332 patients in the dexamethasone group was fatigue (25%). Eight percent (8%) of patients in the VELCADE-treated arm experienced a Grade 4 adverse reaction; the most common reactions were thrombocytopenia (4%) and neutropenia (2%). Nine percent (9%) of dexamethasone-treated patients experienced a Grade 4 adverse reaction. All individual dexamethasone-related Grade 4 adverse reactions were less than 1%.

Serious Adverse Reactions and Adverse Reactions Leading to Treatment Discontinuation in the Relapsed Multiple Myeloma Study of VELCADE vs Dexamethasone

Serious adverse reactions are defined as any reaction that results in death, is life-threatening, requires hospitalization or prolongs a current hospitalization, results in a significant disability, or is deemed to be an important medical event. A total of 80 (24%) patients from the VELCADE treatment arm experienced a serious adverse reaction during the study, as did 83 (25%) dexamethasone-treated patients. The most commonly reported serious adverse reactions in the VELCADE treatment arm were diarrhea (3%), dehydration, herpes zoster, pyrexia, nausea, vomiting, dyspnea, and thrombocytopenia (2% each). In the dexamethasone treatment group, the most commonly reported serious adverse reactions were pneumonia (4%), hyperglycemia (3%), pyrexia, and psychotic disorder (2% each).

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

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

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

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

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

	VELCADE N=331			**Dexamethasone** N=332		
Adverse Reactions	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any Adverse Reactions	324 (98)	193 (58)	28 (8)	297 (89)	110 (33)	29 (9)
Nausea	172 (52)	8 (2)	0	31 (9)	0	0
Diarrhea NOS	171 (52)	22 (7)	0	36 (11)	2 (<1)	0
Fatigue	130 (39)	15 (5)	0	82 (25)	8 (2)	0
Peripheral neuropathies*	115 (35)	23 (7)	2 (<1)	14 (4)	0	1 (<1)
Thrombocytopenia	109 (33)	80 (24)	12 (4)	11 (3)	5 (2)	1 (<1)
Constipation	99 (30)	6 (2)	0	27 (8)	1 (<1)	0
Vomiting NOS	96 (29)	8 (2)	0	10 (3)	1 (<1)	0
Anorexia	68 (21)	8 (2)	0	8 (2)	1 (<1)	0
Pyrexia	66 (20)	2 (<1)	0	21 (6)	3 (<1)	1 (<1)
Paresthesia	64 (19)	5 (2)	0	24 (7)	0	0
Anemia NOS	63 (19)	20 (6)	1 (<1)	21 (6)	8 (2)	0
Headache NOS	62 (19)	3 (<1)	0	23 (7)	1 (<1)	0
Neutropenia	58 (18)	37 (11)	8 (2)	1 (<1)	1 (<1)	0
Rash NOS	43 (13)	3 (<1)	0	7 (2)	0	0
Appetite decreased NOS	36 (11)	0	0	12 (4)	0	0
Dyspnea NOS	35 (11)	11 (3)	1 (<1)	37 (11)	7 (2)	1 (<1)
Abdominal pain NOS	35 (11)	5 (2)	0	7 (2)	0	0
Weakness	34 (10)	10 (3)	0	28 (8)	8 (2)	0

* Represents High Level Term Peripheral Neuropathies NEC

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

In the Phase 2 extension study of 63 patients, no new cumulative or new long-term toxicities were observed with prolonged VELCADE treatment. These patients were treated for a total of 5.3 to 23 months, including time on VELCADE in the prior VELCADE study *[see Clinical Studies (14.1)]*.

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

The safety and efficacy of VELCADE administered subcutaneously were evaluated in one Phase 3 study at the recommended dose of 1.3 mg/m^2. This was a randomized, comparative study of VELCADE subcutaneous vs intravenous in 222 patients with relapsed multiple myeloma. The safety data described below and in Table 11 reflect exposure to either VELCADE subcutaneous (n=147) or VELCADE intravenous (n=74) *[see Clinical Studies (14.1)]*.

Table 11: Most Commonly Reported Adverse Reactions (≥10%), with Grade 3 and ≥4 Intensity in the Relapsed Multiple Myeloma Study (N=221) of VELCADE Subcutaneous vs Intravenous

	Subcutaneous (N=147)			Intravenous (N=74)		
Body System	Total	Toxicity Grade, n (%)		Total	Toxicity Grade, n (%)	
Adverse Reaction	n (%)	3	≥4	n (%)	3	≥4
Blood and Lymphatic System Disorders						
Anemia	28 (19)	8 (5)	0	17 (23)	3 (4)	0
Leukopenia	26 (18)	8 (5)	0	15 (20)	4 (5)	1 (1)
Neutropenia	34 (23)	15 (10)	4 (3)	20 (27)	10 (14)	3 (4)
Thrombocytopenia	44 (30)	7 (5)	5 (3)	25 (34)	7 (9)	5 (7)
Gastrointestinal Disorders						
Diarrhea	28 (19)	1 (1)	0	21 (28)	3 (4)	0
Nausea	24 (16)	0	0	10 (14)	0	0
Vomiting	13 (9)	3 (2)	0	8 (11)	0	0
General Disorders and Administration Site Conditions						
Asthenia	10 (7)	1 (1)	0	12 (16)	4 (5)	0
Fatigue	11 (7)	3 (2)	0	11 (15)	3 (4)	0
Pyrexia	18 (12)	0	0	6 (8)	0	0
Nervous System Disorders						
Neuralgia	34 (23)	5 (3)	0	17 (23)	7 (9)	0
Peripheral neuropathies*	55 (37)	8 (5)	1 (1)	37 (50)	10 (14)	1 (1)

Note: Safety population: 147 patients in the subcutaneous treatment group and 74 patients in the intravenous treatment group who received at least one dose of study medication

* Represents High Level Term Peripheral Neuropathies NEC

In general, safety data were similar for the subcutaneous and intravenous treatment groups. Differences were observed in the rates of some Grade ≥3 adverse reactions. Differences of ≥5% were reported in neuralgia (3% subcutaneous vs 9% intravenous), peripheral neuropathies (6% subcutaneous vs 15% intravenous), neutropenia (13% subcutaneous vs 18% intravenous), and thrombocytopenia (8% subcutaneous vs 16% intravenous).

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

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

Serious Adverse Reactions and Adverse Reactions Leading to Treatment Discontinuation in the Relapsed Multiple Myeloma Study of VELCADE Subcutaneous vs Intravenous

The incidence of serious adverse reactions was similar for the subcutaneous treatment group (20%) and the intravenous treatment group (19%). The most commonly reported serious adverse reactions in the subcutaneous treatment arm were pneumonia and pyrexia (2% each). In the intravenous treatment group, the most commonly reported serious adverse reactions were pneumonia, diarrhea, and peripheral sensory neuropathy (3% each).

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

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

Safety Experience from the Clinical Trial in Patients with Previously Untreated Mantle Cell Lymphoma

Table 12 describes safety data from 240 patients with previously untreated mantle cell lymphoma who received VELCADE (1.3 mg/m^2) administered intravenously in combination with rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), and prednisone (100 mg/m^2) (VcR-CAP) in a prospective randomized study.

Infections were reported for 31% of patients in the VcR-CAP arm and 23% of the patients in the comparator (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) arm, including the predominant preferred term of pneumonia (VcR-CAP 8% vs R-CHOP 5%).

Table 12: Most Commonly Reported Adverse Reactions (≥5%) with Grades 3 and ≥4 Intensity in the Previously Untreated Mantle Cell Lymphoma Study

	VcR-CAP n=240			R-CHOP n=242		
Body System Adverse Reactions	All n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)	All n (%)	Toxicity Grade 3 n (%)	Toxicity Grade ≥4 n (%)
Blood and lymphatic system disorders						
Neutropenia	209 (87)	32 (13)	168 (70)	172 (71)	31 (13)	125 (52)
Leukopenia	116 (48)	34 (14)	69 (29)	87 (36)	39 (16)	27 (11)
Anemia	106 (44)	27 (11)	4 (2)	71 (29)	23 (10)	4 (2)
Thrombocytopenia	172 (72)	59 (25)	76 (32)	42 (17)	9 (4)	3 (1)
Febrile neutropenia	41 (17)	24 (10)	12 (5)	33 (14)	17 (7)	15 (6)
Lymphopenia	68 (28)	25 (10)	36 (15)	28 (12)	15 (6)	2 (1)
Nervous system disorders						
Peripheral neuropathy*	71 (30)	17 (7)	1 (<1)	65 (27)	10 (4)	0
Hypoesthesia	14 (6)	3 (1)	0	13 (5)	0	0
Paresthesia	14 (6)	2 (1)	0	11 (5)	0	0
Neuralgia	25 (10)	9 (4)	0	1 (<1)	0	0
General disorders and administration site conditions						
Fatigue	43 (18)	11 (5)	1 (<1)	38 (16)	5 (2)	0
Pyrexia	48 (20)	7 (3)	0	23 (10)	5 (2)	0
Asthenia	29 (12)	4 (2)	1 (<1)	18 (7)	1 (<1)	0
Edema peripheral	16 (7)	1 (<1)	0	13 (5)	0	0
Gastrointestinal disorders						
Nausea	54 (23)	1 (<1)	0	28 (12)	0	0
Constipation	42 (18)	1 (<1)	0	22 (9)	2 (1)	0
Stomatitis	20 (8)	2 (1)	0	19 (8)	0	1 (<1)
Diarrhea	59 (25)	11 (5)	0	11 (5)	3 (1)	1 (<1)
Vomiting	24 (10)	1 (<1)	0	8 (3)	0	0
Abdominal distension	13 (5)	0	0	4 (2)	0	0
Infections and infestations						
Pneumonia	20 (8)	8 (3)	5 (2)	11 (5)	5 (2)	3 (1)
Skin and subcutaneous tissue disorders						
Alopecia	31 (13)	1 (<1)	1 (<1)	33 (14)	4 (2)	0
Metabolism and nutrition disorders						
Hyperglycemia	10 (4)	1 (<1)	0	17 (7)	10 (4)	0
Decreased appetite	36 (15)	2 (1)	0	15 (6)	1 (<1)	0
Vascular disorders						
Hypertension	15 (6)	1 (<1)	0	3 (1)	0	0
Psychiatric disorders						
Insomnia	16 (7)	1 (<1)	0	8 (3)	0	0

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

* Represents High Level Term Peripheral Neuropathies NEC

The incidence of herpes zoster reactivation was 4.6% in the VcR-CAP arm and 0.8% in the R-CHOP arm. Antiviral prophylaxis was mandated by protocol amendment.

The incidences of Grade ≥3 bleeding events were similar between the two arms (four patients in the VcR-CAP arm and three patients in the R-CHOP arm). All of the Grade ≥3 bleeding events resolved without sequelae in the VcR-CAP arm.

Adverse reactions leading to discontinuation occurred in 8% of patients in VcR-CAP group and 6% of patients in R-CHOP group. In the VcR-CAP group, the most commonly reported adverse reaction leading to discontinuation was peripheral sensory neuropathy (1%; three patients). The most commonly reported adverse reaction leading to discontinuation in the R-CHOP group was febrile neutropenia (<1%; two patients).

Integrated Summary of Safety (Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma)
Safety data from Phase 2 and 3 studies of single agent VELCADE 1.3 mg/m^2/dose twice weekly for two weeks followed by a ten day rest period in 1163 patients with previously-treated multiple myeloma (N=1008) and previously-treated mantle cell lymphoma (N=155) were integrated and tabulated. This analysis does not include data from the Phase 3 Open-Label Study of VELCADE subcutaneous vs intravenous in relapsed multiple myeloma. In the integrated studies, the safety profile of VELCADE was similar in patients with multiple myeloma and mantle cell lymphoma.

In the integrated analysis, the most commonly reported (>20%) adverse reactions were nausea (49%), diarrhea (46%), asthenic conditions including fatigue (41%) and weakness (11%), peripheral neuropathies (38%), thrombocytopenia (32%), vomiting (28%), constipation (25%), and pyrexia (21%). Eleven percent (11%) of patients experienced at least one episode of ≥Grade 4 toxicity, most commonly thrombocytopenia (4%) and neutropenia (2%).

In the Phase 2 relapsed multiple myeloma clinical trials of VELCADE administered intravenously, local skin irritation was reported in 5% of patients, but extravasation of VELCADE was not associated with tissue damage.

Serious Adverse Reactions and Adverse Reactions Leading to Treatment Discontinuation in the Integrated Summary of Safety
A total of 26% of patients experienced a serious adverse reaction during the studies. The most commonly reported serious adverse reactions included diarrhea, vomiting and pyrexia (3% each), nausea, dehydration, and thrombocytopenia (2% each) and pneumonia, dyspnea, peripheral neuropathies, and herpes zoster (1% each).

Adverse reactions leading to discontinuation occurred in 22% of patients. The reasons for discontinuation included peripheral neuropathy (8%), and fatigue, thrombocytopenia, and diarrhea (2% each).

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

Most Commonly Reported Adverse Reactions in the Integrated Summary of Safety
The most common adverse reactions are shown in Table 13. All adverse reactions occurring at ≥10% are included. In the absence of a randomized comparator arm, it is often not possible to distinguish between adverse events that are drug-caused and those that reflect the patient's underlying disease. Please see the discussion of specific adverse reactions that follows.

Table 13: Most Commonly Reported (≥10% Overall) Adverse Reactions in Integrated Analyses of Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma Studies using the 1.3 mg/m^2 Dose (N=1163)

	All Patients N=1163		Multiple Myeloma N=1008		Mantle Cell Lymphoma N=155	
Adverse Reactions	All	≥Grade 3	All	≥Grade 3	All	≥Grade 3
Nausea	567 (49)	36 (3)	511 (51)	32 (3)	56 (36)	4 (3)
Diarrhea NOS	530 (46)	83 (7)	470 (47)	72 (7)	60 (39)	11 (7)
Fatigue	477 (41)	86 (7)	396 (39)	71 (7)	81 (52)	15 (10)
Peripheral neuropathies*	443 (38)	129 (11)	359 (36)	110 (11)	84 (54)	19 (12)
Thrombocytopenia	369 (32)	295 (25)	344 (34)	283 (28)	25 (16)	12 (8)
Vomiting NOS	321 (28)	44 (4)	286 (28)	40 (4)	35 (23)	4 (3)
Constipation	296 (25)	17 (1)	244 (24)	14 (1)	52 (34)	3 (2)
Pyrexia	249 (21)	16 (1)	233 (23)	15 (1)	16 (10)	1 (<1)
Anorexia	227 (20)	19 (2)	205 (20)	16 (2)	22 (14)	3 (2)
Anemia NOS	209 (18)	65 (6)	190 (19)	63 (6)	19 (12)	2 (1)
Headache NOS	175 (15)	8 (<1)	160 (16)	8 (<1)	15 (10)	0
Neutropenia	172 (15)	121 (10)	164 (16)	117 (12)	8 (5)	4 (3)
Rash NOS	156 (13)	8 (<1)	120 (12)	4 (<1)	36 (23)	4 (3)
Paresthesia	147 (13)	9 (<1)	136 (13)	8 (<1)	11 (7)	1 (<1)
Dizziness (excl vertigo)	129 (11)	13 (1)	101 (10)	9 (<1)	28 (18)	4 (3)
Weakness	124 (11)	31 (3)	106 (11)	28 (3)	18 (12)	3 (2)

* Represents High Level Term Peripheral Neuropathies NEC

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

Gastrointestinal Toxicity

A total of 75% of patients experienced at least one gastrointestinal disorder. The most common gastrointestinal disorders included nausea, diarrhea, constipation, vomiting, and appetite decreased. Other gastrointestinal disorders included dyspepsia and dysgeusia. Grade 3 adverse reactions occurred in 14% of patients; ≥Grade 4 adverse reactions were ≤1%. Gastrointestinal adverse reactions were considered serious in 7% of patients. Four percent (4%) of patients discontinued due to a gastrointestinal adverse reaction. Nausea was reported more often in patients with multiple myeloma (51%) compared to patients with mantle cell lymphoma (36%).

Thrombocytopenia

Across the studies, VELCADE-associated thrombocytopenia was characterized by a decrease in platelet count during the dosing period (Days 1 to 11) and a return toward baseline during the ten day rest period during each treatment cycle. Overall, thrombocytopenia was reported in 32% of patients. Thrombocytopenia was Grade 3 in 22%, ≥Grade 4 in 4%, and serious in 2% of patients, and the reaction resulted in VELCADE discontinuation in 2% of patients *[see Warnings and Precautions (5.7)]*. Thrombocytopenia was reported more often in patients with multiple myeloma (34%) compared to patients with mantle cell lymphoma (16%). The incidence of ≥Grade 3 thrombocytopenia also was higher in patients with multiple myeloma (28%) compared to patients with mantle cell lymphoma (8%).

Peripheral Neuropathy

Overall, peripheral neuropathies occurred in 38% of patients. Peripheral neuropathy was Grade 3 for 11% of patients and ≥Grade 4 for <1% of patients. Eight percent (8%) of patients discontinued

VELCADE due to peripheral neuropathy. The incidence of peripheral neuropathy was higher among patients with mantle cell lymphoma (54%) compared to patients with multiple myeloma (36%).

In the VELCADE vs dexamethasone Phase 3 relapsed multiple myeloma study, among the 62 VELCADE-treated patients who experienced ≥Grade 2 peripheral neuropathy and had dose adjustments, 48% had improved or resolved with a median of 3.8 months from first onset.

In the Phase 2 relapsed multiple myeloma studies, among the 30 patients who experienced Grade 2 peripheral neuropathy resulting in discontinuation or who experienced ≥Grade 3 peripheral neuropathy, 73% reported improvement or resolution with a median time of 47 days to improvement of one Grade or more from the last dose of VELCADE.

Hypotension
The incidence of hypotension (postural, orthostatic and hypotension NOS) was 8% in patients treated with VELCADE. Hypotension was Grade 1 or 2 in the majority of patients and Grade 3 in 2% and ≥Grade 4 in <1%. Two percent (2%) of patients had hypotension reported as a serious adverse reaction, and 1% discontinued due to hypotension. The incidence of hypotension was similar in patients with multiple myeloma (8%) and those with mantle cell lymphoma (9%). In addition, <1% of patients experienced hypotension associated with a syncopal reaction.

Neutropenia
Neutrophil counts decreased during the VELCADE dosing period (Days 1 to 11) and returned toward baseline during the ten day rest period during each treatment cycle. Overall, neutropenia occurred in 15% of patients and was Grade 3 in 8% of patients and ≥Grade 4 in 2%. Neutropenia was reported as a serious adverse reaction in <1% of patients and <1% of patients discontinued due to neutropenia. The incidence of neutropenia was higher in patients with multiple myeloma (16%) compared to patients with mantle cell lymphoma (5%). The incidence of ≥Grade 3 neutropenia also was higher in patients with multiple myeloma (12%) compared to patients with mantle cell lymphoma (3%).

Asthenic conditions (Fatigue, Malaise, Weakness, Asthenia)
Asthenic conditions were reported in 54% of patients. Fatigue was reported as Grade 3 in 7% and ≥Grade 4 in <1% of patients. Asthenia was reported as Grade 3 in 2% and ≥Grade 4 in < 1% of patients. Two percent (2%) of patients discontinued treatment due to fatigue and < 1% due to weakness and asthenia. Asthenic conditions were reported in 53% of patients with multiple myeloma and 59% of patients with mantle cell lymphoma.

Pyrexia
Pyrexia (> 38ºC) was reported as an adverse reaction for 21% of patients. The reaction was Grade 3 in 1% and ≥Grade 4 in <1%. Pyrexia was reported as a serious adverse reaction in 3% of patients and led to VELCADE discontinuation in <1% of patients. The incidence of pyrexia was higher among patients with multiple myeloma (23%) compared to patients with mantle cell lymphoma (10%). The incidence of ≥Grade 3 pyrexia was 1% in patients with multiple myeloma and <1% in patients with mantle cell lymphoma.

Herpes Virus Infection
Consider using antiviral prophylaxis in subjects being treated with VELCADE. In the randomized studies in previously untreated and relapsed multiple myeloma, herpes zoster reactivation was more common in subjects treated with VELCADE (ranging between 6 to 11%) than in the control groups (3 to 4%). Herpes simplex was seen in 1 to 3% in subjects treated with VELCADE and 1 to 3% in the control groups. In the previously untreated multiple myeloma study, herpes zoster virus reactivation in the VELCADE, melphalan and prednisone arm was less common in subjects receiving prophylactic antiviral therapy (3%) than in subjects who did not receive prophylactic antiviral therapy (17%).

Retreatment in Relapsed Multiple Myeloma

A single-arm trial was conducted in 130 patients with relapsed multiple myeloma to determine the efficacy and safety of retreatment with intravenous VELCADE. The safety profile of patients in this trial is consistent with the known safety profile of VELCADE-treated patients with relapsed multiple myeloma as demonstrated in Tables 10, 11, and 13; no cumulative toxicities were observed upon retreatment. The most common adverse drug reaction was thrombocytopenia which occurred in 52% of the patients. The incidence of ≥Grade 3 thrombocytopenia was 24%. Peripheral neuropathy occurred in 28% of patients, with the incidence of ≥Grade 3 peripheral neuropathy reported at 6%. The incidence of serious adverse reactions was 12.3%. The most commonly reported serious adverse reactions were thrombocytopenia (3.8%), diarrhea (2.3%), and herpes zoster and pneumonia (1.5% each).

Adverse reactions leading to discontinuation occurred in 13% of patients. The reasons for discontinuation included peripheral neuropathy (5%) and diarrhea (3%).

Two deaths considered to be VELCADE-related occurred within 30 days of the last VELCADE dose; one in a patient with cerebrovascular accident and one in a patient with sepsis.

Additional Adverse Reactions from Clinical Studies

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

Blood and Lymphatic System Disorders: Anemia, disseminated intravascular coagulation, febrile neutropenia, lymphopenia, leukopenia

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

Ear and Labyrinth Disorders: Hearing impaired, vertigo

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

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

General Disorders and Administration Site Conditions: Chills, edema, edema peripheral, injection site erythema, neuralgia, injection site pain, irritation, malaise, phlebitis

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

Immune System Disorders: Anaphylactic reaction, drug hypersensitivity, immune complex mediated hypersensitivity, angioedema, laryngeal edema

Infections and Infestations: Aspergillosis, bacteremia, bronchitis, urinary tract infection, herpes viral infection, listeriosis, nasopharyngitis, pneumonia, respiratory tract infection, septic shock, toxoplasmosis, oral candidiasis, sinusitis, catheter related infection

Injury, Poisoning and Procedural Complications: Catheter related complication, skeletal fracture, subdural hematoma

Investigations: Weight decreased

Metabolism and Nutrition Disorders: Dehydration, hypocalcemia, hyperuricemia, hypokalemia, hyperkalemia, hyponatremia, hypernatremia

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, bone pain, myalgia, pain in extremity

Nervous System Disorders: Ataxia, coma, dizziness, dysarthria, dysesthesia, dysautonomia, encephalopathy, cranial palsy, grand mal convulsion, headache, hemorrhagic stroke, motor dysfunction, neuralgia, spinal cord compression, paralysis, postherpetic neuralgia, transient ischemic attack

Psychiatric Disorders: Agitation, anxiety, confusion, insomnia, mental status change, psychotic disorder, suicidal ideation

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

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

Skin and Subcutaneous Tissue disorders: Urticaria, face edema, rash (which may be pruritic), leukocytoclastic vasculitis, pruritus.

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

6.2 Postmarketing Experience

The following adverse reactions have been identified from the worldwide postmarketing experience with VELCADE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Cardiac Disorders: Cardiac tamponade

Ear and Labyrinth Disorders: Deafness bilateral

Eye Disorders: Optic neuropathy, blindness, chalazion/blepharitis

Gastrointestinal Disorders: Ischemic colitis

Infections and Infestations: Progressive multifocal leukoencephalopathy (PML), ophthalmic herpes, herpes meningoencephalitis

Nervous System Disorders: Posterior reversible encephalopathy syndrome (PRES, formerly RPLS)

Respiratory, Thoracic and Mediastinal Disorders: Acute diffuse infiltrative pulmonary disease

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute febrile neutrophilic dermatosis (Sweet’s syndrome)

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on VELCADE

Strong CYP3A4 Inducers

Coadministration with a strong CYP3A4 inducer decreases the exposure of bortezomib *[see Clinical Pharmacology (12.3)]* which may decrease VELCADE efficacy. Avoid coadministration with strong CYP3A4 inducers.

Strong CYP3A4 Inhibitors

Coadministration with a strong CYP3A4 inhibitor increases the exposure of bortezomib *[see Clinical Pharmacology (12.3)]* which may increase the risk of VELCADE toxicities. Monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors.

7.2 Drugs Without Clinically Significant Interactions with VELCADE

No clinically significant drug interactions have been observed when VELCADE was coadministered with dexamethasone, omeprazole, or melphalan in combination with prednisone *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1)]* and findings in animals, VELCADE can cause fetal harm when administered to a pregnant woman. There are no studies with the use of VELCADE in pregnant women to inform drug-associated risks. Bortezomib caused embryo-fetal lethality in rabbits at doses lower than the clinical dose *(see Data)*. Advise pregnant women of the potential risk to the fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

There are no data on the presence of bortezomib or its metabolites in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in a breastfed child from VELCADE is unknown, advise nursing women not to breastfeed during treatment with VELCADE and for two months after treatment.

8.3 Females and Males of Reproductive Potential

Based on its mechanism of action and findings in animals, VELCADE can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].*

Pregnancy Testing

Conduct pregnancy testing in females of reproductive potential prior to initiating VELCADE treatment.

Contraception

Females

Advise females of reproductive potential to avoid pregnancy and use effective contraception during treatment with VELCADE and for at least seven months after the last dose.

Males

Males with female sexual partners of reproductive potential should use effective contraception during treatment with VELCADE and for at least four months after the last dose.

Infertility

Based on the mechanism of action and findings in animals, VELCADE may have an effect on either male or female fertility *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

The activity and safety of VELCADE in combination with intensive reinduction chemotherapy was evaluated in pediatric and young adult patients with lymphoid malignancies (pre-B cell ALL 77%, 16% with T-cell ALL, and 7% T-cell lymphoblastic lymphoma (LL)), all of whom relapsed within 36 months of initial diagnosis in a single-arm multicenter, non-randomized cooperative group trial. An effective reinduction multiagent chemotherapy regimen was administered in three blocks. Block 1 included vincristine, prednisone, doxorubicin and pegaspargase; Block 2 included cyclophosphamide, etoposide and methotrexate; Block 3 included high dose cytosine arabinoside and asparaginase. VELCADE was administered at a dose of 1.3 mg/m^2 as a bolus intravenous injection on Days 1, 4, 8, and 11 of Block 1 and Days 1, 4, and 8 of Block 2. There were 140 patients with ALL or LL enrolled and evaluated for safety. The median age was ten years (range 1 to 26), 57% were male, 70% were white, 14% were black, 4% were Asian, 2% were American Indian/ Alaska Native, 1% were Pacific Islander.

The activity was evaluated in a pre-specified subset of the first 60 evaluable patients enrolled on the study with pre-B ALL ≤21 years and relapsed <36 months from diagnosis. The complete remission (CR) rate at day 36 was compared to that in a historical control set of patients who had received the identical backbone therapy without VELCADE. There was no evidence that the addition of VELCADE had any impact on the CR rate.

No new safety concerns were observed when VELCADE was added to a chemotherapy backbone regimen as compared with a historical control group in which the backbone regimen was given without VELCADE.

The BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

8.5 Geriatric Use

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

patients ≤50, 51 to 64 and ≥65 years old, respectively *[see Adverse Reactions (6.1); Clinical Studies (14.1)]*.

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

8.6 Renal Impairment

No starting dosage adjustment of VELCADE is recommended for patients with renal impairment. In patients requiring dialysis, VELCADE should be administered after the dialysis procedure *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No starting dosage adjustment of VELCADE is recommended for patients with mild hepatic impairment (total bilirubin ≤1x ULN and AST > ULN, or total bilirubin >1 to 1.5x ULN and any AST). The exposure of bortezomib is increased in patients with moderate (total bilirubin ≥1.5 to 3x ULN and any AST) and severe (total bilirubin >3x ULN and any AST) hepatic impairment. Reduce the starting dose in patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.8), Clinical Pharmacology (12.3)]*.

8.8 Patients with Diabetes

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

10 OVERDOSAGE

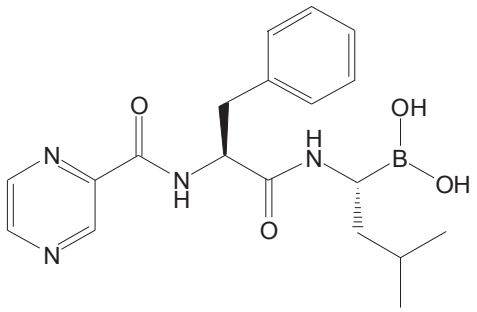
There is no known specific antidote for VELCADE overdosage. In humans, fatal outcomes following the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension (5.2) and thrombocytopenia (5.7). In the event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

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

11 DESCRIPTION

VELCADE® for Injection contains bortezomib which is an antineoplastic agent. Bortezomib is a modified dipeptidyl boronic acid. The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid.

Bortezomib has the following chemical structure:



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

VELCADE is available for intravenous injection or subcutaneous use. Each single-dose vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. It also contains the inactive ingredient: 35 mg mannitol, USP. The product is provided as a mannitol boronic ester which, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its cyclic anhydride form as a trimeric boroxine.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro*. Bortezomib causes a delay in tumor growth *in vivo* in nonclinical tumor models, including multiple myeloma.

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Following intravenous administration of 1 mg/m^2 and 1.3 mg/m^2 doses, the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. When administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose.

Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m^2 dose to patients with multiple myeloma, the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administration. The AUC_{last} geometric mean ratio (90% confidence interval) was 0.99 (0.80 – 1.23). The C_{max} after subcutaneous administration (20.4 ng/mL) was lower than after intravenous administration (223 ng/mL) with repeat dose administration.

Distribution

The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m^2 following single- or repeat-dose administration of 1 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma. The

binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.

Elimination
The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours after the 1 mg/m^2 dose and 76 to 108 hours after the 1.3 mg/m^2 dose. The mean total body clearances were 102 and 112 L/h following the first dose for doses of 1 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1 and 1.3 mg/m^2, respectively.

Metabolism
Bortezomib is primarily oxidatively metabolized to several inactive metabolites in vitro via cytochrome P450 (CYP) enzymes 3A4, CYP2C19, and CYP1A2, and to a lesser extent by CYP2D6 and CYP2C9.

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

Specific Populations
No clinically significant differences in the pharmacokinetics of bortezomib were observed based on age, sex, or renal impairment (including patients administered VELCADE after dialysis). The effect of race on bortezomib pharmacokinetics is unknown.

Patients with Hepatic Impairment
Following administration of bortezomib doses ranging from 0.5 to 1.3 mg/m^2, mild (total bilirubin ≤1x ULN and AST > ULN, or total bilirubin >1 to 1.5x ULN and any AST) hepatic impairment did not alter dose-normalized bortezomib AUC when compared to patients with normal hepatic function. Dose normalized mean bortezomib AUC increased by approximately 60% in patients with moderate (total bilirubin >1.5 to 3x ULN and any AST) or severe (total bilirubin >3x ULN and any AST) hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment.

Drug Interaction Studies
Clinical Studies
No clinically significant differences in bortezomib pharmacokinetics were observed when coadministered with dexamethasone (weak CYP3A4 inducer), omeprazole (strong CYP2C19 inhibitor), or melphalan in combination with prednisone.

Strong CYP3A4 inhibitor
Coadministration with ketoconazole (strong CYP3A4 inhibitor) increased bortezomib exposure by 35%.

Strong CYP3A4 inducer
Coadministration with rifampin (strong CYP3A4 inducer) decreased bortezomib exposure by approximately 45%.

In Vitro Studies
Bortezomib may inhibit CYP2C19 activity and increase exposure to drugs that are substrates for this enzyme.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been conducted with bortezomib.

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

Fertility studies with bortezomib were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the six 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.

13.2 Animal Toxicology and/or Pharmacology

Cardiovascular Toxicity

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

Chronic Administration

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

14 CLINICAL STUDIES

14.1 Multiple Myeloma

Randomized, Open-Label Clinical Study in Patients with Previously Untreated Multiple Myeloma

A prospective, international, randomized (1:1), open-label clinical study (NCT00111319) of 682 patients was conducted to determine whether VELCADE administered intravenously (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in patients with previously untreated multiple myeloma. Treatment was administered for a maximum of nine cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Antiviral prophylaxis was recommended for patients on the VELCADE study arm.

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

Efficacy results for the trial are presented in Table 14. At a prespecified interim analysis (with median follow-up of 16.3 months), the combination of VELCADE, melphalan and prednisone therapy resulted in significantly superior results for time to progression, progression-free survival, overall survival and response rate. Further enrollment was halted, and patients receiving melphalan and prednisone were offered VELCADE in addition. A later, prespecified analysis of overall survival (with median follow-up of 36.7 months with a hazard ratio of 0.65, 95% CI: 0.51, 0.84) resulted in a statistically significant survival benefit for the VELCADE, melphalan and prednisone treatment arm despite subsequent therapies including VELCADE based regimens. In an updated analysis of overall survival based on 387 deaths (median follow-up 60.1 months), the median overall survival for the VELCADE, melphalan and prednisone treatment arm was 56.4 months and for the melphalan and prednisone treatment arm was 43.1 months, with a hazard ratio of 0.695 (95% CI: 0.57, 0.85).

Table 14: Summary of Efficacy Analyses in the Previously Untreated Multiple Myeloma Study		
Efficacy Endpoint	**VELCADE, Melphalan and Prednisone n=344**	**Melphalan and Prednisone n=338**
Time to Progression		
Events n (%)	101 (29)	152 (45)
Median* (months) (95% CI)	20.7 (17.6, 24.7)	15.0 (14.1, 17.9)
Hazard ratio† (95% CI)	0.54 (0.42, 0.70)	
p-value‡	0.000002	
Progression-free Survival		
Events n (%)	135 (39)	190 (56)
Median* (months) (95% CI)	18.3 (16.6, 21.7)	14.0 (11.1, 15.0)
Hazard ratio† (95% CI)	0.61 (0.49, 0.76)	
p-value ‡	0.00001	
Response Rate		
CR§ n (%)	102 (30)	12 (4)
PR§ n (%)	136 (40)	103 (30)
nCR n (%)	5 (1)	0
CR + PR§ n (%)	238 (69)	115 (34)
p-value¶	$<10^{-10}$	
Overall Survival at median follow up of 36.7 months		
Events (deaths) n (%)	109 (32)	148 (44)
Median* (months) (95% CI)	Not Reached (46.2, NR)	43.1 (34.8, NR)
Hazard ratio† (95% CI)	0.65 (0.51, 0.84)	
p-value‡	0.00084	

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

* Kaplan-Meier estimate

† Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors: $beta_2$-microglobulin, albumin, and region. A hazard ratio less than one indicates an advantage for VELCADE, melphalan and prednisone

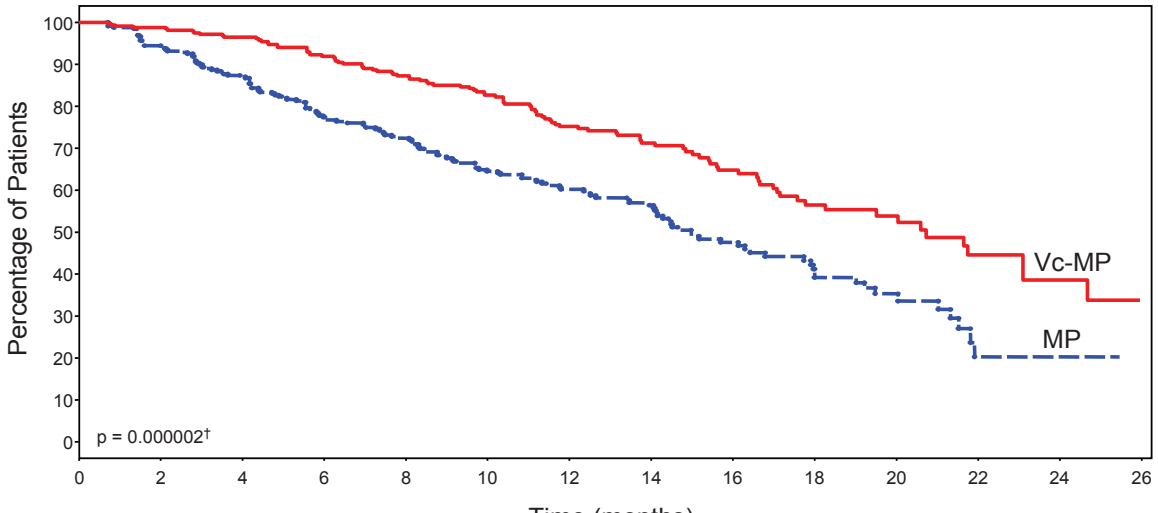
‡ p-value based on the stratified log-rank test adjusted for stratification factors: $beta_2$-microglobulin, albumin, and region

§ EBMT criteria

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

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

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



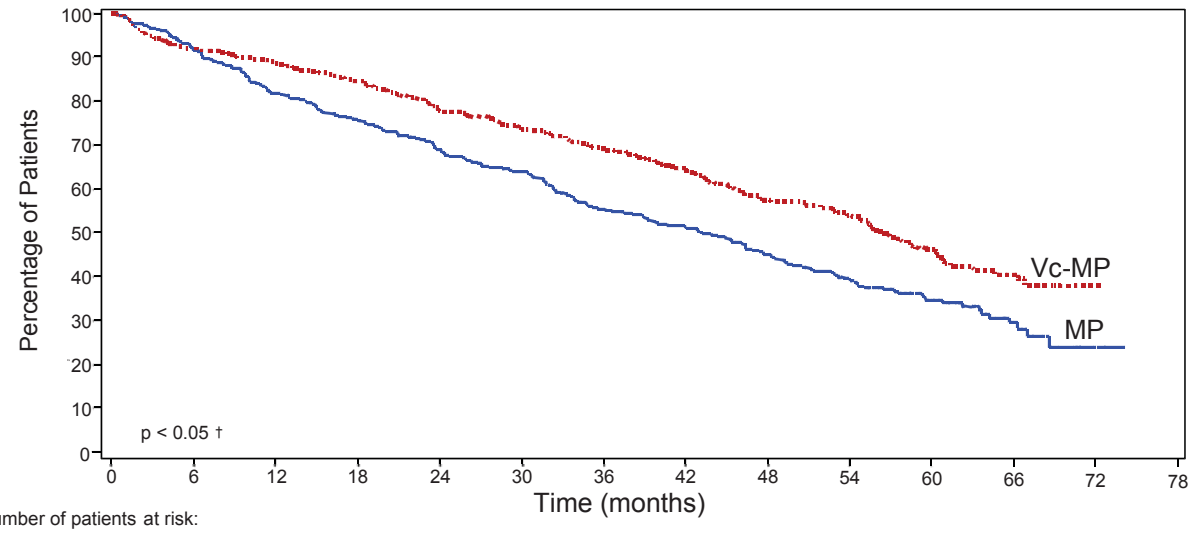
Number of patients at risk:

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

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

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

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



Number of patients at risk:

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

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

<u>Randomized, Clinical Study in Relapsed Multiple Myeloma of VELCADE vs Dexamethasone</u>
A prospective Phase 3, international, randomized (1:1), stratified, open-label clinical study (NCT00048230) 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 (one previous line vs more than one line of therapy), time of progression relative to prior treatment (progression during or within six months of stopping their most recent therapy vs relapse >6 months after receiving their most recent therapy), and screening beta$_2$-microglobulin levels (≤2.5 mg/L vs >2.5 mg/L).

Baseline patient and disease characteristics are summarized in Table 15.

Table 15: Summary of Baseline Patient and Disease Characteristics in the Relapsed Multiple Myeloma Study

Patient Characteristics	**VELCADE N=333**	**Dexamethasone N=336**
Median age in years (range)	62.0 (33, 84)	61.0 (27, 86)
Gender: Male/female	56%/44%	60%/40%
Race: Caucasian/black/other	90%/6%/4%	88%/7%/5%
Karnofsky performance status score ≤70	13%	17%
Hemoglobin <100 g/L	32%	28%
Platelet count <75 x 10^9/L	6%	4%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	60%/23%/12%	59%/24%/13%
Median beta$_2$-microglobulin (mg/L)	3.7	3.6
Median albumin (g/L)	39.0	39.0
Creatinine clearance ≤30 mL/min [n (%)]	17 (5%)	11 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	3.5	3.1
Number of Prior Therapeutic Lines of Treatment		
Median	2	2
1 prior line	40%	35%
>1 prior line	60%	65%
Previous Therapy		
Any prior steroids, e.g., dexamethasone, VAD	98%	99%
Any prior anthracyclines, e.g., VAD, mitoxantrone	77%	76%
Any prior alkylating agents, e.g., MP, VBMCP	91%	92%
Any prior thalidomide therapy	48%	50%
Vinca alkaloids	74%	72%
Prior stem cell transplant/other high-dose therapy	67%	68%
Prior experimental or other types of therapy	3%	2%

Patients in the VELCADE treatment group were to receive 8, three week treatment cycles followed by 3, five week treatment cycles of VELCADE. Patients achieving a CR were treated for four cycles beyond first evidence of CR. Within each three week treatment cycle, VELCADE 1.3 mg/m^2/dose alone was administered by intravenous bolus twice weekly for two weeks on Days 1, 4, 8, and 11 followed by a ten day rest period (Days 12 to 21). Within each five week treatment cycle, VELCADE 1.3 mg/m^2/dose alone was administered by intravenous bolus once weekly for four weeks on Days 1, 8, 15, and 22 followed by a 13 day rest period (Days 23 to 35) *[see Dosage and Administration (2.2)]*.

Patients in the dexamethasone treatment group were to receive 4 five week treatment cycles followed by 5, four week treatment cycles. Within each five week treatment cycle, dexamethasone 40 mg/day

PO was administered once daily on Days 1 to 4, 9 to 12, and 17 to 20 followed by a 15 day rest period (Days 21 to 35). Within each four week treatment cycle, dexamethasone 40 mg/day PO was administered once daily on Days 1 to 4 followed by a 24 day rest period (Days 5 to 28). Patients with documented progressive disease on dexamethasone were offered VELCADE at a standard dose and schedule on a companion study. Following a preplanned interim analysis of time to progression, the dexamethasone arm was halted and all patients randomized to dexamethasone were offered VELCADE, regardless of disease status.

In the VELCADE arm, 34% of patients received at least one VELCADE dose in all eight of the three 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 four of the five week treatment cycles of therapy, and 6% received at least one dose in all nine cycles.

The time to event analyses and response rates from the relapsed multiple myeloma study are presented in Table 16. Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria. Complete response (CR) required <5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF^-). Partial response (PR) requires ≥50% reduction in serum myeloma protein and ≥90% reduction of urine myeloma protein on at least two occasions for a minimum of at least six weeks along with stable bone disease and normal calcium. Near complete response (nCR) was defined as meeting all the criteria for complete response including 100% reduction in M-protein by protein electrophoresis; however, M-protein was still detectable by immunofixation (IF^+).

Table 16: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study						
Efficacy Endpoint	**All Patients**		**1 Prior Line of Therapy**		**>1 Prior Line of Therapy**	
	VELCADE	**Dex**	**VELCADE**	**Dex**	**VELCADE**	**Dex**
	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* (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7.0 mo (6.2, 8.8)	5.6 mo (3.4, 6.3)	4.9 mo (4.2, 6.3)	2.9 mo (2.8, 3.5)
Hazard ratio† (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.72)	
p-value‡	<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† (95% CI)	0.57 (0.40, 0.81)		0.39 (0.19, 0.81)		0.65 (0.43, 0.97)	
p-value‡, §	<0.05		<0.05		<0.05	
Response Rate Population¶ n=627	n=315	n=312	n=128	n=110	n=187	n=202
CR# n (%)	20 (6)	2 (<1)	8 (6)	2 (2)	12 (6)	0 (0)
PR# n(%)	101 (32)	54 (17)	49 (38)	27 (25)	52 (28)	27 (13)
nCR#, ♠ n(%)	21 (7)	3 (<1)	8 (6)	2 (2)	13 (7)	1 (<1)
CR + PR# n (%)	121 (38)	56 (18)	57 (45)	29 (26)	64 (34)	27 (13)
p-value ♥	<0.0001		0.0035		<0.0001	

* Kaplan-Meier estimate

† Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than one indicates an advantage for VELCADE

‡ p-value based on the stratified log-rank test including randomization stratification factors

§ Precise p-value cannot be rendered

¶ Response population includes patients who had measurable disease at baseline and received at least one dose of study drug

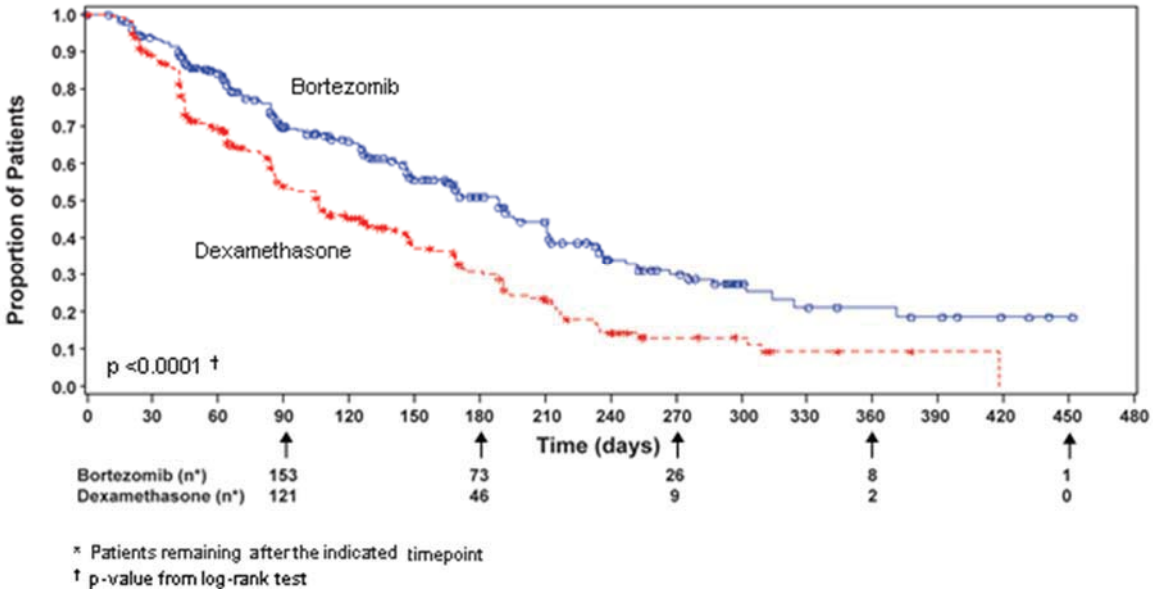
EBMT criteria; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria nCR is in the PR category

♠ In two patients, the IF was unknown

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

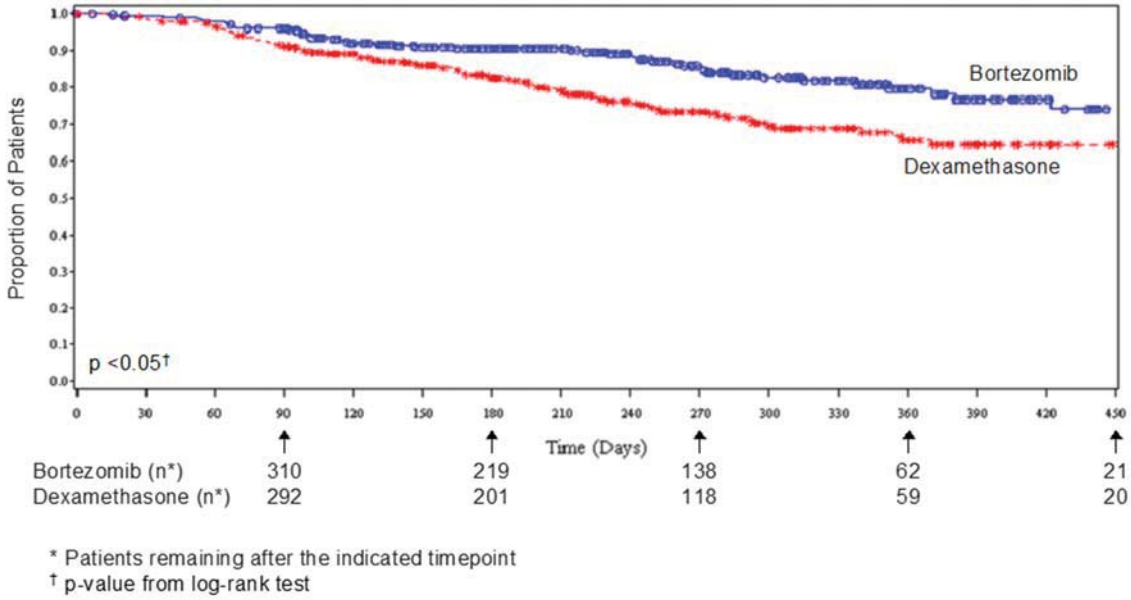
TTP was statistically significantly longer on the VELCADE arm (*see Figure 3*).

Figure 3: Time to Progression Bortezomib vs Dexamethasone (Relapsed Multiple Myeloma Study)



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

Figure 4: Overall Survival Bortezomib vs Dexamethasone (Relapsed Multiple Myeloma Study)



For the 121 patients achieving a response (CR or PR) on the VELCADE arm, the median duration was 8.0 months (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI: 4.8, 9.2 months) for the 56 responders on the dexamethasone arm. The response rate was significantly higher on the VELCADE arm regardless of beta$_2$-microglobulin levels at baseline.

<u>Randomized, Open-Label Clinical Study of VELCADE Subcutaneous vs Intravenous in Relapsed Multiple Myeloma</u>

An open-label, randomized, Phase 3 noninferiority study (NCT00722566) compared the efficacy and safety of the subcutaneous administration of VELCADE versus the intravenous administration. This

study included 222 bortezomib naïve patients with relapsed multiple myeloma, who were randomized in a 2:1 ratio to receive 1.3 mg/m^2 of VELCADE by either the subcutaneous (n=148) or intravenous (n=74) route for eight cycles. Patients who did not obtain an optimal response (less than Complete Response (CR)) to therapy with VELCADE alone after four cycles were allowed to receive oral dexamethasone 20 mg daily on the day of and after VELCADE administration (82 patients in subcutaneous treatment group and 39 patients in the intravenous treatment group). Patients with baseline Grade ≥2 peripheral neuropathy or neuropathic pain, or platelet counts <50,000/μL were excluded. A total of 218 patients were evaluable for response.

Stratification factors were based on the number of lines of prior therapy the patient had received (one previous line vs more than one line of therapy), and international staging system (ISS) stage (incorporating $beta_2$-microglobulin and albumin levels; Stages I, II, or III).

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

This study met its primary (noninferiority) objective that single agent subcutaneous VELCADE retains at least 60% of the overall response rate after four cycles relative to single agent intravenous VELCADE. The results are provided in Table 17.

Table 17: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study of VELCADE Subcutaneous vs Intravenous

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

* Median duration of follow up is 11.8 months

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

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

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

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

A Single-Arm Trial of Retreatment in Relapsed Multiple Myeloma

A single arm, open-label trial (NCT00431769) was conducted to determine the efficacy and safety of retreatment with VELCADE. One hundred and thirty patients (≥18 years of age) with multiple myeloma who previously had at least partial response on a VELCADE-containing regimen (median of two prior lines of therapy [range 1 to 7]) were retreated upon progression with VELCADE administered intravenously. Patients were excluded from trial participation if they had peripheral neuropathy or neuropathic pain of Grade ≥2. At least six months after prior VELCADE therapy, VELCADE was restarted at the last tolerated dose of 1.3 mg/m^2 (n=93) or ≤1 mg/m^2 (n=37) and given on Days 1, 4, 8 and 11 every three weeks for maximum of eight cycles either as single agent or in combination with dexamethasone in accordance with the standard of care. Dexamethasone was administered in combination with VELCADE to 83 patients in Cycle 1 with an additional 11 patients receiving dexamethasone during the course of VELCADE retreatment cycles.

The primary endpoint was best confirmed response to retreatment as assessed by European Group for Blood and Marrow Transplantation (EBMT) criteria. Fifty of the 130 patients achieved a best confirmed response of Partial Response or better for an overall response rate of 38.5% (95% CI: 30.1, 47.4). One patient achieved a Complete Response and 49 achieved Partial Response. In the 50 responding patients, the median duration of response was 6.5 months and the range was 0.6 to 19.3 months.

14.2 Mantle Cell Lymphoma

A Randomized, Open-Label Clinical Study in Patients with Previously Untreated Mantle Cell Lymphoma

A randomized, open-label, Phase 3 study (NCT00722137) was conducted in 487 adult patients with previously untreated mantle cell lymphoma (Stage II, III or IV) who were ineligible or not considered for bone marrow transplantation to determine whether VELCADE administered in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP) resulted in improvement in progression free survival (PFS) when compared to the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). This clinical study utilized independent pathology confirmation and independent radiologic response assessment.

Patients in the VcR-CAP treatment arm received VELCADE (1.3 mg/m^2) administered intravenously on Days 1, 4, 8, and 11 (rest period days 12 to 21); rituximab (375 mg/m^2) on Day 1;

cyclophosphamide (750 mg/m^2) on Day 1; doxorubicin (50 mg/m^2) on Day 1; and prednisone (100 mg/m^2) on Day 1 through Day 5 of the 21 day treatment cycle. For patients with a response first documented at Cycle six, two additional treatment cycles were allowed.

Median patient age was 66 years, 74% were male, 66% were Caucasian and 32% were Asian. Sixty nine percent of patients had a positive bone marrow aspirate and/or a positive bone marrow biopsy for MCL, 54% of patients had an International Prognostic Index (IPI) score of three (high-intermediate) or higher and 76% had Stage IV disease.

The majority of the patients in both groups received six or more cycles of treatment, 84% in the VcR-CAP group and 83% in the R-CHOP group. Median number of cycles received by patients in both treatment arms was six with 17% of patients in the R-CHOP group and 14% of subjects in the VcR-CAP group receiving up to two additional cycles.

The efficacy results for PFS, CR and ORR with a median follow-up of 40 months are presented in Table 18. The response criteria used to assess efficacy were based on the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC). Final overall survival results at a median follow up of 78.5 months are also presented in Table 18 and Figure 6. The combination of VcR-CAP resulted in statistically significant prolongation of PFS compared with R-CHOP (*see Table 18, Figure 5*).

Table 18: Summary of Efficacy Analyses in the Previously Untreated Mantle Cell Lymphoma Study		
Efficacy Endpoint **n: Intent to Treat patients**	**VcR-CAP** **n=243**	**R-CHOP** **n=244**
Progression-free Survival (by independent radiographic assessment)		
Events n (%)	133 (55)	165 (68)
Median* (months) (95% CI)	25 (20, 32)	14 (12, 17)
Hazard ratio† (95% CI)	0.63 (0.50, 0.79)	
p-value‡	<0.001	
Complete Response Rate (CR)§		
n (%) (95% CI)	108 (44) (38, 51)	82 (34) (28, 40)
Overall Response Rate (CR+CRu+PR)¶		
n (%)	214 (88)	208 (85)
(95% CI)	(83, 92)	(80, 89)
Overall Survival		
Events n(%)	103 (42)	138 (57)
Median* (months) (95% CI)	91 (71, NE)	56 (47, 69)
Hazard Ratio† (95% CI)	0.66 (0.51, 0.85)	

Note: All results are based on the analysis performed at a median follow-up duration of 40 months except for the overall survival analysis, which was performed at a median follow-up of 78.5 months.

* Based on Kaplan-Meier product limit estimates.

† Hazard ratio estimate is based on a Cox's model stratified by IPI risk and stage of disease. A hazard ratio <1 indicates an advantage for VcR-CAP.

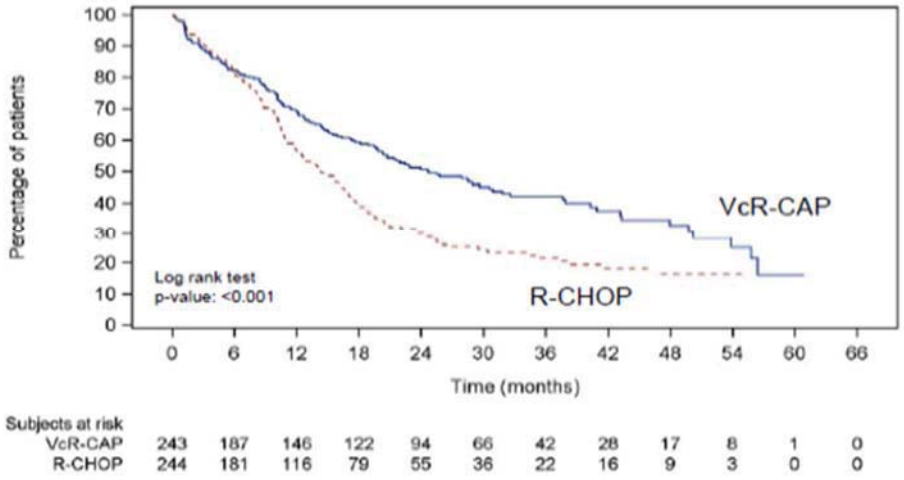
‡ Based on Log rank test stratified with IPI risk and stage of disease.

§ Includes CR by independent radiographic assessment, bone marrow, and LDH using ITT population.

¶ Includes CR+ CRu+PR by independent radiographic assessment, regardless of the verification by bone marrow and LDH, using ITT population.

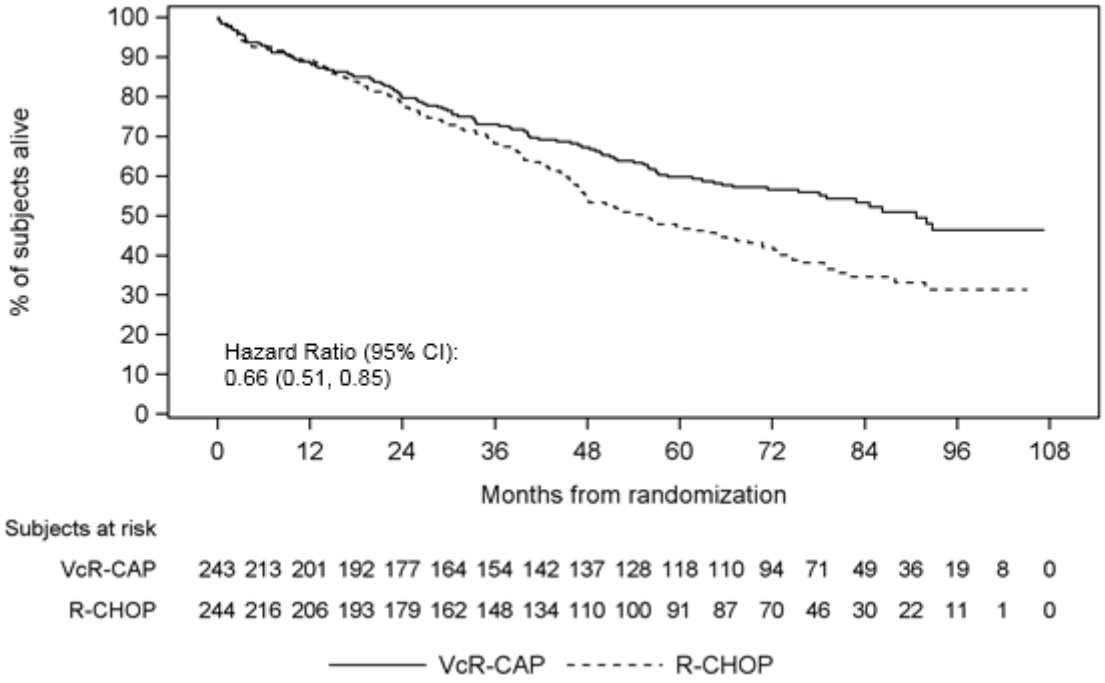
CI=Confidence Interval; IPI=International Prognostic Index; LDH=Lactate dehydrogenase

Figure 5: Progression Free Survival VcR-CAP vs R-CHOP (previously Untreated Mantle Cell Lymphoma Study)



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

Figure 6: Overall Survival VcR-CAP vs R-CHOP (previously Untreated Mantle Cell Lymphoma Study)



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

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

The safety and efficacy of VELCADE in relapsed or refractory mantle cell lymphoma were evaluated in an open-label, single-arm, multicenter study (NCT00063713) of 155 patients with progressive disease who had received at least one prior therapy. The median age of the patients was 65 years (42, 89), 81% were male, and 92% were Caucasian. Of the total, 75% had one or more extra-nodal sites of disease, and 77% were Stage 4. In 91% of the patients, prior therapy included all of the following: an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. A total of thirty seven

percent (37%) of patients were refractory to their last prior therapy. An intravenous bolus injection of VELCADE 1.3 mg/m^2/dose was administered twice weekly for two weeks on Days 1, 4, 8, and 11 followed by a ten day rest period (Days 12 to 21) for a maximum of 17 treatment cycles. Patients achieving a CR or CRu were treated for four cycles beyond first evidence of CR or CRu. The study employed dose modifications for toxicity *[see Dosage and Administration (2.6, 2.7)]*.

Responses to VELCADE are shown in Table 19. Response rates to VELCADE were determined according to the International Workshop Response Criteria (IWRC) based on independent radiologic review of CT scans. The median number of cycles administered across all patients was four; in responding patients the median number of cycles was eight. The median time to response was 40 days (range 31 to 204 days). The median duration of follow-up was more than 13 months.

Table 19: Response Outcomes in a Phase 2 Relapsed Mantle Cell Lymphoma Study		
Response Analyses (N=155)	**N (%)**	**95% CI**
Overall Response Rate (IWRC) (CR + CRu + PR)	48 (31)	(24, 39)
Complete Response (CR + CRu)	12 (8)	(4, 13)
CR	10 (6)	(3, 12)
CRu	2 (1)	(0, 5)
Partial Response (PR)	36 (23)	(17, 31)
Duration of Response	**Median**	**95% CI**
CR + CRu + PR (N=48)	9.3 months	(5.4, 13.8)
CR + CRu (N=12)	15.4 months	(13.4, 15.4)
PR (N=36)	6.1 months	(4.2, 9.3)

15 REFERENCES

1. “OSHA Hazardous Drugs” (refer to antineoplastic weblinks including OSHA Technical Manual). *OSHA.* http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

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

NDC 63020-049-01
3.5 mg single-dose vial

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

Follow guidelines for handling and disposal for cytotoxic drugs, including the use of gloves and other protective clothing to prevent skin contact[1].

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients prior to treatment with VELCADE:

Peripheral Neuropathy
Advise patients to report the development or worsening of sensory and motor peripheral neuropathy to their healthcare provider *[see Warnings and Precautions (5.1)].*

Hypotension
Advise patients to drink adequate fluids to avoid dehydration and to report symptoms of hypotension to their healthcare provider *[see Warnings and Precautions (5.2)].*

Instruct patients to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells, or muscle cramps.

Cardiac Toxicity
Advise patients to report signs or symptoms of heart failure to their healthcare provider *[see Warnings and Precautions (5.3)]*.

Pulmonary Toxicity
Advise patients to report symptoms of ARDS, pulmonary hypertension, pneumonitis, and pneumonia immediately to their healthcare provider *[see Warnings and Precautions (5.4)]*.

Posterior Reversible Encephalopathy Syndrome (PRES)
Advise patients to seek immediate medical attention for signs or symptoms of PRES *[see Warnings and Precautions (5.5)].*

Gastrointestinal Toxicity
Advise patients to report symptoms of gastrointestinal toxicity to their healthcare provider and to drink adequate fluids to avoid dehydration. Instruct patients to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells, or muscle cramps *[see Warnings and Precautions (5.6)].*

Thrombocytopenia/Neutropenia
Advise patients to report signs or symptoms of bleeding or infection immediately to their healthcare provider *[see Warnings and Precautions (5.7)]*.

Tumor Lysis Syndrome
Advise patients of the risk of tumor lysis syndrome and to drink adequate fluids to avoid dehydration *[see Warnings and Precautions (5.8)].*

Hepatic Toxicity
Advise patients to report signs or symptoms of hepatic toxicity to their healthcare provider *[see Warnings and Precautions (5.9)].*

Thrombotic Microangiopathy
Advise patients to seek immediate medical attention if any signs or symptoms of thrombotic microangiopathy occur *[see Warnings and Precautions (5.10)].*

Ability to Drive or Operate Machinery or Impairment of Mental Ability
VELCADE may cause fatigue, dizziness, syncope, orthostatic/postural hypotension. Advise patients not to drive or operate machinery if they experience any of these symptoms *[see Warnings and Precautions (5.2, 5.5)]*.

Embryo-fetal Toxicity
Advise females of the potential risk to the fetus and to avoid pregnancy and use effective contraception during treatment with VELCADE and for seven months following the final dose. Advise male patients with female sexual partners of reproductive potential to use effective contraception during treatment with VELCADE and for four months following the last dose. Instruct patients to report pregnancy to their physicians immediately if they or their female partner becomes pregnant during treatment or within seven months following last dose *[see Warnings and Precautions (5.11)]*.

Lactation
Advise patients to avoid breastfeeding while receiving VELCADE and for two months after last dose *[see Use in Specific Populations (8.2)]*.

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

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

Dermal
Advise patients to contact their physicians if they experience rash, severe injection site reactions *[see Dosage and Administration (2.9)]*, or skin pain. Discuss with patients the option for antiviral prophylaxis for herpes virus infection *[see Clinical Trials Safety Experience (6.1)]*.

Other
Instruct patients to contact their physicians if they develop an increase in blood pressure, bleeding, fever, constipation, or decreased appetite.

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Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

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VEL347 R20

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VELCADE 1 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 mg bortezomib (as a mannitol boronic ester).

After reconstitution, 1 ml of solution for intravenous injection contains 1 mg bortezomib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White to off-white cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VELCADE as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation.

VELCADE in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

VELCADE in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

VELCADE in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

4.2 Posology and method of administration

VELCADE treatment must be initiated under supervision of a physician experienced in the treatment of cancer patients, however VELCADE may be administered by a healthcare professional experienced in use of chemotherapeutic agents. VELCADE must be reconstituted by a healthcare professional (see section 6.6).

Posology for treatment of progressive multiple myeloma (patients who have received at least one prior therapy)

Monotherapy

VELCADE 1 mg powder for solution for injection is administered via intravenous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. It is recommended that patients receive 2 cycles of VELCADE following a confirmation of a complete response. It is also recommended that responding patients who do not achieve a complete remission receive a total of

8 cycles of VELCADE therapy. At least 72 hours should elapse between consecutive doses of VELCADE.

Dose adjustments during treatment and re-initiation of treatment for monotherapy
VELCADE treatment must be withheld at the onset of any Grade 3 non-haematological or any Grade 4 haematological toxicities, excluding neuropathy as discussed below (see also section 4.4). Once the symptoms of the toxicity have resolved, VELCADE treatment may be re-initiated at a 25% reduced dose (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of VELCADE must be considered unless the benefit of treatment clearly outweighs the risk.

Neuropathic pain and/or peripheral neuropathy
Patients who experience bortezomib-related neuropathic pain and/or peripheral neuropathy are to be managed as presented in Table 1 (see section 4.4). Patients with pre-existing severe neuropathy may be treated with VELCADE only after careful risk/benefit assessment.

Table 1: Recommended posology modifications for bortezomib-related neuropathy*

Severity of neuropathy	**Posology modification**
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or loss of function	None
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)**)	Reduce VELCADE to 1.0 mg/m^2 or Change VELCADE treatment schedule to 1.3 mg/m^2 once per week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL***)	Withhold VELCADE treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate VELCADE treatment and reduce dose to 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy	Discontinue VELCADE

* Based on posology modifications in Phase II and III multiple myeloma studies and post-marketing experience. Grading based on NCI Common Toxicity Criteria CTCAE v 4.0.
** *Instrumental ADL*: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc;
*** *Self care ADL*: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medicinal products, and not bedridden.

Combination therapy with pegylated liposomal doxorubicin
VELCADE 1 mg powder for solution for injection is administered via intravenous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VELCADE.
Pegylated liposomal doxorubicin is administered at 30 mg/m² on day 4 of the VELCADE treatment cycle as a 1 hour intravenous infusion administered after the VELCADE injection.
Up to 8 cycles of this combination therapy can be administered as long as patients have not progressed and tolerate treatment. Patients achieving a complete response can continue treatment for at least 2 cycles after the first evidence of complete response, even if this requires treatment for more than 8 cycles. Patients whose levels of paraprotein continue to decrease after 8 cycles can also continue for as long as treatment is tolerated and they continue to respond.

For additional information concerning pegylated liposomal doxorubicin, see the corresponding Summary of Product Characteristics.

Combination with dexamethasone
VELCADE 1 mg powder for solution for injection is administered via intravenous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and

11 in a 21 day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VELCADE.
Dexamethasone is administered orally at 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of the VELCADE treatment cycle.
Patients achieving a response or a stable disease after 4 cycles of this combination therapy can continue to receive the same combination for a maximum of 4 additional cycles.
For additional information concerning dexamethasone, see the corresponding Summary of Product Characteristics.

Dose adjustments for combination therapy for patients with progressive multiple myeloma
For VELCADE dosage adjustments for combination therapy follow dose modification guidelines described under monotherapy above.

Posology for previously untreated multiple myeloma patients not eligible for haematopoietic stem cell transplantation
Combination therapy with melphalan and prednisone
VELCADE 1 mg powder for solution for injection is administered via intravenous injection in combination with oral melphalan and oral prednisone as shown in Table 2. A 6-week period is considered a treatment cycle. In Cycles 1-4, VELCADE is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32. In Cycles 5-9, VELCADE is administered once weekly on days 1, 8, 22 and 29. At least 72 hours should elapse between consecutive doses of VELCADE.
Melphalan and prednisone should both be given orally on days 1, 2, 3 and 4 of the first week of each VELCADE treatment cycle.
Nine treatment cycles of this combination therapy are administered.

Table 2: Recommended posology for VELCADE in combination with melphalan and prednisone

Twice weekly VELCADE (cycles 1-4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Vc (1.3 mg/m$^{2)}$	Day 1	--	--	Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	rest period
M (9 mg/m^2) P (60 mg/m$^{2)}$	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period
Once weekly VELCADE (cycles 5-9)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Vc (1.3 mg/m$^{2)}$	Day 1	--	--	--	Day 8		rest period	Day 22		Day 29		rest period
M (9 mg/m^2) P (60 mg/m$^{2)}$	Day 1	Day 2	Day 3	Day 4	--		rest period	--				rest period

Vc=VELCADE; M=melphalan, P=prednisone

Dose adjustments during treatment and re-initiation of treatment for combination therapy with melphalan and prednisone
Prior to initiating a new cycle of therapy:
- Platelet counts should be ≥ 70 x 10^9/l and the absolute neutrophils count should be ≥ 1.0 x 10^9/l
- Non-haematological toxicities should have resolved to Grade 1 or baseline

Table 3: Posology modifications during subsequent cycles of VELCADE therapy in combination with melphalan and prednisone

Toxicity	**Posology modification or delay**
Haematological toxicity during a cycle • If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle.
• If platelet counts ≤ 30 x 10^9/l or ANC ≤ 0.75 x 10^9/l on a VELCADE dosing day (other than day 1)	VELCADE therapy should be withheld

• If several VELCADE doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	VELCADE dose should be reduced by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)
Grade ≥ 3 non-haematological toxicities	VELCADE therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, VELCADE may be reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For VELCADE-related neuropathic pain and/or peripheral neuropathy, hold and/or modify VELCADE as outlined in Table 1.

For additional information concerning melphalan and prednisone, see the corresponding Summary of Product Characteristics.

Posology for previously untreated multiple myeloma patients eligible for haematopoietic stem cell transplantation (induction therapy)

Combination therapy with dexamethasone

VELCADE 1 mg powder for solution for injection is administered via intravenous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VELCADE.
Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the VELCADE treatment cycle.
Four treatment cycles of this combination therapy are administered.

Combination therapy with dexamethasone and thalidomide

VELCADE 1 mg powder for solution for injection is administered via intravenous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 28 day treatment cycle. This 4-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VELCADE.
Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the VELCADE treatment cycle.
Thalidomide is administered orally at 50 mg daily on days 1-14 and if tolerated the dose is increased to 100 mg on days 15-28, and thereafter may be further increased to 200 mg daily from cycle 2 (see Table 4).
Four treatment cycles of this combination are administered. It is recommended that patients with at least partial response receive 2 additional cycles.

Table 4: Posology for VELCADE combination therapy for patients with previously untreated multiple myeloma eligible for haematopoietic stem cell transplantation

Vc+ Dx	**Cycles 1 to 4**				
	Week	**1**	**2**	**3**	
	Vc (1.3 mg/m^2)	Day 1, 4	Day 8, 11	Rest Period	
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-	
Vc+Dx+T	**Cycle 1**				
	Week	**1**	**2**	**3**	**4**
	Vc (1.3 mg/m^2)	Day 1, 4	Day 8, 11	Rest Period	Rest Period
	T 50 mg	Daily	Daily	-	-
	T 100 mg[a]	-	-	Daily	Daily
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-	-
	Cycles 2 to 4[b]				
	Vc (1.3 mg/m^2)	Day 1, 4	Day 8, 11	Rest Period	Rest Period
	T 200 mg[a]	Daily	Daily	Daily	Daily
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-	-

Vc=VELCADE; Dx=dexamethasone; T=thalidomide

[a] Thalidomide dose is increased to 100 mg from week 3 of Cycle 1 only if 50 mg is tolerated and to 200 mg from cycle 2 onwards if 100 mg is tolerated.

[b] Up to 6 cycles may be given to patients who achieve at least a partial response after 4 cycles

Dosage adjustments for transplant eligible patients
For VELCADE dosage adjustments, dose modification guidelines described for monotherapy should be followed.
In addition, when VELCADE is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these products should be considered in the event of toxicities according to the recommendations in the Summary of Product Characteristics.

Posology for patients with previously untreated mantle cell lymphoma (MCL)
Combination therapy with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP)
VELCADE 1 mg powder for solution for injection is administered via intravenous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11, followed by a 10-day rest period on days 12-21. This 3-week period is considered a treatment cycle. Six VELCADE cycles are recommended, although for patients with a response first documented at cycle 6, two additional VELCADE cycles may be given. At least 72 hours should elapse between consecutive doses of VELCADE.

The following medicinal products are administered on day 1 of each VELCADE 3 week treatment cycle as intravenous infusions: rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2 and doxorubicin at 50 mg/m^2.
Prednisone is administered orally at 100 mg/m^2 on days 1, 2, 3, 4 and 5 of each VELCADE treatment cycle.

Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma
Prior to initiating a new cycle of therapy:

- Platelet counts should be ≥ 100,000 cells/μL and the absolute neutrophils count (ANC) should be ≥ 1,500 cells/μL
- Platelet counts should be ≥ 75,000 cells/μL in patients with bone marrow infiltration or splenic sequestration
- Haemoglobin ≥ 8 g/dL
- Non-haematological toxicities should have resolved to Grade 1 or baseline.

VELCADE treatment must be withheld at the onset of any ≥ Grade 3 VELCADE-related non-haematological toxicities (excluding neuropathy) or ≥ Grade 3 haematological toxicities (see also section 4.4). For dose adjustments, see Table 5 below.
Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration. Platelet transfusion for the treatment of thrombocytopenia should be considered when clinically appropriate.

Table 5: Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma

Toxicity	**Posology modification or delay**
Haematological toxicity	
• ≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10,000 cells/μL	VELCADE therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 750 cells/μL and a platelet count ≥ 25,000 cells/μL. • If, after VELCADE has been held, the toxicity does not resolve, as defined above, then VELCADE must be discontinued. • If toxicity resolves i.e. patient has an ANC ≥ 750 cells/μL and a platelet count ≥ 25,000 cells/μL, VELCADE may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2).
• If platelet counts < 25,000 cells/μL. or ANC < 750 cells/μL on a VELCADE dosing day (other than Day 1 of each cycle)	VELCADE therapy should be withheld
Grade ≥ 3 non-haematological toxicities considered to be related to VELCADE	VELCADE therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, VELCADE may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For VELCADE-related neuropathic pain and/or peripheral neuropathy, hold and/or modify VELCADE as outlined in Table 1.

In addition, when VELCADE is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these medicinal products should be considered in the event of toxicities, according to the recommendations in the respective Summary of Product Characteristics.

Special populations

Elderly
There is no evidence to suggest that dose adjustments are necessary in patients over 65 years of age with multiple myeloma or with mantle cell lymphoma.
There are no studies on the use of VELCADE in elderly patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. Therefore no dose recommendations can be made in this population.
In a study in previously untreated mantle cell lymphoma patients, 42.9% and 10.4% of patients exposed to VELCADE were in the range 65-74 years and ≥ 75 years of age, respectively. In patients aged ≥ 75 years, both regimens, VcR-CAP as well as R-CHOP, were less tolerated (see section 4.8).

Hepatic impairment
Patients with mild hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. Patients with moderate or severe hepatic impairment should be started on VELCADE at a reduced dose of 0.7 mg/m^2 per injection during the first treatment cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerability (see Table 6 and sections 4.4 and 5.2).

Table 6: Recommended starting dose modification for VELCADE in patients with hepatic impairment

Grade of hepatic impairment*	Bilirubin level	SGOT (AST) levels	Modification of starting dose
Mild	≤ 1.0 x ULN	> ULN	None
	> 1.0 x –1.5 x ULN	Any	None
Moderate	> 1.5 x –3 x ULN	Any	Reduce VELCADE to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	> 3 x ULN	Any	

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

* Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).

Renal impairment
The pharmacokinetics of bortezomib are not influenced in patients with mild to moderate renal impairment (Creatinine Clearance [CrCL] > 20 ml/min/1.73 m^2); therefore, dose adjustments are not necessary for these patients. It is unknown if the pharmacokinetics of bortezomib are influenced in patients with severe renal impairment not undergoing dialysis (CrCL < 20 ml/min/1.73 m^2). Since dialysis may reduce bortezomib concentrations, VELCADE should be administered after the dialysis procedure (see section 5.2).

Paediatric population
The safety and efficacy of VELCADE in children below 18 years of age have not been established (see sections 5.1 and 5.2). Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

VELCADE 1 mg powder for solution for injection is available for intravenous administration only.

VELCADE 3.5 mg powder for solution for injection is available for intravenous or subcutaneous administration.

VELCADE should not be given by other routes. Intrathecal administration has resulted in death.

Intravenous injection
VELCADE 1 mg powder for solution for injection is for intravenous administration only. The reconstituted solution is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with sodium chloride 9 mg/ml (0.9%) solution for injection. At least 72 hours should elapse between consecutive doses of VELCADE.

When VELCADE is given in combination with other medicinal products, refer to the Summary of Product Characteristics of these products for instructions for administration.

4.3 Contraindications

Hypersensitivity to the active substance, to boron or to any of the excipients listed in section 6.1.
Acute diffuse infiltrative pulmonary and pericardial disease.

When VELCADE is given in combination with other medicinal products, refer to their Summaries of Product Characteristics for additional contraindications.

4.4 Special warnings and precautions for use

When VELCADE is given in combination with other medicinal products, the Summary of Product Characteristics of these other medicinal products must be consulted prior to initiation of treatment with VELCADE. When thalidomide is used, particular attention to pregnancy testing and prevention requirements is needed (see section 4.6).

Intrathecal administration
There have been fatal cases of inadvertent intrathecal administration of VELCADE. VELCADE 1 mg powder for solution for injection is for intravenous use only, while VELCADE 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. VELCADE should not be administered intrathecally.

Gastrointestinal toxicity
Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with VELCADE treatment. Cases of ileus have been uncommonly reported (see section 4.8). Therefore, patients who experience constipation should be closely monitored.

Haematological toxicity
VELCADE treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). In studies in patients with relapsed multiple myeloma treated with VELCADE and in patients with previously untreated MCL treated with VELCADE in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP), one of the most common haematologic toxicity was transient thrombocytopenia. Platelets were lowest at Day 11 of each cycle of VELCADE treatment and typically recovered to baseline by the next cycle. There was no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured was approximately 40% of baseline in the single-agent multiple myeloma studies and 50% in the MCL study. In patients with advanced myeloma the severity of thrombocytopenia was related to pre-treatment platelet count: for baseline platelet counts < 75,000/µl, 90% of 21 patients had a count ≤ 25,000/µl during the study, including 14% < 10,000/µl; in contrast, with a baseline platelet count > 75,000/µl, only 14% of 309 patients had a count ≤ 25,000/µl during the study.

In patients with MCL (study LYM-3002), there was a higher incidence (56.7% versus 5.8%) of Grade ≥ 3 thrombocytopenia in the VELCADE treatment group (VcR-CAP) as compared to the non-VELCADE treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]). The two treatment groups were similar with regard to the overall incidence of all-grade bleeding events (6.3% in the VcR-CAP group and 5.0% in the R-CHOP group) as well as Grade 3 and higher bleeding events (VcR-CAP: 4 patients [1.7%]; R-CHOP: 3 patients [1.2%]). In the VcR-CAP group, 22.5% of patients received platelet transfusions compared to 2.9% of patients in the R-CHOP group.

Gastrointestinal and intracerebral haemorrhage, have been reported in association with VELCADE treatment. Therefore, platelet counts should be monitored prior to each dose of VELCADE. VELCADE therapy should be withheld when the platelet count is < 25,000/µl or, in the case of combination with melphalan and prednisone, when the platelet count is ≤ 30,000/µl (see section 4.2). Potential benefit of the treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding.

Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment with VELCADE. Platelet transfusion should be considered when clinically appropriate (see section 4.2).

In patients with MCL, transient neutropenia that was reversible between cycles was observed, with no evidence of cumulative neutropenia. Neutrophils were lowest at Day 11 of each cycle of VELCADE treatment and typically recovered to baseline by the next cycle. In study LYM-3002, colony stimulating factor support was given to 78% of patients in the VcR-CAP arm and 61% of patients in the R-CHOP arm. Since patients with neutropenia are at increased risk of infections, they should be

monitored for signs and symptoms of infection and treated promptly. Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration (see section 4.2).

Herpes zoster virus reactivation
Antiviral prophylaxis is recommended in patients being treated with VELCADE.
In the Phase III study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with VELCADE+Melphalan+Prednisone compared with Melphalan+Prednisone (14% versus 4% respectively).
In patients with MCL (study LYM-3002), the incidence of herpes zoster infection was 6.7% in the VcR-CAP arm and 1.2% in the R-CHOP arm (see section 4.8).

Hepatitis B Virus (HBV) reactivation and infection
When rituximab is used in combination with VELCADE, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Carriers of hepatitis B and patients with a history of hepatitis B must be closely monitored for clinical and laboratory signs of active HBV infection during and following rituximab combination treatment with VELCADE. Antiviral prophylaxis should be considered. Refer to the Summary of Product Characteristics of rituximab for more information.

Progressive multifocal leukoencephalopathy (PML)
Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with VELCADE. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of VELCADE. Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue VELCADE if PML is diagnosed.

Peripheral neuropathy
Treatment with VELCADE is very commonly associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. The incidence of peripheral neuropathy increases early in the treatment and has been observed to peak during cycle 5.

It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness.

Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require a change in the dose or schedule of VELCADE (see section 4.2). Neuropathy has been managed with supportive care and other therapies.

Early and regular monitoring for symptoms of treatment-emergent neuropathy with neurological evaluation should be considered in patients receiving VELCADE in combination with medicinal products known to be associated with neuropathy (e.g. thalidomide) and appropriate dose reduction or treatment discontinuation should be considered.

In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited.

Seizures
Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.

Hypotension
VELCADE treatment is commonly associated with orthostatic/postural hypotension. Most adverse reactions are mild to moderate in nature and are observed throughout treatment. Patients who developed orthostatic hypotension on VELCADE (injected intravenously) did not have evidence of orthostatic hypotension prior to treatment with VELCADE. Most patients required treatment for their orthostatic hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Orthostatic/postural hypotension was not acutely related to bolus infusion of VELCADE. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to bortezomib or bortezomib may aggravate an underlying condition such as diabetic or amyloidotic neuropathy. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicinal products, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

Posterior Reversible Encephalopathy Syndrome (PRES)
There have been reports of PRES in patients receiving VELCADE. PRES is a rare, often reversible, rapidly evolving neurological condition, which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably Magnetic Resonance Imaging (MRI), is used to confirm the diagnosis. In patients developing PRES, VELCADE should be discontinued.

Heart failure
Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Patients with risk factors for or existing heart disease should be closely monitored.

Electrocardiogram investigations
There have been isolated cases of QT-interval prolongation in clinical studies, causality has not been established.

Pulmonary disorders
There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration, and acute respiratory distress syndrome (ARDS) in patients receiving VELCADE (see section 4.8). Some of these events have been fatal. A pre-treatment chest radiograph is recommended to serve as a baseline for potential post-treatment pulmonary changes.

In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients treated appropriately. The benefit/risk ratio should be considered prior to continuing VELCADE therapy.

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

Renal impairment
Renal complications are frequent in patients with multiple myeloma. Patients with renal impairment should be monitored closely (see sections 4.2 and 5.2).

Hepatic impairment
Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with VELCADE at reduced doses and closely monitored for toxicities (see sections 4.2 and 5.2).

Hepatic reactions
Rare cases of hepatic failure have been reported in patients receiving VELCADE and concomitant medicinal products and with serious underlying medical conditions. Other reported hepatic reactions include increases in liver enzymes, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib (see section 4.8).

Tumour lysis syndrome
Because bortezomib is a cytotoxic agent and can rapidly kill malignant plasma cells and MCL cells, the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Concomitant medicinal products
Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates (see section 4.5).

Normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycemics (see section 4.5).

Potentially immunocomplex-mediated reactions
Potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis have been reported uncommonly. Bortezomib should be discontinued if serious reactions occur.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies indicate that bortezomib is a weak inhibitor of the cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. Based on the limited contribution (7%) of CYP2D6 to the metabolism of bortezomib, the CYP2D6 poor metaboliser phenotype is not expected to affect the overall disposition of bortezomib.

A drug-drug interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC increase of 35% ($CI_{90\%}$ [1.032 to 1.772]) based on data from 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

In a drug-drug interaction study assessing the effect of omeprazole, a potent CYP2C19 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of bortezomib based on data from 17 patients.

A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC reduction of 45% based on data from 6 patients. Therefore, the concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced.

In the same drug-drug interaction study assessing the effect of dexamethasone, a weaker CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of bortezomib based on data from 7 patients.

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

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy
No clinical data are available for bortezomib with regard to exposure during pregnancy. The teratogenic potential of bortezomib has not been fully investigated.

In non-clinical studies, bortezomib had no effects on embryonal/foetal development in rats and rabbits at the highest maternally tolerated doses. Animal studies to determine the effects of bortezomib on parturition and post-natal development were not conducted (see section 5.3). VELCADE should not be used during pregnancy unless the clinical condition of the woman requires treatment with VELCADE. If VELCADE is used during pregnancy, or if the patient becomes pregnant while receiving this medicinal product, the patient should be informed of potential for hazard to the foetus.

Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Thalidomide is contraindicated during pregnancy and in women of childbearing potential unless all the conditions of the thalidomide pregnancy prevention programme are met. Patients receiving VELCADE in combination with thalidomide should adhere to the pregnancy prevention programme of thalidomide. Refer to the Summary of Product Characteristics of thalidomide for additional information.

Breast-feeding
It is not known whether bortezomib is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants, breast-feeding should be discontinued during treatment with VELCADE.

Fertility
Fertility studies were not conducted with VELCADE (see section 5.3).

4.7 Effects on ability to drive and use machines

VELCADE may have a moderate influence on the ability to drive and use machines. VELCADE may be associated with fatigue very commonly, dizziness commonly, syncope uncommonly and orthostatic/postural hypotension or blurred vision commonly. Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
Serious adverse reactions uncommonly reported during treatment with VELCADE include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and rarely autonomic neuropathy.
The most commonly reported adverse reactions during treatment with VELCADE are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia,

peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

Tabulated summary of adverse reactions

Multiple Myeloma

Undesirable effects in Table 7 were considered by the investigators to have at least a possible or probable causal relationship to VELCADE. These adverse reactions are based on an integrated data set of 5,476 patients of whom 3,996 were treated with VELCADE at 1.3 mg/m^2 and included in Table 7. Overall, VELCADE was administered for the treatment of multiple myeloma in 3,974 patients.

Adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Table 7 has been generated using Version 14.1 of the MedDRA.
Post-marketing adverse reactions not seen in clinical trials are also included.

Table 7: Adverse reactions in patients with Multiple Myeloma treated with VELCADE in clinical trials, and all post-marketing adverse reactions regardless of indication[#]

System Organ Class	**Incidence**	**Adverse reaction**
Infections and infestations	Common	Herpes zoster (inc disseminated & ophthalmic), Pneumonia*, Herpes simplex*, Fungal infection*
	Uncommon	Infection*, Bacterial infections*, Viral infections*, Sepsis (inc septic shock)*, Bronchopneumonia, Herpes virus infection*, Meningoencephalitis herpetic[#], Bacteraemia (inc staphylococcal), Hordeolum, Influenza, Cellulitis, Device related infection, Skin infection*, Ear infection*, Staphylococcal infection, Tooth infection*
	Rare	Meningitis (inc bacterial), Epstein-Barr virus infection, Genital herpes, Tonsillitis, Mastoiditis, Post viral fatigue syndrome
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rare	Neoplasm malignant, Leukaemia plasmacytic, Renal cell carcinoma, Mass, Mycosis fungoides, Neoplasm benign*
Blood and lymphatic system disorders	Very Common	Thrombocytopenia*, Neutropenia*, Anaemia*
	Common	Leukopenia*, Lymphopenia*
	Uncommon	Pancytopenia*, Febrile neutropenia, Coagulopathy*, Leukocytosis*, Lymphadenopathy, Haemolytic anaemia[#]
	Rare	Disseminated intravascular coagulation, Thrombocytosis*, Hyperviscosity syndrome, Platelet disorder NOS, Thrombotic microangiopathy (inc thrombocytopenic purpura)[#], Blood disorder NOS, Haemorrhagic diathesis, Lymphocytic infiltration
Immune system disorders	Uncommon	Angioedema[#], Hypersensitivity*
	Rare	Anaphylactic shock, Amyloidosis, Type III immune complex mediated reaction
Endocrine disorders	Uncommon	Cushing's syndrome*, Hyperthyroidism*, Inappropriate antidiuretic hormone secretion
	Rare	Hypothyroidism
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Dehydration, Hypokalaemia*, Hyponatraemia*, Blood glucose abnormal*, Hypocalcaemia*, Enzyme abnormality*

	Uncommon	Tumour lysis syndrome, Failure to thrive*, Hypomagnesaemia*, Hypophosphataemia*, Hyperkalaemia*, Hypercalcaemia*, Hypernatraemia*, Uric acid abnormal*, Diabetes mellitus*, Fluid retention
	Rare	Hypermagnesaemia*, Acidosis, Electrolyte imbalance*, Fluid overload, Hypochloraemia*, Hypovolaemia, Hyperchloraemia*, Hyperphosphataemia*, Metabolic disorder, Vitamin B complex deficiency, Vitamin B12 deficiency, Gout, Increased appetite, Alcohol intolerance
Psychiatric disorders	Common	Mood disorders and disturbances*, Anxiety disorder*, Sleep disorders and disturbances*
	Uncommon	Mental disorder*, Hallucination*, Psychotic disorder*, Confusion*, Restlessness
	Rare	Suicidal ideation*, Adjustment disorder, Delirium, Libido decreased
Nervous system disorders	Very Common	Neuropathies*, Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	Common	Motor neuropathy*, Loss of consciousness (inc syncope), Dizziness*, Dysgeusia*, Lethargy, Headache*
	Uncommon	Tremor, Peripheral sensorimotor neuropathy, Dyskinesia*, Cerebellar coordination and balance disturbances*, Memory loss (exc dementia)*, Encephalopathy*, Posterior Reversible Encephalopathy Syndrome[#], Neurotoxicity, Seizure disorders*, Post herpetic neuralgia, Speech disorder*, Restless legs syndrome, Migraine, Sciatica, Disturbance in attention, Reflexes abnormal*, Parosmia
	Rare	Cerebral haemorrhage*, Haemorrhage intracranial (inc subarachnoid)*, Brain oedema, Transient ischaemic attack, Coma, Autonomic nervous system imbalance, Autonomic neuropathy, Cranial palsy*, Paralysis*, Paresis*, Presyncope, Brain stem syndrome, Cerebrovascular disorder, Nerve root lesion, Psychomotor hyperactivity, Spinal cord compression, Cognitive disorder NOS, Motor dysfunction, Nervous system disorder NOS, Radiculitis, Drooling, Hypotonia
Eye disorders	Common	Eye swelling*, Vision abnormal*, Conjunctivitis*
	Uncommon	Eye haemorrhage*, Eyelid infection*, Chalazion[#], Blepharitis[#], Eye inflammation*, Diplopia, Dry eye*, Eye irritation*, Eye pain, Lacrimation increased, Eye discharge
	Rare	Corneal lesion*, Exophthalmos, Retinitis, Scotoma, Eye disorder (inc. eyelid) NOS, Dacryoadenitis acquired, Photophobia, Photopsia, Optic neuropathy[#], Different degrees of visual impairment (up to blindness)*
Ear and labyrinth disorders	Common	Vertigo*
	Uncommon	Dysacusis (inc tinnitus)*,Hearing impaired (up to and inc deafness), Ear discomfort*
	Rare	Ear haemorrhage, Vestibular neuronitis, Ear disorder NOS
Cardiac disorders	Uncommon	Cardiac tamponade[#], Cardio-pulmonary arrest*, Cardiac fibrillation (inc atrial), Cardiac failure (inc left and right ventricular)*, Arrhythmia*, Tachycardia*, Palpitations, Angina pectoris, Pericarditis (inc pericardial effusion)*, Cardiomyopathy*, Ventricular dysfunction*, Bradycardia
	Rare	Atrial flutter, Myocardial infarction*, Atrioventricular block*, Cardiovascular disorder (inc cardiogenic shock), Torsade de pointes, Angina unstable, Cardiac valve disorders*, Coronary artery insufficiency, Sinus arrest
Vascular disorders	Common	Hypotension*, Orthostatic hypotension, Hypertension*

	Uncommon	Cerebrovascular accident[#], Deep vein thrombosis*, Haemorrhage*, Thrombophlebitis (inc superficial), Circulatory collapse (inc hypovolaemic shock), Phlebitis, Flushing*, Haematoma (inc perirenal)*, Poor peripheral circulation*, Vasculitis, Hyperaemia (inc ocular)*
	Rare	Peripheral embolism, Lymphoedema, Pallor, Erythromelalgia, Vasodilatation, Vein discolouration, Venous insufficiency
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Epistaxis, Upper/lower respiratory tract infection*, Cough*
	Uncommon	Pulmonary embolism, Pleural effusion, Pulmonary oedema (inc acute), Pulmonary alveolar haemorrhage[#], Bronchospasm, Chronic obstructive pulmonary disease*, Hypoxaemia*, Respiratory tract congestion*, Hypoxia, Pleurisy*, Hiccups, Rhinorrhoea, Dysphonia, Wheezing
	Rare	Respiratory failure, Acute respiratory distress syndrome, Apnoea, Pneumothorax, Atelectasis, Pulmonary hypertension, Haemoptysis, Hyperventilation, Orthopnoea, Pneumonitis, Respiratory alkalosis, Tachypnoea, Pulmonary fibrosis, Bronchial disorder*, Hypocapnia*, Interstitial lung disease, Lung infiltration, Throat tightness, Dry throat, Increased upper airway secretion, Throat irritation, Upper-airway cough syndrome
Gastrointestinal disorders	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Constipation
	Common	Gastrointestinal haemorrhage (inc mucosal)*, Dyspepsia, Stomatitis*, Abdominal distension, Oropharyngeal pain*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*, Flatulence
	Uncommon	Pancreatitis (inc chronic)*, Haematemesis, Lip swelling*, Gastrointestinal obstruction (inc small intestinal obstruction, ileus)*, Abdominal discomfort, Oral ulceration*, Enteritis*, Gastritis*, Gingival bleeding, Gastrooesophageal reflux disease*, Colitis (inc clostridium difficile)*, Colitis ischaemic[#], Gastrointestinal inflammation*, Dysphagia, Irritable bowel syndrome, Gastrointestinal disorder NOS, Tongue coated, Gastrointestinal motility disorder*, Salivary gland disorder*
	Rare	Pancreatitis acute, Peritonitis*, Tongue oedema*, Ascites, Oesophagitis, Cheilitis, Faecal incontinence, Anal sphincter atony, Faecaloma*, Gastrointestinal ulceration and perforation*, Gingival hypertrophy, Megacolon, Rectal discharge, Oropharyngeal blistering*, Lip pain, Periodontitis, Anal fissure, Change of bowel habit, Proctalgia, Abnormal faeces
Hepatobiliary disorders	Common	Hepatic enzyme abnormality*
	Uncommon	Hepatotoxicity (inc liver disorder), Hepatitis*, Cholestasis
	Rare	Hepatic failure, Hepatomegaly, Budd-Chiari syndrome, Cytomegalovirus hepatitis, Hepatic haemorrhage, Cholelithiasis
Skin and subcutaneous tissue disorders	Common	Rash*, Pruritus*, Erythema, Dry skin
	Uncommon	Erythema multiforme, Urticaria, Acute febrile neutrophilic dermatosis, Toxic skin eruption, Toxic epidermal necrolysis[#], Stevens-Johnson syndrome[#], Dermatitis*, Hair disorder*, Petechiae, Ecchymosis, Skin lesion, Purpura, Skin mass*, Psoriasis, Hyperhidrosis, Night sweats, Decubitus ulcer[#], Acne*, Blister*, Pigmentation disorder*

	Rare	Skin reaction, Jessner's lymphocytic infiltration, Palmar-plantar erythrodysaesthesia syndrome, Haemorrhage subcutaneous, Livedo reticularis, Skin induration, Papule, Photosensitivity reaction, Seborrhoea, Cold sweat, Skin disorder NOS, Erythrosis, Skin ulcer, Nail disorder
Musculoskeletal and connective tissue disorders	Very Common	Musculoskeletal pain*
	Common	Muscle spasms*, Pain in extremity, Muscular weakness
	Uncommon	Muscle twitching, Joint swelling, Arthritis*, Joint stiffness, Myopathies*,Sensation of heaviness
	Rare	Rhabdomyolysis, Temporomandibular joint syndrome, Fistula, Joint effusion, Pain in jaw, Bone disorder, Musculoskeletal and connective tissue infections and inflammations*, Synovial cyst
Renal and urinary disorders	Common	Renal impairment*
	Uncommon	Renal failure acute, Renal failure chronic*, Urinary tract infection*, Urinary tract signs and symptoms*, Haematuria*, Urinary retention, Micturition disorder*, Proteinuria, Azotaemia, Oliguria*, Pollakiuria
	Rare	Bladder irritation
Reproductive system and breast disorders	Uncommon	Vaginal haemorrhage, Genital pain*, Erectile dysfunction,
	Rare	Testicular disorder*, Prostatitis, Breast disorder female, Epididymal tenderness, Epididymitis, Pelvic pain, Vulval ulceration
Congenital, familial and genetic disorders	Rare	Aplasia, Gastrointestinal malformation, Ichthyosis
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc peripheral), Chills, Pain*, Malaise*
	Uncommon	General physical health deterioration*, Face oedema*, Injection site reaction*, Mucosal disorder*, Chest pain, Gait disturbance, Feeling cold, Extravasation*, Catheter related complication*, Change in thirst*, Chest discomfort, Feeling of body temperature change*, Injection site pain*
	Rare	Death (inc sudden), Multi-organ failure, Injection site haemorrhage*, Hernia(inc hiatus)*, Impaired healing*, Inflammation, Injection site phlebitis*, Tenderness, Ulcer, Irritability, Non-cardiac chest pain, Catheter site pain, Sensation of foreign body
Investigations	Common	Weight decreased
	Uncommon	Hyperbilirubinaemia*, Protein analyses abnormal*, Weight increased, Blood test abnormal*,C-reactive protein increased
	Rare	Blood gases abnormal*, Electrocardiogram abnormalities (inc QT prolongation)*, International normalised ratio abnormal*, Gastric pH decreased, Platelet aggregation increased, Troponin I increased, Virus identification and serology*, Urine analysis abnormal*
Injury, poisoning and procedural complications	Uncommon	Fall, Contusion
	Rare	Transfusion reaction, Fractures*, Rigors*, Face injury, Joint injury*, Burns, Laceration, Procedural pain, Radiation injuries*
Surgical and medical procedures	Rare	Macrophage activation

NOS=not otherwise specified

* Grouping of more than one MedDRA preferred term.

Post-marketing adverse reaction regardless of indication

Mantle Cell Lymphoma (MCL)
The safety profile of VELCADE in 240 MCL patients treated with VELCADE at 1.3 mg/m^2 in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP), versus 242 patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] was relatively consistent to that observed in patients with multiple myeloma with main differences described below. Additional adverse drug reactions identified associated with the use of the combination therapy (VcR-CAP) were hepatitis B infection (< 1%) and myocardial ischaemia (1.3%). The similar incidences of these events in both treatment arms, indicated that these adverse drug reactions are not attributable to VELCADE alone. Notable differences in the MCL patient population as compared to patients in the multiple myeloma studies were a ≥ 5% higher incidence of the haematological adverse reactions (neutropenia, thrombocytopenia, leukopenia, anemia, lymphopenia), peripheral sensory neuropathy, hypertension, pyrexia, pneumonia, stomatitis, and hair disorders.
Adverse drug reactions identified as those with a ≥ 1% incidence, similar or higher incidence in the VcR-CAP arm and with at least a possible or probable causal relationship to the components of the VcR-CAP arm, are listed in Table 8 below. Also included are adverse drug reactions identified in the VcR-CAP arm that were considered by investigators to have at least a possible or probable causal relationship to VELCADE based on historical data in the multiple myeloma studies.

Adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Table 8 has been generated using Version 16 of the MedDRA.

Table 8: Adverse reactions in patients with Mantle Cell Lymphoma treated with VcR-CAP in a clinical trial

System Organ Class	**Incidence**	**Adverse reaction**
Infections and infestations	Very Common	Pneumonia*
	Common	Sepsis (inc septic shock)*, Herpes zoster (inc disseminated & ophthalmic), Herpes virus infection*, Bacterial infections*, Upper/lower respiratory tract infection*, Fungal infection*, Herpes simplex*
	Uncommon	Hepatitis B, Infection*, Bronchopneumonia
Blood and lymphatic system disorders	Very Common	Thrombocytopenia*, Febrile neutropenia, Neutropenia*, Leukopenia*, Anaemia*, Lymphopenia*
	Uncommon	Pancytopenia*
Immune system disorders	Common	Hypersensitivity*
	Uncommon	Anaphylactic reaction
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Hypokalaemia*, Blood glucose abnormal*, Hyponatraemia*, Diabetes mellitus*, Fluid retention
	Uncommon	Tumour lysis syndrome
Psychiatric disorders	Common	Sleep disorders and disturbances*
Nervous system disorders	Very Common	Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	Common	Neuropathies*, Motor neuropathy*, Loss of consciousness (inc syncope), Encephalopathy*, Peripheral sensorimotor neuropathy, Dizziness*, Dysgeusia*, Autonomic neuropathy
	Uncommon	Autonomic nervous system imbalance
Eye disorders	Common	Vision abnormal*
Ear and labyrinth disorders	Common	Dysacusis (inc tinnitus)*
	Uncommon	Vertigo*, Hearing impaired (up to and inc deafness)
Cardiac disorders	Common	Cardiac fibrillation (inc atrial), Arrhythmia*, Cardiac failure (inc left and right ventricular)*, Myocardial ischaemia, Ventricular dysfunction*

	Uncommon	Cardiovascular disorder (inc cardiogenic shock)
Vascular disorders	Common	Hypertension*, Hypotension*, Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Cough*, Hiccups
	Uncommon	Acute respiratory distress syndrome, Pulmonary embolism, Pneumonitis, Pulmonary hypertension, Pulmonary oedema (inc acute)
Gastrointestinal disorders	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Stomatitis*, Constipation
	Common	Gastrointestinal haemorrhage (inc mucosal)*, Abdominal distension, Dyspepsia, Oropharyngeal pain*, Gastritis*, Oral ulceration*, Abdominal discomfort, Dysphagia, Gastrointestinal inflammation*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*
	Uncommon	Colitis (inc clostridium difficile)*
Hepatobiliary disorders	Common	Hepatotoxicity (inc liver disorder)
	Uncommon	Hepatic failure
Skin and subcutaneous tissue disorders	Very Common	Hair disorder*
	Common	Pruritus*, Dermatitis*, Rash*
Musculoskeletal and connective tissue disorders	Common	Muscle spasms*, Musculoskeletal pain*, Pain in extremity
Renal and urinary disorders	Common	Urinary tract infection*
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc peripheral), Chills, Injection site reaction*, Malaise*
Investigations	Common	Hyperbilirubinaemia*, Protein analyses abnormal*, Weight decreased, Weight increased

* Grouping of more than one MedDRA preferred term.

Description of selected adverse reactions

Herpes zoster virus reactivation

Multiple Myeloma

Antiviral prophylaxis was administered to 26% of the patients in the Vc+M+P arm. The incidence of herpes zoster among patients in the Vc+M+P treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

Mantle cell lymphoma

Antiviral prophylaxis was administered to 137 of 240 patients (57%) in the VcR-CAP arm. The incidence of herpes zoster among patients in the VcR-CAP arm was 10.7% for patients not administered antiviral prophylaxis compared to 3.6% for patients administered antiviral prophylaxis (see section 4.4).

Hepatitis B Virus (HBV) reactivation and infection

Mantle cell lymphoma

HBV infection with fatal outcomes occurred in 0.8% (n=2) of patients in the non-VELCADE treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP) and 0.4% (n=1) of patients receiving VELCADE in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP). The overall incidence of hepatitis B infections was similar in patients treated with VcR-CAP or with R-CHOP (0.8% vs 1.2% respectively).

Peripheral neuropathy in combination regimens

Multiple Myeloma

In trials in which VELCADE was administered as induction treatment in combination with dexamethasone (study IFM-2005-01), and dexamethasone-thalidomide (study MMY-3010), the incidence of peripheral neuropathy in the combination regimens is presented in the table below:

Table 9: Incidence of peripheral neuropathy during induction treatment by toxicity and treatment discontinuation due to peripheral neuropathy

	IFM-2005-01		MMY-3010	
	VDDx (N=239)	VcDx (N=239)	TDx (N=126)	VcTDx (N=130)
Incidence of PN (%)				
All GradePN	3	15	12	45
≥ Grade 2 PN	1	10	2	31
≥ Grade 3 PN	< 1	5	0	5
Discontinuation due to PN (%)	< 1	2	1	5

VDDx=vincristine, doxorubicin, dexamethasone; VcDx=VELCADE, dexamethasone; TDx=thalidomide, dexamethasone; VcTDx=VELCADE, thalidomide, dexamethasone; PN=peripheral neuropathy
Note: Peripheral neuropathy included the preferred terms: neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

Mantle cell lymphoma
In study LYM-3002 in which VELCADE was administered with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CAP), the incidence of peripheral neuropathy in the combination regimens is presented in the table below:

Table 10: Incidence of peripheral neuropathy in study LYM-3002 by toxicity and treatment discontinuation due to peripheral neuropathy

	VcR-CAP (N=240)	R-CHOP (N=242)
Incidence of PN (%)		
All GradePN	30	29
≥ Grade 2 PN	18	9
≥ Grade 3 PN	8	4
Discontinuation due to PN (%)	2	< 1

VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP= rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; PN=peripheral neuropathy
Peripheral neuropathy included the preferred terms: peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

Elderly MCL patients
42.9% and 10.4% of patients in the VcR-CAP arm were in the range 65-74 years and ≥ 75 years of age, respectively. Although in patients aged ≥ 75 years, both VcR-CAP and R-CHOP were less tolerated, the serious adverse event rate in the VcR-CAP groups was 68%, compared to 42% in the R-CHOP group.

Retreatment of patients with relapsed multiple myeloma
In a study in which VELCADE retreatment was administered in 130 patients with relapsed multiple myeloma, who previously had at least partial response on a VELCADE-containing regimen, the most common all-grade adverse events occurring in at least 25% of patients were thrombocytopenia (55%), neuropathy (40%), anaemia (37%), diarrhoea (35%), and constipation (28%). All grade peripheral neuropathy and grade ≥ 3 peripheral neuropathy were observed in 40% and 8.5% of patients, respectively.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In patients, overdose more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes. For preclinical cardiovascular safety pharmacology studies, see section 5.3.

There is no known specific antidote for bortezomib overdose. In the event of an overdose, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature (see sections 4.2 and 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX32.

Mechanism of action
Bortezomib is a proteasome inhibitor. It is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death.

Bortezomib is highly selective for the proteasome. At 10 μM concentrations, bortezomib does not inhibit any of a wide variety of receptors and proteases screened and is more than 1,500-fold more selective for the proteasome than for its next preferable enzyme. The kinetics of proteasome inhibition were evaluated *in vitro*, and bortezomib was shown to dissociate from the proteasome with a $t_{½}$ of 20 minutes, thus demonstrating that proteasome inhibition by bortezomib is reversible.

Bortezomib mediated proteasome inhibition affects cancer cells in a number of ways, including, but not limited to, altering regulatory proteins, which control cell cycle progression and nuclear factor kappa B (NF-kB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF-kB is a transcription factor whose activation is required for many aspects of tumourigenesis, including cell growth and survival, angiogenesis, cell-cell interactions, and metastasis. In myeloma, bortezomib affects the ability of myeloma cells to interact with the bone marrow microenvironment.

Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types and that cancer cells are more sensitive to the pro-apoptotic effects of proteasome inhibition than normal cells. Bortezomib causes reduction of tumour growth *in vivo* in many preclinical tumour models, including multiple myeloma.

Data from *in vitro*, *ex-vivo*, and animal models with bortezomib suggest that it increases osteoblast differentiation and activity and inhibits osteoclast function. These effects have been observed in patients with multiple myeloma affected by an advanced osteolytic disease and treated with bortezomib.

Clinical efficacy in previously untreated multiple myeloma
A prospective Phase III, international, randomised (1:1), open-label clinical study (MMY-3002 VISTA) of 682 patients was conducted to determine whether VELCADE (1.3 mg/m^2 injected intravenously) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in patients with previously untreated multiple myeloma. Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. The median age of the patients in the study was 71 years, 50% were male, 88% were Caucasian and the median Karnofsky performance status score for the patients was 80. Patients

had IgG/IgA/Light chain myeloma in 63%/25%/8% instances, a median hemoglobin of 105 g/l, and a median platelet count of 221.5 x 10^9/l. Similar proportions of patients had creatinine clearance ≤ 30 ml/min (3% in each arm).
At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the M+P arm were offered Vc+M+P treatment. Median follow-up was 16.3 months. The final survival update was performed with a median duration of follow-up of 60.1 months. A statistically significant survival benefit in favour of the Vc+M+P treatment group was observed (HR=0.695; p=0.00043) despite subsequent therapies including VELCADE-based regimens. Median survival for the Vc+M+P treatment group was 56.4 months compared to 43.1 for the M+P treatment group. Efficacy results are presented in Table 11:

Table 11: Efficacy results following the final survival update to VISTA study

Efficacy endpoint	**Vc+M+P n=344**	**M+P n=338**
Time to progression		
Events n (%)	101 (29)	152 (45)
Median[a] (95% CI)	20.7 mo (17.6, 24,7)	15.0 mo (14.1, 17.9)
Hazard ratio[b] (95% CI)	0.54 (0.42, 0.70)	
p-value[c]	0.000002	
Progression-free survival		
Events n (%)	135 (39)	190 (56)
Median[a] (95% CI)	18.3 mo (16.6, 21.7)	14.0 mo (11.1, 15.0)
Hazard ratio[b] (95% CI)	0.61 (0.49, 0.76)	
p-value[c]	0.00001	
Overall survival*		
Events (deaths) n (%)	176 (51.2)	211 (62.4)
Median[a] (95% CI)	56.4 mo (52.8, 60.9)	43.1 mo (35.3, 48.3)
Hazard ratio[b] (95% CI)	0.695 (0.567, 0.852)	
p-value[c]	0.00043	
Response rate population[e] n=668	n=337	n=331
CR[f] n (%)	102 (30)	12 (4)
PR[f] n (%)	136 (40)	103 (31)
nCR n (%)	5 (1)	0
CR+PR[f] n (%)	238 (71)	115 (35)
p-value[d]	< 10^{-10}	
Reduction in serum M-protein population[g] n=667	n=336	n=331
≥90% n (%)	151 (45)	34 (10)
Time to first response in CR + PR		
Median	1.4 mo	4.2 mo
Median[a] response duration		
CR[f]	24.0 mo	12.8 mo
CR+PR[f]	19.9 mo	13.1 mo
Time to next therapy		
Events n (%)	224 (65.1)	260 (76.9)
Median[a] (95% CI)	27.0 mo (24.7, 31.1)	19.2 mo (17.0, 21.0)
Hazard ratio[b] (95% CI)	0.557 (0.462, 0.671)	

p-value[c]	< 0.000001

[a] Kaplan-Meier estimate.
[b] Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors: β_2-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for VMP
[c] Nominal p-value based on the stratified log-rank test adjusted for stratification factors: β_2-microglobulin, albumin, and region
[d] p-value for Response Rate (CR+PR) from the Cochran Mantel-Haenszel chi-square test adjusted for the stratification factors
[e] Response population includes patients who had measurable disease at baseline
[f] CR=Complete Response; PR=Partial Response. EBMT criteria
[g] All randomised patients with secretory disease
* Survival update based on a median duration of follow-up at 60.1 months
mo: months
CI=Confidence Interval

Patients eligible for stem cell transplantation
Two randomised, open-label, multicenter Phase III trials (IFM-2005-01, MMY-3010) were conducted to demonstrate the safety and efficacy of VELCADE in dual and triple combinations with other chemotherapeutic agents, as induction therapy prior to stem cell transplantation in patients with previously untreated multiple myeloma.

In study IFM-2005-01 VELCADE combined with dexamethasone [VcDx, n=240] was compared to vincristine- doxorubicin-dexamethasone [VDDx, n=242]. Patients in the VcDx group received four 21 day cycles, each consisting of VELCADE (1.3 mg/m^2 administered intravenously twice weekly on days 1, 4, 8, and 11), and oral dexamethasone (40 mg/day on days 1 to 4 and days 9 to 12, in Cycles 1 and 2, and on days 1 to 4 in Cycles 3 and 4).
Autologous stem cell transplants were received by 198 (82%) patients and 208 (87%) patients in the VDDx and VcDx groups respectively; the majority of patients underwent one single transplant procedure. Patient demographic and baseline disease charateristics were similar between the treatment groups. Median age of the patients in the study was 57 years, 55% were male and 48% of patients had high-risk cytogenetics. The median duration of treatment was 13 weeks for the VDDx group and 11 weeks for the VcDx group. The median number of cycles received for both groups was 4 cycles. The primary efficacy endpoint of the study was post-induction response rate (CR+nCR). A statistically significant difference in CR+nCR was observed in favour of the VELCADE combined with dexamethasone group. Secondary efficacy endpoints included post-transplant response rates (CR+nCR, CR+nCR+VGPR+PR), Progression Free Survival and Overall Survival. Main efficacy results are presented in Table 12.

Table 12: Efficacy results from study IFM-2005-01

Endpoints	**VcDx**	**VDDx**	**OR; 95% CI; P value[a]**
IFM-2005-01	N=240 (ITT population)	N=242 (ITT population)	
RR (Post-induction) *CR+nCR CR+nCR+VGPR+PR % (95% CI)	 14.6 (10.4, 19.7) 77.1 (71.2, 82.2)	 6.2 (3.5, 10.0) 60.7 (54.3, 66.9)	 2.58 (1.37, 4.85); 0.003 2.18 (1.46, 3.24); < 0.001
RR (Post-transplant)[b] CR+nCR CR+nCR+VGPR+PR % (95% CI)	 37.5 (31.4, 44.0) 79.6 (73.9, 84.5)	 23.1 (18.0, 29.0) 74.4 (68.4, 79.8)	 1.98 (1.33, 2.95); 0.001 1.34 (0.87, 2.05); 0.179

CI=confidence interval; CR=complete response; nCR=near complete response; ITT=intent to treat; RR=response rate; Vc=VELCADE; VcDx=VELCADE, dexamethasone; VDDx=vincristine, doxorubicin, dexamethasone; VGPR=very good partial response; PR=partial response; OR=odds ratio.
* Primary endpoint
[a] OR for response rates based on Mantel-Haenszel estimate of the common odds ratio for stratified tables; p-values by Cochran Mantel-Haenszel test.
[b] Refers to response rate after second transplant for subjects who received a second transplant (42/240 [18%] in VcDx group and 52/242 [21%] in VDDx group).
Note: An OR > 1 indicates an advantage for Vc-containing induction therapy.

In study MMY-3010 induction treatment withVELCADE combined with thalidomide and dexamethasone [VcTDx, n=130] was compared to thalidomide-dexamethasone [TDx, n=127]. Patients in the VcTDx group received six 4-week cycles, each consisting of VELCADE (1.3 mg/m^2 administered twice weekly days 1, 4, 8, and 11, followed by a 17-day rest period from day 12 to day 28), dexamethasone (40 mg administered orally on days 1 to 4 and days 8 to 11), and thalidomide (administered orally at 50 mg daily on days 1-14, increased to 100 mg on days 15-28 and thereafter to 200 mg daily).
One single autologous stem cell transplant was received by 105 (81%) patients and 78 (61%) patients in the VcTDx and TDx groups, respectively. Patient demographic and baseline disease charateristics were similar between the treatment groups. Patients in the VcTDx and TDx groups respectively had a median age of 57 versus 56 years, 99% versus 98% patients were Caucasians, and 58% versus 54% were males. In the VcTDx group 12% of patients were cytogenetically classified as high risk versus 16% of patients in the TDx group. The median duration of treatment was 24.0 weeks and the median number of treatment cycles received was 6.0, and was consistent across treatment groups.
The primary efficacy endpoints of the study were post-induction and post-transplant response rates (CR+nCR). A statistically significant difference in CR+nCR was observed in favour of the VELCADE combined with dexamethasone and thalidomide group. Secondary efficacy endpoints included Progression Free Survival and Overall Survival. Main efficacy results are presented in Table 13.

Table 13: Efficacy results from study MMY-3010

Endpoints	**VcTDx**	**TDx**	**OR; 95% CI; P value[a]**
MMY-3010	N=130 (ITT population)	N=127 (ITT population)	
**RR (Post-induction)*			
CR+nCR	49.2 (40.4, 58.1)	17.3 (11.2, 25.0)	4.63 (2.61, 8.22); < 0.001[a]
CR+nCR+PR % (95% CI)	84.6 (77.2, 90.3)	61.4 (52.4, 69.9)	3.46 (1.90, 6.27); < 0.001[a]
**RR (Post-transplant)*			
CR+nCR	55.4 (46.4, 64.1)	34.6 (26.4, 43.6)	2.34 (1.42, 3.87); 0.001[a]
CR+nCR+PR % (95% CI)	77.7 (69.6, 84.5)	56.7 (47.6, 65.5)	2.66 (1.55, 4.57); < 0.001[a]

CI=confidence interval; CR=complete response; nCR=near complete response; ITT=intent to treat; RR=response rate; Vc=VELCADE; VcTDx=VELCADE, thalidomide, dexamethasone; TDx=thalidomide, dexamethasone; PR=partial response; OR=odds ratio

* Primary endpoint

[a] OR for response rates based on Mantel-Haenszel estimate of the common odds ratio for stratified tables; p-values by Cochran Mantel-Haenszel test.

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

Clinical efficacy in relapsed or refractory multiple myeloma

The safety and efficacy of VELCADE (injected intravenously) were evaluated in 2 studies at the recommended dose of 1.3 mg/m^2: a Phase III randomised, comparative study (APEX), versus dexamethasone (Dex), of 669 patients with relapsed or refractory multiple myeloma who had received 1-3 prior lines of therapy, and a Phase II single-arm study of 202 patients with relapsed and refractory multiple myeloma, who had received at least 2 prior lines of treatment and who were progressing on their most recent treatment.

In the Phase III study, treatment with VELCADE led to a significantly longer time to progression, a significantly prolonged survival and a significantly higher response rate, compared to treatment with dexamethasone (see Table 14), in all patients as well as in patients who have received 1 prior line of therapy. As a result of a pre-planned interim analysis, the dexamethasone arm was halted at the recommendation of the data monitoring committee and all patients randomised to dexamethasone were then offered VELCADE, regardless of disease status. Due to this early crossover, the median duration of follow-up for surviving patients is 8.3 months. Both in patients who were refractory to their last prior therapy and those who were not refractory, overall survival was significantly longer and response rate was significantly higher on the VELCADE arm.

Of the 669 patients enrolled, 245 (37%) were 65 years of age or older. Response parameters as well as TTP remained significantly better for VELCADE independently of age. Regardless of

β_2-microglobulin levels at baseline, all efficacy parameters (time to progression and overall survival, as well as response rate) were significantly improved on the VELCADE arm.

In the refractory population of the Phase II study, responses were determined by an independent review committee and the response criteria were those of the European Bone Marrow Transplant Group. The median survival of all patients enrolled was 17 months (range < 1 to 36+ months). This survival was greater than the six-to-nine month median survival anticipated by consultant clinical investigators for a similar patient population. By multivariate analysis, the response rate was independent of myeloma type, performance status, chromosome 13 deletion status, or the number or type of previous therapies. Patients who had received 2 to 3 prior therapeutic regimens had a response rate of 32% (10/32) and patients who received greater than 7 prior therapeutic regimens had a response rate of 31% (21/67).

Table 14: Summary of disease outcomes from the Phase III (APEX) and Phase II studies

	Phase III		**Phase III**		**Phase III**		**Phase II**
	All patients		**1 prior line of therapy**		**> 1 prior line of therapy**		**≥ 2 prior lines**
Time related events	**Vc n=333[a]**	**Dex n=336[a]**	**Vc n=132[a]**	**Dex n=119[a]**	**Vc n=200[a]**	**Dex n=217[a]**	**Vc n=202[a]**
TTP, days [95% CI]	189[b] [148, 211]	106[b] [86, 128]	212[d] [188, 267]	169[d] [105, 191]	148[b] [129, 192]	87[b] [84, 107]	210 [154, 281]
1 year survival, % [95% CI]	80[d] [74,85]	66[d] [59,72]	89[d] [82,95]	72[d] [62,83]	73 [64,82]	62 [53,71]	60
Best response (%)	**Vc n=315[c]**	**Dex n=312[c]**	**Vc n=128**	**Dex n=110**	**Vc n=187**	**Dex n=202**	**Vc n=193**
CR	20 (6)[b]	2 (< 1)[b]	8 (6)	2 (2)	12 (6)	0 (0)	(4)**
CR+nCR	41 (13)[b]	5 (2)[b]	16 (13)	4 (4)	25 (13)	1 (< 1)	(10)**
CR+nCR+PR	121 (38)[b]	56 (18)[b]	57 (45)[d]	29 (26)[d]	64 (34)[b]	27 (13)[b]	(27)**
CR+nCR+ PR+MR	146 (46)	108 (35)	66 (52)	45 (41)	80 (43)	63 (31)	(35)**
Median duration Days (months)	242 (8.0)	169 (5.6)	246 (8.1)	189 (6.2)	238 (7.8)	126 (4.1)	385*
Time to response CR+PR (days)	43	43	44	46	41	27	38*

[a] Intent to Treat (ITT) population

[b] p-value from the stratified log-rank test; analysis by line of therapy excludes stratification for therapeutic history; p < 0.0001

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

[d] p-value from the Cochran Mantel-Haenszel chi-square test adjusted for the stratification factors; analysis by line of therapy excludes stratification for therapeutic history

* CR+PR+MR **CR=CR, (IF-); nCR=CR (IF+)

NA=not applicable, NE=not estimated
TTP-Time to Progression
CI=Confidence Interval
Vc=VELCADE; Dex=dexamethasone
CR=Complete Response; nCR=near Complete response
PR=Partial Response; MR=Minimal response

In the Phase II study, patients who did not obtain an optimal response to therapy with VELCADE alone were able to receive high-dose dexamethasone in conjunction with VELCADE. The protocol allowed patients to receive dexamethasone if they had had a less than optimal response to VELCADE alone. A total of 74 evaluable patients were administered dexamethasone in combination with VELCADE. Eighteen percent of patients achieved, or had an improved response [MR (11%) or PR (7%)] with combination treatment.

VELCADE combination treatment with pegylated liposomal doxorubicin (study DOXIL-MMY-3001)
A Phase III randomised, parallel-group, open-label, multicentre study was conducted in 646 patients comparing the safety and efficacy of VELCADE plus pegylated liposomal doxorubicin versus VELCADE monotherapy in patients with multiple myeloma who had received at least 1 prior therapy and who did not progress while receiving anthracycline-based therapy. The primary efficacy endpoint was TTP while the secondary efficacy endpoints were OS and ORR (CR+PR), using the European Group for Blood and Marrow Transplantation (EBMT) criteria.
A protocol-defined interim analysis (based on 249 TTP events) triggered early study termination for efficacy. This interim analysis showed a TTP risk reduction of 45% (95% CI; 29-57%, $p < 0.0001$) for patients treated with combination therapy of VELCADE and pegylated liposomal doxorubicin. The median TTP was 6.5 months for the VELCADE monotherapy patients compared with 9.3 months for the VELCADE plus pegylated liposomal doxorubicin combination therapy patients. These results, though not mature, constituted the protocol defined final analysis.
The final analysis for OS performed after a median follow-up of 8.6 years showed no significant difference in OS between the two treatment arms. The median OS was 30.8 months (95% CI; 25.2-36.5 months) for the VELCADE monotherapy patients and 33.0 months (95% CI; 28.9-37.1 months) for the VELCADE plus pegylated liposomal doxorubicin combination therapy patients.

VELCADE combination treatment with dexamethasone
In the absence of any direct comparison between VELCADE and VELCADE in combination with dexamethasone in patients with progressive multiple myeloma, a statistical matched-pair analysis was conducted to compare results from the non randomised arm of VELCADE in combination with dexamethasone (Phase II open-label study MMY-2045), with results obtained in the VELCADE monotherapy arms from different Phase III randomised studies (M34101-039 [APEX] and DOXIL MMY-3001) in the same indication.
The matched-pair analysis is a statistical method in which patients in the treatment group (e.g. VELCADE in combination with dexamethasone) and patients in the comparison group (e.g. VELCADE) are made comparable with respect to confounding factors by individually pairing study subjects. This minimises the effects of observed confounders when estimating treatment effects using non-randomised data.
One hundred and twenty seven matched pairs of patients were identified. The analysis demonstrated improved ORR (CR+PR) (odds ratio 3.769; 95% CI 2.045-6.947; $p < 0.001$), PFS (hazard ratio 0.511; 95% CI 0.309-0.845; p=0.008), TTP (hazard ratio 0.385; 95% CI 0.212-0.698; p=0.001) for VELCADE in combination with dexamethasone over VELCADE monotherapy.

Limited information on VELCADE retreatment in relapsed multiple myeloma is available.
Phase II study MMY-2036 (RETRIEVE), single arm, open-label study was conducted to determine the efficacy and safety of retreatment with VELCADE. One hundred and thirty patients (≥ 18 years of age) with multiple myeloma who previously had at least partial response on a VELCADE-containing regimen were retreated upon progression. At least 6 months after prior therapy, VELCADE was started at the last tolerated dose of 1.3 mg/m^2 (n=93) or ≤ 1.0 mg/m^2 (n=37) and given on days 1, 4, 8 and 11 every 3 weeks for maximum of 8 cycles either as single agent or in combination with dexamethasone in accordance with the standard of care. Dexamethasone was administered in combination with VELCADE to 83 patients in Cycle 1 with an additional 11 patients receiving dexamethasone during the course of VELCADE retreatment cycles.
The primary endpoint was best confirmed response to retreatment as assessed by EBMT criteria. The overall best response rate (CR + PR), to retreatment in 130 patients was 38.5% (95% CI: 30.1, 47.4).

<u>Clinical efficacy in previously untreated mantle cell lymphoma (MCL)</u>
Study LYM-3002 was a Phase III, randomised, open-label study comparing the efficacy and safety of the combination of VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP; n=243) to that of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; n=244) in adult patients with previously untreated MCL (Stage II, III or IV). Patients in the VcR-CAP treatment arm received VELCADE (1.3 mg/m^2; on days 1, 4, 8, 11, rest period days 12-21), rituximab 375 mg/m^2 IV on day 1; cyclophosphamide 750 mg/m^2 IV on day 1; doxorubicin 50 mg/m^2 IV on day 1; and prednisone 100 mg/m^2 orally on day 1 through day 5 of the 21 day VELCADE

treatment cycle. For patients with a response first documented at cycle 6, two additional treatment cycles were given.
The primary efficacy endpoint was progression-free survival based on Independent Review Committee (IRC) assessment. Secondary endpoints included, time to progression (TTP), time to next anti-lymphoma treatment (TNT), duration of treatment free interval (TFI), overall response rate (ORR) and complete response (CR/CRu) rate, overall survival (OS) and response duration.

The demographic and baseline disease characteristics were generally well balanced between the two treatment arms: median patient age was 66 years, 74% were male, 66% were Caucasian and 32% Asian, 69% of patients had a positive bone marrow aspirate and/or a positive bone marrow biopsy for MCL, 54% of patients had an International Prognostic Index (IPI) score of ≥ 3, and 76% had Stage IV disease. Treatment duration (median=17 weeks) and duration of follow-up (median=40 months) were comparable in both treatment arms. A median of 6 cycles was received by patients in both treatment arms with 14% of subjects in the VcR-CAP group and 17% of patients in the R-CHOP group receiving 2 additional cycles. The majority of the patients in both groups completed treatment, 80% in the VcR-CAP group and 82% in the R-CHOP group. Efficacy results are presented in Table 15:

Table 15: Efficacy results from study LYM-3002

Efficacy endpoint	**VcR-CAP**	**R-CHOP**	
n: ITT patients	243	244	
Progression free survival (IRC)[a]			
Events n (%)	133 (54.7%)	165 (67.6%)	HR[b] (95% CI)=0.63 (0.50; 0.79)
Median[c](95% CI) (months)	24.7 (19.8; 31.8)	14.4 (12; 16.9)	p-value[d] < 0.001
Response rate			
n: response-evaluable patients	229	228	
Overall complete response (CR+CRu)[f] n(%)	122 (53.3%)	95 (41.7%)	OR[e] (95% CI)=1.688 (1.148; 2.481) p-value[g]=0.007
Overall response (CR+CRu+PR)[h] n(%)	211 (92.1%)	204 (89.5%)	OR[e] (95% CI)=1.428 (0.749; 2.722) p-value[g]=0.275

[a] Based on Independent Review Committee (IRC) assessment (radiological data only).
[b] Hazard ratio estimate is based on a Cox's model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for VcR-CAP.
[c] Based on Kaplan-Meier product limit estimates.
[d] Based on Log rank test stratified with IPI risk and stage of disease.
[e] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used, with IPI risk and stage of disease as stratification factors. An odds ratio (OR) > 1 indicates an advantage for VcR-CAP.
[f] Include all CR+CRu, by IRC, bone marrow and LDH.
[g] P-value from the Cochran Mantel-Haenszel chi-square test, with IPI and stage of disease as stratification factors.
[h] Include all radiological CR+CRu+PR by IRC regardless the verification by bone marrow and LDH.
CR=Complete Response; CRu=Complete Response unconfirmed; PR=Partial Response; CI=Confidence Interval, HR=Hazard Ratio; OR=Odds Ratio; ITT=Intent to Treat

Median PFS by investigator assessment was 30.7 months in the VcR-CAP group and 16.1 months in the R-CHOP group (Hazard Ratio [HR]=0.51; p < 0.001). A statistically significant benefit (p < 0.001) in favour of the VcR-CAP treatment group over the R-CHOP group was observed for TTP (median 30.5 versus 16.1 months), TNT (median 44.5 versus 24.8 months) and TFI (median 40.6 versus 20.5 months). The median duration of complete response was 42.1 months in the VcR-CAP group compared with 18 months in the R-CHOP group. The duration of overall response was 21.4 months longer in the VcR-CAP group (median 36.5 months versus 15.1 months in the R-CHOP group). The final analysis for OS was performed after a median follow-up of 82 months. Median OS was 90.7 months for the VcR-CAP group compared with 55.7 months for the R-CHOP group (HR=0.66; p=0.001). The observed final median difference in the OS between the 2 treatment groups was 35 months.

Patients with previously treated light-chain (AL) Amyloidosis
An open label non randomised Phase I/II study was conducted to determine the safety and efficacy of VELCADE in patients with previously treated light-chain (AL) Amyloidosis. No new safety concerns

were observed during the study, and in particular VELCADE did not exacerbate target organ damage (heart, kidney and liver). In an exploratory efficacy analysis, a 67.3% response rate (including a 28.6% CR rate) as measured by hematologic response (M-protein) was reported in 49 evaluable patients treated with the maximum allowed doses of 1.6 mg/m^2 weekly and 1.3 mg/m^2 twice-weekly. For these dose cohorts, the combined 1-year survival rate was 88.1%.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with VELCADE in all subsets of the paediatric population in multiple myeloma and in mantle cell lymphoma (see section 4.2 for information on paediatric use).

A Phase II, single-arm activity, safety, and pharmacokinetic trial conducted by the Children's Oncology Group assessed the activity of the addition of bortezomib to multi-agent re-induction chemotherapy in paediatric and young adult patients with lymphoid malignancies (pre-B cell acute lymphoblastic leukemia [ALL], T-cell ALL, and T-cell lymphoblastic lymphoma [LL]). An effective re-induction multi-agent chemotherapy regimen was administered in 3 blocks. VELCADE was administered only in Blocks 1 and 2 to avoid potential overlapping toxicities with coadministered drugs in Block 3.

Complete response (CR) was evaluated at the end of Block 1. In B-ALL patients with relapse within 18 months of diagnosis (n = 27) the CR rate was 67% (95% CI: 46, 84); the 4-month event free survival rate was 44% (95% CI: 26, 62). In B-ALL patients with relapse 18-36 months from diagnosis (n = 33) the CR rate was 79% (95% CI: 61, 91) and the 4-month event free survival rate was 73% (95% CI: 54, 85). The CR rate in first-relapsed T-cell ALL patients (n = 22) was 68% (95% CI: 45, 86) and the 4-month event free survival rate was 67% (95% CI: 42, 83). The reported efficacy data are considered inconclusive (see section 4.2).

There were 140 patients with ALL or LL enrolled and evaluated for safety; median age was 10 years (range 1 to 26). No new safety concerns were observed when VELCADE was added to the standard pediatric pre-B cell ALL chemotherapy backbone. The following adverse reactions (Grade ≥ 3) were observed at a higher incidence in the VELCADE containing treatment regimen as compared with a historical control study in which the backbone regimen was given alone: in Block 1 peripheral sensory neuropathy (3% versus 0%); ileus (2.1% versus 0%); hypoxia (8% versus 2%). No information on possible sequelae or rates of peripheral neuropathy resolution were available in this study. Higher incidences were also noted for infections with Grade ≥ 3 neutropenia (24% versus 19% in Block 1 and 22% versus 11% in Block 2), increased ALT (17% versus 8% in Block 2), hypokalaemia (18% versus 6% in Block 1 and 21% versus 12% in Block 2) and hyponatraemia (12% versus 5% in Block 1 and 4% versus 0 in Block 2).

5.2 Pharmacokinetic properties

Absorption
Following intravenous bolus administration of a 1.0 mg/m^2 and 1.3 mg/m^2 dose to 11 patients with multiple myeloma and creatinine clearance values greater than 50 ml/min, 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.

Distribution
The mean distribution volume (V_d) of bortezomib ranged from 1,659 l to 3,294 l following single- or repeated-dose intravenous 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. Over a bortezomib concentration range of 0.01 to 1.0 µg/ml, the *in vitro* protein binding averaged 82.9% in human plasma. The fraction of bortezomib bound to plasma proteins was not concentration-dependent.

Biotransformation
In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolised via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors.

Elimination
The mean elimination half-life ($t_{1/2}$) of bortezomib upon multiple dosing ranged from 40-193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 l/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 l/h and 18 to 32 l/h following subsequent doses for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively.

Special populations
Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed in a Phase I study during the first treatment cycle, including 61 patients primarily with solid tumors and varying degrees of hepatic impairment at bortezomib doses ranging from 0.5 to 1.3 mg/m^2.

When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalised bortezomib AUC. However, the dose-normalised mean AUC values were increased by approximately 60% in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be closely monitored (see section 4.2, Table 6).

Renal impairment
A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCL) into the following groups: Normal (CrCL $\geq$ 60 ml/min/1.73 m^2, n=12), Mild (CrCL=40-59 ml/min/1.73 m^2, n=10), Moderate (CrCL=20-39 ml/min/1.73 m^2, n=9), and Severe (CrCL < 20 ml/min/1.73 m^2, n=3). A group of dialysis patients who were dosed after dialysis was also included in the study (n=8). Patients were administered intravenous doses of 0.7 to 1.3 mg/m^2 of VELCADE twice weekly. Exposure of VELCADE (dose-normalised AUC and C_{max}) was comparable among all the groups (see section 4.2).

Age
The pharmacokinetics of bortezomib were characterized following twice weekly intravenous bolus administration of 1.3 mg/m^2 doses to 104 pediatric patients (2-16 years old) with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). Based on a population pharmacokinetic analysis, clearance of bortezomib increased with increasing body surface area (BSA). Geometric mean (%CV) clearance was 7.79 (25%) L/hr/m^2, volume of distribution at steady-state was 834 (39%) L/m^2, and the elimination half-life was 100 (44%) hours. After correcting for the BSA effect, other demographics such as age, body weight and sex did not have clinically significant effects on bortezomib clearance. BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

5.3 Preclinical safety data

Bortezomib was positive for clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary (CHO) cells at concentrations as low as 3.125 μg/ml, which was the lowest concentration evaluated. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames assay) and *in vivo* micronucleus assay in mice.

Developmental toxicity studies in the rat and rabbit have shown embryo-fetal lethality at maternally toxic doses, but no direct embryo-foetal toxicity below maternally toxic doses. Fertility studies were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6-month rat study, degenerative effects in both the testes and the ovary have been

observed. It is, therefore, likely that bortezomib could have a potential effect on either male or female fertility. Peri- and postnatal development studies were not conducted.

In multi-cycle general toxicity studies conducted in the rat and monkey, the principal target organs included the gastrointestinal tract, resulting in vomiting and/or diarrhoea; haematopoietic and lymphatic tissues, resulting in peripheral blood cytopenias, lymphoid tissue atrophy and haematopoietic bone marrow hypocellularity; peripheral neuropathy (observed in monkeys, mice and dogs) involving sensory nerve axons; and mild changes in the kidneys. All these target organs have shown partial to full recovery following discontinuation of treatment.

Based on animal studies, the penetration of bortezomib through the blood-brain barrier appears to be limited, if any and the relevance to humans is unknown.

Cardiovascular safety pharmacology studies in monkeys and dogs show that intravenous 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 death. In dogs, the decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. Moreover, in dog studies, a slight increase in the corrected QT interval was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E 421)
Nitrogen

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
3 years

Reconstituted solution
The reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. However, the chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 25°C stored in the original vial and/or a syringe. The total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration.

6.4 Special precautions for storage

Do not store above 30°C.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type 1 glass 5 ml-vial with a grey bromobutyl stopper and an aluminium seal, with a green cap containing 1 mg bortezomib.

The vial is contained in a transparent blister pack consisting of a tray with a lid. Each pack contains 1 single-use vial.

6.6 Special precautions for disposal and other handling

General precautions
Bortezomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation of VELCADE. Use of gloves and other protective clothing to prevent skin contact is recommended.

Aseptic technique must be strictly observed throughout the handling of VELCADE, since it contains no preservative.

There have been fatal cases of inadvertent intrathecal administration of VELCADE. VELCADE 1 mg powder for solution for injection is for intravenous use only, while VELCADE 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. VELCADE should not be administered intrathecally.

Instructions for reconstitution
VELCADE must be reconstituted by a healthcare professional.
Each 5 ml vial of VELCADE must be carefully reconstituted with 1 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a 1 ml syringe, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.
After reconstitution, each ml solution contains 1 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7.
The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

Disposal
VELCADE is for single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

JANSSEN-CILAG INTERNATIONAL NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER

EU/1/04/274/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 April 2004
Date of latest renewal: 10 January 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

VELCADE 3.5 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3.5 mg bortezomib (as a mannitol boronic ester).

After reconstitution, 1 ml of solution for subcutaneous injection contains 2.5 mg bortezomib.

After reconstitution, 1 ml of solution for intravenous injection contains 1 mg bortezomib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White to off-white cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VELCADE as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation.

VELCADE in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

VELCADE in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

VELCADE in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

4.2 Posology and method of administration

VELCADE treatment must be initiated under supervision of a physician experienced in the treatment of cancer patients, however VELCADE may be administered by a healthcare professional experienced in use of chemotherapeutic agents. VELCADE must be reconstituted by a healthcare professional (see section 6.6).

Posology for treatment of progressive multiple myeloma (patients who have received at least one prior therapy)

Monotherapy

VELCADE 3.5 mg powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. It

is recommended that patients receive 2 cycles of VELCADE following a confirmation of a complete response. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of VELCADE therapy. At least 72 hours should elapse between consecutive doses of VELCADE.

Dose adjustments during treatment and re-initiation of treatment for monotherapy
VELCADE treatment must be withheld at the onset of any Grade 3 non-haematological or any Grade 4 haematological toxicities, excluding neuropathy as discussed below (see also section 4.4). Once the symptoms of the toxicity have resolved, VELCADE treatment may be re-initiated at a 25% reduced dose (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of VELCADE must be considered unless the benefit of treatment clearly outweighs the risk.

Neuropathic pain and/or peripheral neuropathy
Patients who experience bortezomib-related neuropathic pain and/or peripheral neuropathy are to be managed as presented in Table 1 (see section 4.4). Patients with pre-existing severe neuropathy may be treated with VELCADE only after careful risk/benefit assessment.

Table 1: Recommended posology modifications for bortezomib-related neuropathy*

Severity of neuropathy	**Posology modification**
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or loss of function	None
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)**)	Reduce VELCADE to 1.0 mg/m^2 or Change VELCADE treatment schedule to 1.3 mg/m^2 once per week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL***)	Withhold VELCADE treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate VELCADE treatment and reduce dose to 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy	Discontinue VELCADE

* Based on posology modifications in Phase II and III multiple myeloma studies and post-marketing experience. Grading based on NCI Common Toxicity Criteria CTCAE v 4.0.
** *Instrumental ADL*: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc;
*** *Self care ADL*: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medicinal products, and not bedridden.

Combination therapy with pegylated liposomal doxorubicin
VELCADE 3.5 mg powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VELCADE.
Pegylated liposomal doxorubicin is administered at 30 mg/m² on day 4 of the VELCADE treatment cycle as a 1 hour intravenous infusion administered after the VELCADE injection.
Up to 8 cycles of this combination therapy can be administered as long as patients have not progressed and tolerate treatment. Patients achieving a complete response can continue treatment for at least 2 cycles after the first evidence of complete response, even if this requires treatment for more than 8 cycles. Patients whose levels of paraprotein continue to decrease after 8 cycles can also continue for as long as treatment is tolerated and they continue to respond.
For additional information concerning pegylated liposomal doxorubicin, see the corresponding Summary of Product Characteristics.

Combination with dexamethasone
VELCADE 3.5 mg powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on

days 1, 4, 8, and 11 in a 21 day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VELCADE.
Dexamethasone is administered orally at 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of the VELCADE treatment cycle.
Patients achieving a response or a stable disease after 4 cycles of this combination therapy can continue to receive the same combination for a maximum of 4 additional cycles.
For additional information concerning dexamethasone, see the corresponding Summary of Product Characteristics.

Dose adjustments for combination therapy for patients with progressive multiple myeloma
For VELCADE dosage adjustments for combination therapy follow dose modification guidelines described under monotherapy above.

Posology for previously untreated multiple myeloma patients not eligible for haematopoietic stem cell transplantation
Combination therapy with melphalan and prednisone
VELCADE 3.5 mg powder for solution for injection is administered via intravenous or subcutaneous injection in combination with oral melphalan and oral prednisone as shown in Table 2. A 6-week period is considered a treatment cycle. In Cycles 1-4, VELCADE is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32. In Cycles 5-9, VELCADE is administered once weekly on days 1, 8, 22 and 29. At least 72 hours should elapse between consecutive doses of VELCADE.
Melphalan and prednisone should both be given orally on days 1, 2, 3 and 4 of the first week of each VELCADE treatment cycle.
Nine treatment cycles of this combination therapy are administered.

Table 2: Recommended posology for VELCADE in combination with melphalan and prednisone

Twice weekly VELCADE (cycles 1-4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Vc (1.3 mg/m$^{2)}$	Day 1	--	--	Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	rest period
M (9 mg/m^2) P (60 mg/m$^{2)}$	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period
Once weekly VELCADE (cycles 5-9)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
Vc (1.3 mg/m$^{2)}$	Day 1	--	--	--	Day 8		rest period	Day 22		Day 29		rest period
M (9 mg/m^2) P (60 mg/m$^{2)}$	Day 1	Day 2	Day 3	Day 4	--		rest period	--				rest period

Vc=VELCADE; M=melphalan, P=prednisone

Dose adjustments during treatment and re-initiation of treatment for combination therapy with melphalan and prednisone
Prior to initiating a new cycle of therapy:
- Platelet counts should be ≥ 70 x 10^9/l and the absolute neutrophils count should be ≥ 1.0 x 10^9/l
- Non-haematological toxicities should have resolved to Grade 1 or baseline

Table 3: Posology modifications during subsequent cycles of VELCADE therapy in combination with melphalan and prednisone

Toxicity	**Posology modification or delay**
Haematological toxicity during a cycle • If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25% in the next cycle.
• If platelet counts ≤ 30 x 10^9/l or ANC ≤ 0.75 x 10^9/l on a VELCADE dosing day (other than day 1)	VELCADE therapy should be withheld

• If several VELCADE doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	VELCADE dose should be reduced by 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)
Grade ≥ 3 non-haematological toxicities	VELCADE therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, VELCADE may be reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For VELCADE-related neuropathic pain and/or peripheral neuropathy, hold and/or modify VELCADE as outlined in Table 1.

For additional information concerning melphalan and prednisone, see the corresponding Summary of Product Characteristics.

Posology for previously untreated multiple myeloma patients eligible for haematopoietic stem cell transplantation (induction therapy)

Combination therapy with dexamethasone

VELCADE 3.5 mg powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VELCADE.
Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the VELCADE treatment cycle.
Four treatment cycles of this combination therapy are administered.

Combination therapy with dexamethasone and thalidomide

VELCADE 3.5 mg powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 in a 28-day treatment cycle. This 4-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VELCADE.
Dexamethasone is administered orally at 40 mg on days 1, 2, 3, 4, 8, 9, 10 and 11 of the VELCADE treatment cycle.
Thalidomide is administered orally at 50 mg daily on days 1-14 and if tolerated the dose is increased to 100 mg on days 15-28, and thereafter may be further increased to 200 mg daily from cycle 2 (see Table 4).
Four treatment cycles of this combination are administered. It is recommended that patients with at least partial response receive 2 additional cycles.

Table 4: Posology for VELCADE combination therapy for patients with previously untreated multiple myeloma eligible for haematopoietic stem cell transplantation

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

Vc+Dx+T	**Cycle 1**				
	Week	**1**	**2**	**3**	**4**
	Vc (1.3 mg/m^2)	Day 1, 4	Day 8, 11	Rest Period	Rest Period
	T 50 mg	Daily	Daily	-	-
	T 100 mg[a]	-	-	Daily	Daily
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-	-
	Cycles 2 to 4[b]				
	Vc (1.3 mg/m^2)	Day 1, 4	Day 8, 11	Rest Period	Rest Period
	T 200 mg[a]	Daily	Daily	Daily	Daily
	Dx 40 mg	Day 1, 2, 3, 4	Day 8, 9, 10, 11	-	-

Vc=VELCADE; Dx=dexamethasone; T=thalidomide

[a] Thalidomide dose is increased to 100 mg from week 3 of Cycle 1 only if 50 mg is tolerated and to 200 mg from cycle 2 onwards if 100 mg is tolerated.

[b] Up to 6 cycles may be given to patients who achieve at least a partial response after 4 cycles

Dosage adjustments for transplant eligible patients
For VELCADE dosage adjustments, dose modification guidelines described for monotherapy should be followed.
In addition, when VELCADE is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these products should be considered in the event of toxicities according to the recommendations in the Summary of Product Characteristics.

Posology for patients with previously untreated mantle cell lymphoma (MCL)
Combination therapy with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP)
VELCADE 3.5 mg powder for solution for injection is administered via intravenous or subcutaneous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11, followed by a 10-day rest period on days 12-21. This 3-week period is considered a treatment cycle. Six VELCADE cycles are recommended, although for patients with a response first documented at cycle 6, two additional VELCADE cycles may be given. At least 72 hours should elapse between consecutive doses of VELCADE.

The following medicinal products are administered on day 1 of each VELCADE 3 week treatment cycle as intravenous infusions: rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2 and doxorubicin at 50 mg/m^2.
Prednisone is administered orally at 100 mg/m^2 on days 1, 2, 3, 4 and 5 of each VELCADE treatment cycle.

Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma
Prior to initiating a new cycle of therapy:

- Platelet counts should be ≥ 100,000 cells/μL and the absolute neutrophils count (ANC) should be ≥ 1,500 cells/μL
- Platelet counts should be ≥ 75,000 cells/μL in patients with bone marrow infiltration or splenic sequestration
- Haemoglobin ≥ 8 g/dL
- Non-haematological toxicities should have resolved to Grade 1 or baseline.

VELCADE treatment must be withheld at the onset of any ≥ Grade 3 VELCADE-related non-haematological toxicities (excluding neuropathy) or ≥ Grade 3 haematological toxicities (see also section 4.4). For dose adjustments, see Table 5 below.
Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration. Platelet transfusion for the treatment of thrombocytopenia should be considered when clinically appropriate.

Table 5: Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma

Toxicity	**Posology modification or delay**
Haematological toxicity	
• ≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10,000 cells/μL	VELCADE therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 750 cells/μL and a platelet count ≥ 25,000 cells/μL. • If, after VELCADE has been held, the toxicity does not resolve, as defined above, then VELCADE must be discontinued. • If toxicity resolves i.e. patient has an ANC ≥ 750 cells/μL and a platelet count ≥ 25,000 cells/μL, VELCADE may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2).
• If platelet counts < 25,000 cells/μL. or ANC < 750 cells/μL on a VELCADE dosing day (other than Day 1 of each cycle)	VELCADE therapy should be withheld
Grade ≥ 3 non-haematological toxicities considered to be related to VELCADE	VELCADE therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, VELCADE may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For VELCADE-related neuropathic pain and/or peripheral neuropathy, hold and/or modify VELCADE as outlined in Table 1.

In addition, when VELCADE is given in combination with other chemotherapeutic medicinal products, appropriate dose reductions for these medicinal products should be considered in the event of toxicities, according to the recommendations in the respective Summary of Product Characteristics.

Special populations

Elderly
There is no evidence to suggest that dose adjustments are necessary in patients over 65 years of age with multiple myeloma or with mantle cell lymphoma.
There are no studies on the use of VELCADE in elderly patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. Therefore no dose recommendations can be made in this population.
In a study in previously untreated mantle cell lymphoma patients, 42.9% and 10.4% of patients exposed to VELCADE were in the range 65-74 years and ≥ 75 years of age, respectively. In patients aged ≥ 75 years, both regimens, VcR-CAP as well as R-CHOP, were less tolerated (see section 4.8).

Hepatic impairment
Patients with mild hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. Patients with moderate or severe hepatic impairment should be started on VELCADE at a reduced dose of 0.7 mg/m^2 per injection during the first treatment cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerability (see Table 6 and sections 4.4 and 5.2).

Table 6: Recommended starting dose modification for VELCADE in patients with hepatic impairment

Grade of hepatic impairment*	**Bilirubin level**	**SGOT (AST) levels**	**Modification of starting dose**
Mild	≤ 1.0 x ULN	> ULN	None
	> 1.0 x –1.5 x ULN	Any	None
Moderate	> 1.5 x –3 x ULN	Any	Reduce VELCADE to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	> 3 x ULN	Any	

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

* Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).

Renal impairment

The pharmacokinetics of bortezomib are not influenced in patients with mild to moderate renal impairment (Creatinine Clearance [CrCL] > 20 ml/min/1.73 m^2); therefore, dose adjustments are not necessary for these patients. It is unknown if the pharmacokinetics of bortezomib are influenced in patients with severe renal impairment not undergoing dialysis (CrCL < 20 ml/min/1.73 m^2). Since dialysis may reduce bortezomib concentrations, VELCADE should be administered after the dialysis procedure (see section 5.2).

Paediatric population

The safety and efficacy of VELCADE in children below 18 years of age have not been established (see sections 5.1 and 5.2). Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

VELCADE 3.5 mg powder for solution for injection is available for intravenous or subcutaneous administration.

VELCADE 1 mg powder for solution for injection is available for intravenous administration only.

VELCADE should not be given by other routes. Intrathecal administration has resulted in death.

Intravenous injection

VELCADE 3.5 mg reconstituted solution is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with sodium chloride 9 mg/ml (0.9%) solution for injection. At least 72 hours should elapse between consecutive doses of VELCADE.

Subcutaneous injection

VELCADE 3.5 mg reconstituted solution is administered subcutaneously through the thighs (right or left) or abdomen (right or left). The solution should be injected subcutaneously, at a 45-90° angle. Injection sites should be rotated for successive injections.

If local injection site reactions occur following VELCADE subcutaneous injection, either a less concentrated VELCADE solution (VELCADE 3.5 mg to be reconstituted to 1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously or a switch to intravenous injection is recommended.

When VELCADE is given in combination with other medicinal products, refer to the Summary of Product Characteristics of these products for instructions for administration.

4.3 Contraindications

Hypersensitivity to the active substance, to boron or to any of the excipients listed in section 6.1.
Acute diffuse infiltrative pulmonary and pericardial disease.

When VELCADE is given in combination with other medicinal products, refer to their Summaries of Product Characteristics for additional contraindications.

4.4 Special warnings and precautions for use

When VELCADE is given in combination with other medicinal products, the Summary of Product Characteristics of these other medicinal products must be consulted prior to initiation of treatment with VELCADE. When thalidomide is used, particular attention to pregnancy testing and prevention requirements is needed (see section 4.6).

Intrathecal administration
There have been fatal cases of inadvertent intrathecal administration of VELCADE. VELCADE 1 mg powder for solution for injection is for intravenous use only, while VELCADE 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. VELCADE should not be administered intrathecally.

Gastrointestinal toxicity
Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with VELCADE treatment. Cases of ileus have been uncommonly reported (see section 4.8). Therefore, patients who experience constipation should be closely monitored.

Haematological toxicity
VELCADE treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). In studies in patients with relapsed multiple myeloma treated with VELCADE and in patients with previously untreated MCL treated with VELCADE in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP), one of the most common haematologic toxicity was transient thrombocytopenia. Platelets were lowest at Day 11 of each cycle of VELCADE treatment and typically recovered to baseline by the next cycle. There was no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured was approximately 40% of baseline in the single-agent multiple myeloma studies and 50% in the MCL study. In patients with advanced myeloma the severity of thrombocytopenia was related to pre-treatment platelet count: for baseline platelet counts < 75,000/µl, 90% of 21 patients had a count ≤ 25,000/µl during the study, including 14% < 10,000/µl; in contrast, with a baseline platelet count > 75,000/µl, only 14% of 309 patients had a count ≤ 25,000/µl during the study.

In patients with MCL (study LYM-3002), there was a higher incidence (56.7% versus 5.8%) of Grade ≥ 3 thrombocytopenia in the VELCADE treatment group (VcR-CAP) as compared to the non-VELCADE treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]). The two treatment groups were similar with regard to the overall incidence of all-grade bleeding events (6.3% in the VcR-CAP group and 5.0% in the R-CHOP group) as well as Grade 3 and higher bleeding events (VcR-CAP: 4 patients [1.7%]; R-CHOP: 3 patients [1.2%]). In the VcR-CAP group, 22.5% of patients received platelet transfusions compared to 2.9% of patients in the R-CHOP group.

Gastrointestinal and intracerebral haemorrhage, have been reported in association with VELCADE treatment. Therefore, platelet counts should be monitored prior to each dose of VELCADE. VELCADE therapy should be withheld when the platelet count is < 25,000/µl or, in the case of combination with melphalan and prednisone, when the platelet count is ≤ 30,000/µl (see section 4.2). Potential benefit of the treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding.

Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment with VELCADE. Platelet transfusion should be considered when clinically appropriate (see section 4.2).

In patients with MCL, transient neutropenia that was reversible between cycles was observed, with no evidence of cumulative neutropenia. Neutrophils were lowest at Day 11 of each cycle of VELCADE treatment and typically recovered to baseline by the next cycle. In study LYM-3002, colony stimulating factor support was given to 78% of patients in the VcR-CAP arm and 61% of patients in the R-CHOP arm. Since patients with neutropenia are at increased risk of infections, they should be monitored for signs and symptoms of infection and treated promptly. Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration (see section 4.2).

Herpes zoster virus reactivation
Antiviral prophylaxis is recommended in patients being treated with VELCADE.
In the Phase III study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more common in patients treated with VELCADE+Melphalan+Prednisone compared with Melphalan+Prednisone (14% versus 4% respectively).
In patients with MCL (study LYM-3002), the incidence of herpes zoster infection was 6.7% in the VcR-CAP arm and 1.2% in the R-CHOP arm (see section 4.8).

Hepatitis B Virus (HBV) reactivation and infection
When rituximab is used in combination with VELCADE, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Carriers of hepatitis B and patients with a history of hepatitis B must be closely monitored for clinical and laboratory signs of active HBV infection during and following rituximab combination treatment with VELCADE. Antiviral prophylaxis should be considered. Refer to the Summary of Product Characteristics of rituximab for more information.

Progressive multifocal leukoencephalopathy (PML)
Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with VELCADE. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of VELCADE. Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue VELCADE if PML is diagnosed.

Peripheral neuropathy
Treatment with VELCADE is very commonly associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. The incidence of peripheral neuropathy increases early in the treatment and has been observed to peak during cycle 5.

It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness.

In the Phase III study comparing VELCADE administered intravenously versus subcutaneously, the incidence of Grade ≥ 2 peripheral neuropathy events was 24% for the subcutaneous injection group and 41% for the intravenous injection group (p=0.0124). Grade ≥ 3 peripheral neuropathy occurred in 6% of patients in the subcutaneous treatment group, compared with 16% in the intravenous treatment group (p=0.0264). The incidence of all grade peripheral neuropathy with VELCADE administered intravenously was lower in the historical studies with VELCADE administered intravenously than in study MMY-3021.

Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require a change in the dose, schedule or route of administration to subcutaneous (see section 4.2). Neuropathy has been managed with supportive care and other therapies.

Early and regular monitoring for symptoms of treatment-emergent neuropathy with neurological evaluation should be considered in patients receiving VELCADE in combination with medicinal products known to be associated with neuropathy (e.g. thalidomide) and appropriate dose reduction or treatment discontinuation should be considered.

In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited.

Seizures
Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.

Hypotension
VELCADE treatment is commonly associated with orthostatic/postural hypotension. Most adverse reactions are mild to moderate in nature and are observed throughout treatment. Patients who developed orthostatic hypotension on VELCADE (injected intravenously) did not have evidence of orthostatic hypotension prior to treatment with VELCADE. Most patients required treatment for their orthostatic hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Orthostatic/postural hypotension was not acutely related to bolus infusion of VELCADE. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to bortezomib or bortezomib may aggravate an underlying condition such as diabetic or amyloidotic neuropathy. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicinal products, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

Posterior Reversible Encephalopathy Syndrome (PRES)
There have been reports of *PRES* in patients receiving VELCADE. *PRES* is a rare, often reversible, rapidly evolving neurological condition, which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably Magnetic Resonance Imaging (MRI), is used to confirm the diagnosis. In patients developing PRES, VELCADE should be discontinued.

Heart failure
Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Patients with risk factors for or existing heart disease should be closely monitored.

Electrocardiogram investigations
There have been isolated cases of QT-interval prolongation in clinical studies, causality has not been established.

Pulmonary disorders
There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration, and acute respiratory distress syndrome (ARDS) in patients receiving VELCADE (see section 4.8). Some of these events have been fatal. A pre-treatment chest radiograph is recommended to serve as a baseline for potential post-treatment pulmonary changes.

In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients treated appropriately. The benefit/risk ratio should be considered prior to continuing VELCADE therapy.

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

Renal impairment
Renal complications are frequent in patients with multiple myeloma. Patients with renal impairment should be monitored closely (see sections 4.2 and 5.2).

Hepatic impairment
Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with VELCADE at reduced doses and closely monitored for toxicities (see sections 4.2 and 5.2).

Hepatic reactions
Rare cases of hepatic failure have been reported in patients receiving VELCADE and concomitant medicinal products and with serious underlying medical conditions. Other reported hepatic reactions include increases in liver enzymes, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib (see section 4.8).

Tumour lysis syndrome
Because bortezomib is a cytotoxic agent and can rapidly kill malignant plasma cells and MCL cells, the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Concomitant medicinal products
Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates (see section 4.5).

Normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycemics (see section 4.5).

Potentially immunocomplex-mediated reactions
Potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis have been reported uncommonly. Bortezomib should be discontinued if serious reactions occur.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies indicate that bortezomib is a weak inhibitor of the cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. Based on the limited contribution (7%) of CYP2D6 to the metabolism of bortezomib, the CYP2D6 poor metaboliser phenotype is not expected to affect the overall disposition of bortezomib.

A drug-drug interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC increase of 35% ($CI_{90\%}$ [1.032 to 1.772]) based on data from 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

In a drug-drug interaction study assessing the effect of omeprazole, a potent CYP2C19 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of bortezomib based on data from 17 patients.

A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC reduction of 45% based on data from 6 patients. Therefore, the concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced.

In the same drug-drug interaction study assessing the effect of dexamethasone, a weaker CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of bortezomib based on data from 7 patients.

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

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy
No clinical data are available for bortezomib with regard to exposure during pregnancy. The teratogenic potential of bortezomib has not been fully investigated.

In non-clinical studies, bortezomib had no effects on embryonal/foetal development in rats and rabbits at the highest maternally tolerated doses. Animal studies to determine the effects of bortezomib on parturition and post-natal development were not conducted (see section 5.3). VELCADE should not be used during pregnancy unless the clinical condition of the woman requires treatment with VELCADE. If VELCADE is used during pregnancy, or if the patient becomes pregnant while receiving this medicinal product, the patient should be informed of potential for hazard to the foetus.

Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Thalidomide is contraindicated during pregnancy and in women of childbearing potential unless all the conditions of the thalidomide pregnancy prevention programme are met. Patients receiving VELCADE in combination with thalidomide should adhere to the pregnancy prevention programme of thalidomide. Refer to the Summary of Product Characteristics of thalidomide for additional information.

Breast-feeding
It is not known whether bortezomib is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants, breast-feeding should be discontinued during treatment with VELCADE.

Fertility
Fertility studies were not conducted with VELCADE (see section 5.3).

4.7 Effects on ability to drive and use machines

VELCADE may have a moderate influence on the ability to drive and use machines. VELCADE may be associated with fatigue very commonly, dizziness commonly, syncope uncommonly and orthostatic/postural hypotension or blurred vision commonly. Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
Serious adverse reactions uncommonly reported during treatment with VELCADE include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and rarely autonomic neuropathy.
The most commonly reported adverse reactions during treatment with VELCADE are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

Tabulated summary of adverse reactions
Multiple Myeloma
Undesirable effects in Table 7 were considered by the investigators to have at least a possible or probable causal relationship to VELCADE. These adverse reactions are based on an integrated data set of 5,476 patients of whom 3,996 were treated with VELCADE at 1.3 mg/m^2 and included in Table 7. Overall, VELCADE was administered for the treatment of multiple myeloma in 3,974 patients.

Adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Table 7 has been generated using Version 14.1 of the MedDRA.
Post-marketing adverse reactions not seen in clinical trials are also included.

Table 7: Adverse reactions in patients with Multiple Myeloma treated with VELCADE in clinical trials, and all post-marketing adverse reactions regardless of indication[#]

System Organ Class	Incidence	Adverse reaction
Infections and infestations	Common	Herpes zoster (inc disseminated & ophthalmic), Pneumonia*, Herpes simplex*, Fungal infection*
	Uncommon	Infection*, Bacterial infections*, Viral infections*, Sepsis (inc septic shock)*, Bronchopneumonia, Herpes virus infection*, Meningoencephalitis herpetic[#], Bacteraemia (inc staphylococcal), Hordeolum, Influenza, Cellulitis, Device related infection, Skin infection*, Ear infection*, Staphylococcal infection, Tooth infection*
	Rare	Meningitis (inc bacterial), Epstein-Barr virus infection, Genital herpes, Tonsillitis, Mastoiditis, Post viral fatigue syndrome
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rare	Neoplasm malignant, Leukaemia plasmacytic, Renal cell carcinoma, Mass, Mycosis fungoides, Neoplasm benign*
Blood and lymphatic system disorders	Very Common	Thrombocytopenia*, Neutropenia*, Anaemia*
	Common	Leukopenia*, Lymphopenia*
	Uncommon	Pancytopenia*, Febrile neutropenia, Coagulopathy*, Leukocytosis*, Lymphadenopathy, Haemolytic anaemia[#]

	Rare	Disseminated intravascular coagulation, Thrombocytosis*, Hyperviscosity syndrome, Platelet disorder NOS, Thrombotic microangiopathy (inc thrombocytopenic purpura)[#], Blood disorder NOS, Haemorrhagic diathesis, Lymphocytic infiltration
Immune system disorders	Uncommon	Angioedema[#], Hypersensitivity*
	Rare	Anaphylactic shock, Amyloidosis, Type III immune complex mediated reaction
Endocrine disorders	Uncommon	Cushing's syndrome*, Hyperthyroidism*, Inappropriate antidiuretic hormone secretion
	Rare	Hypothyroidism
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Dehydration, Hypokalaemia*, Hyponatraemia*, Blood glucose abnormal*, Hypocalcaemia*, Enzyme abnormality*
	Uncommon	Tumour lysis syndrome, Failure to thrive*, Hypomagnesaemia*, Hypophosphataemia*, Hyperkalaemia*, Hypercalcaemia*, Hypernatraemia*, Uric acid abnormal*, Diabetes mellitus*, Fluid retention
	Rare	Hypermagnesaemia*, Acidosis, Electrolyte imbalance*, Fluid overload, Hypochloraemia*, Hypovolaemia, Hyperchloraemia*, Hyperphosphataemia*, Metabolic disorder, Vitamin B complex deficiency, Vitamin B12 deficiency, Gout, Increased appetite, Alcohol intolerance
Psychiatric disorders	Common	Mood disorders and disturbances*, Anxiety disorder*, Sleep disorders and disturbances*
	Uncommon	Mental disorder*, Hallucination*, Psychotic disorder*, Confusion*, Restlessness
	Rare	Suicidal ideation*, Adjustment disorder, Delirium, Libido decreased
Nervous system disorders	Very Common	Neuropathies*, Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	Common	Motor neuropathy*, Loss of consciousness (inc syncope), Dizziness*, Dysgeusia*, Lethargy, Headache*
	Uncommon	Tremor, Peripheral sensorimotor neuropathy, Dyskinesia*, Cerebellar coordination and balance disturbances*, Memory loss (exc dementia)*, Encephalopathy*, Posterior Reversible Encephalopathy Syndrome[#], Neurotoxicity, Seizure disorders*, Post herpetic neuralgia, Speech disorder*, Restless legs syndrome, Migraine, Sciatica, Disturbance in attention, Reflexes abnormal*, Parosmia
	Rare	Cerebral haemorrhage*, Haemorrhage intracranial (inc subarachnoid)*, Brain oedema, Transient ischaemic attack, Coma, Autonomic nervous system imbalance, Autonomic neuropathy, Cranial palsy*, Paralysis*, Paresis*, Presyncope, Brain stem syndrome, Cerebrovascular disorder, Nerve root lesion, Psychomotor hyperactivity, Spinal cord compression, Cognitive disorder NOS, Motor dysfunction, Nervous system disorder NOS, Radiculitis, Drooling, Hypotonia
Eye disorders	Common	Eye swelling*, Vision abnormal*, Conjunctivitis*
	Uncommon	Eye haemorrhage*, Eyelid infection*, Chalazion[#], Blepharitis[#], Eye inflammation*, Diplopia, Dry eye*, Eye irritation*, Eye pain, Lacrimation increased, Eye discharge
	Rare	Corneal lesion*, Exophthalmos, Retinitis, Scotoma, Eye disorder (inc. eyelid) NOS, Dacryoadenitis acquired, Photophobia, Photopsia, Optic neuropathy[#], Different degrees of visual impairment (up to blindness)*

Ear and labyrinth disorders	Common	Vertigo*
	Uncommon	Dysacusis (inc tinnitus)*,Hearing impaired (up to and inc deafness), Ear discomfort*
	Rare	Ear haemorrhage, Vestibular neuronitis, Ear disorder NOS
Cardiac disorders	Uncommon	Cardiac tamponade[#], Cardio-pulmonary arrest*, Cardiac fibrillation (inc atrial), Cardiac failure (inc left and right ventricular)*, Arrhythmia*, Tachycardia*, Palpitations, Angina pectoris, Pericarditis (inc pericardial effusion)*, Cardiomyopathy*, Ventricular dysfunction*, Bradycardia
	Rare	Atrial flutter, Myocardial infarction*, Atrioventricular block*, Cardiovascular disorder (inc cardiogenic shock), Torsade de pointes, Angina unstable, Cardiac valve disorders*, Coronary artery insufficiency, Sinus arrest
Vascular disorders	Common	Hypotension*, Orthostatic hypotension, Hypertension*
	Uncommon	Cerebrovascular accident[#], Deep vein thrombosis*, Haemorrhage*, Thrombophlebitis (inc superficial), Circulatory collapse (inc hypovolaemic shock), Phlebitis, Flushing*, Haematoma (inc perirenal)*, Poor peripheral circulation*, Vasculitis, Hyperaemia (inc ocular)*
	Rare	Peripheral embolism, Lymphoedema, Pallor, Erythromelalgia, Vasodilatation, Vein discolouration, Venous insufficiency
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Epistaxis, Upper/lower respiratory tract infection*, Cough*
	Uncommon	Pulmonary embolism, Pleural effusion, Pulmonary oedema (inc acute), Pulmonary alveolar haemorrhage[#], Bronchospasm, Chronic obstructive pulmonary disease*, Hypoxaemia*, Respiratory tract congestion*, Hypoxia, Pleurisy*, Hiccups, Rhinorrhoea, Dysphonia, Wheezing
	Rare	Respiratory failure, Acute respiratory distress syndrome, Apnoea, Pneumothorax, Atelectasis, Pulmonary hypertension, Haemoptysis, Hyperventilation, Orthopnoea, Pneumonitis, Respiratory alkalosis, Tachypnoea, Pulmonary fibrosis, Bronchial disorder*, Hypocapnia*, Interstitial lung disease, Lung infiltration, Throat tightness, Dry throat, Increased upper airway secretion, Throat irritation, Upper-airway cough syndrome
Gastrointestinal disorders	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Constipation
	Common	Gastrointestinal haemorrhage (inc mucosal)*, Dyspepsia, Stomatitis*, Abdominal distension, Oropharyngeal pain*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*, Flatulence
	Uncommon	Pancreatitis (inc chronic)*, Haematemesis, Lip swelling*, Gastrointestinal obstruction (inc small intestinal obstruction, ileus)*, Abdominal discomfort, Oral ulceration*, Enteritis*, Gastritis*, Gingival bleeding, Gastrooesophageal reflux disease*, Colitis (inc clostridium difficile)*, Colitis ischaemic[#], Gastrointestinal inflammation*, Dysphagia, Irritable bowel syndrome, Gastrointestinal disorder NOS, Tongue coated, Gastrointestinal motility disorder*, Salivary gland disorder*

	Rare	Pancreatitis acute, Peritonitis*, Tongue oedema*, Ascites, Oesophagitis, Cheilitis, Faecal incontinence, Anal sphincter atony, Faecaloma*, Gastrointestinal ulceration and perforation*, Gingival hypertrophy, Megacolon, Rectal discharge, Oropharyngeal blistering*, Lip pain, Periodontitis, Anal fissure, Change of bowel habit, Proctalgia, Abnormal faeces
Hepatobiliary disorders	Common	Hepatic enzyme abnormality*
	Uncommon	Hepatotoxicity (inc liver disorder), Hepatitis*, Cholestasis
	Rare	Hepatic failure, Hepatomegaly, Budd-Chiari syndrome, Cytomegalovirus hepatitis, Hepatic haemorrhage, Cholelithiasis
Skin and subcutaneous tissue disorders	Common	Rash*, Pruritus*, Erythema, Dry skin
	Uncommon	Erythema multiforme, Urticaria, Acute febrile neutrophilic dermatosis, Toxic skin eruption, Toxic epidermal necrolysis[#], Stevens-Johnson syndrome[#], Dermatitis*, Hair disorder*, Petechiae, Ecchymosis, Skin lesion, Purpura, Skin mass*, Psoriasis, Hyperhidrosis, Night sweats, Decubitus ulcer[#], Acne*, Blister*, Pigmentation disorder*
	Rare	Skin reaction, Jessner's lymphocytic infiltration, Palmar-plantar erythrodysaesthesia syndrome, Haemorrhage subcutaneous, Livedo reticularis, Skin induration, Papule, Photosensitivity reaction, Seborrhoea, Cold sweat, Skin disorder NOS, Erythrosis, Skin ulcer, Nail disorder
Musculoskeletal and connective tissue disorders	Very Common	Musculoskeletal pain*
	Common	Muscle spasms*, Pain in extremity, Muscular weakness
	Uncommon	Muscle twitching, Joint swelling, Arthritis*, Joint stiffness, Myopathies*,Sensation of heaviness
	Rare	Rhabdomyolysis, Temporomandibular joint syndrome, Fistula, Joint effusion, Pain in jaw, Bone disorder, Musculoskeletal and connective tissue infections and inflammations*, Synovial cyst
Renal and urinary disorders	Common	Renal impairment*
	Uncommon	Renal failure acute, Renal failure chronic*, Urinary tract infection*, Urinary tract signs and symptoms*, Haematuria*, Urinary retention, Micturition disorder*, Proteinuria, Azotaemia, Oliguria*, Pollakiuria
	Rare	Bladder irritation
Reproductive system and breast disorders	Uncommon	Vaginal haemorrhage, Genital pain*, Erectile dysfunction,
	Rare	Testicular disorder*, Prostatitis, Breast disorder female, Epididymal tenderness, Epididymitis, Pelvic pain, Vulval ulceration
Congenital, familial and genetic disorders	Rare	Aplasia, Gastrointestinal malformation, Ichthyosis
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc peripheral), Chills, Pain*, Malaise*
	Uncommon	General physical health deterioration*, Face oedema*, Injection site reaction*, Mucosal disorder*, Chest pain, Gait disturbance, Feeling cold, Extravasation*, Catheter related complication*, Change in thirst*, Chest discomfort, Feeling of body temperature change*, Injection site pain*

	Rare	Death (inc sudden), Multi-organ failure, Injection site haemorrhage*, Hernia(inc hiatus)*, Impaired healing*, Inflammation, Injection site phlebitis*, Tenderness, Ulcer, Irritability, Non-cardiac chest pain, Catheter site pain, Sensation of foreign body
Investigations	Common	Weight decreased
	Uncommon	Hyperbilirubinaemia*, Protein analyses abnormal*, Weight increased, Blood test abnormal*,C-reactive protein increased
	Rare	Blood gases abnormal*, Electrocardiogram abnormalities (inc QT prolongation)*, International normalised ratio abnormal*, Gastric pH decreased, Platelet aggregation increased, Troponin I increased, Virus identification and serology*, Urine analysis abnormal*
Injury, poisoning and procedural complications	Uncommon	Fall, Contusion
	Rare	Transfusion reaction, Fractures*, Rigors*, Face injury, Joint injury*, Burns, Laceration, Procedural pain, Radiation injuries*
Surgical and medical procedures	Rare	Macrophage activation

NOS=not otherwise specified

* Grouping of more than one MedDRA preferred term.

Post-marketing adverse reaction regardless of indication

Mantle Cell Lymphoma (MCL)

The safety profile of VELCADE in 240 MCL patients treated with VELCADE at 1.3 mg/m^2 in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP) versus 242 patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] was relatively consistent to that observed in patients with multiple myeloma with main differences described below. Additional adverse drug reactions identified associated with the use of the combination therapy (VcR-CAP) were hepatitis B infection (< 1%) and myocardial ischaemia (1.3%). The similar incidences of these events in both treatment arms, indicated that these adverse drug reactions are not attributable to VELCADE alone. Notable differences in the MCL patient population as compared to patients in the multiple myeloma studies were a ≥ 5% higher incidence of the haematological adverse reactions (neutropenia, thrombocytopenia, leukopenia, anemia, lymphopenia), peripheral sensory neuropathy, hypertension, pyrexia, pneumonia, stomatitis, and hair disorders.

Adverse drug reactions identified as those with a ≥ 1% incidence, similar or higher incidence in the VcR-CAP arm and with at least a possible or probable causal relationship to the components of the VcR-CAP arm, are listed in Table 8 below. Also included are adverse drug reactions identified in the VcR-CAP arm that were considered by investigators to have at least a possible or probable causal relationship to VELCADE based on historical data in the multiple myeloma studies.

Adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Table 8 has been generated using Version 16 of the MedDRA.

Table 8: Adverse reactions in patients with Mantle Cell Lymphoma treated with VcR-CAP in a clinical trial

System Organ Class	**Incidence**	**Adverse reaction**
Infections and	Very Common	Pneumonia*

infestations	Common	Sepsis (inc septic shock)*, Herpes zoster (inc disseminated & ophthalmic), Herpes virus infection*, Bacterial infections*, Upper/lower respiratory tract infection*, Fungal infection*, Herpes simplex*
	Uncommon	Hepatitis B, Infection*, Bronchopneumonia
Blood and lymphatic system disorders	Very Common	Thrombocytopenia*, Febrile neutropenia, Neutropenia*, Leukopenia*, Anaemia*, Lymphopenia*
	Uncommon	Pancytopenia*
Immune system disorders	Common	Hypersensitivity*
	Uncommon	Anaphylactic reaction
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Hypokalaemia*, Blood glucose abnormal*, Hyponatraemia*, Diabetes mellitus*, Fluid retention
	Uncommon	Tumour lysis syndrome
Psychiatric disorders	Common	Sleep disorders and disturbances*
Nervous system disorders	Very Common	Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	Common	Neuropathies*, Motor neuropathy*, Loss of consciousness (inc syncope), Encephalopathy*, Peripheral sensorimotor neuropathy, Dizziness*, Dysgeusia*, Autonomic neuropathy
	Uncommon	Autonomic nervous system imbalance
Eye disorders	Common	Vision abnormal*
Ear and labyrinth disorders	Common	Dysacusis (inc tinnitus)*
	Uncommon	Vertigo*, Hearing impaired (up to and inc deafness)
Cardiac disorders	Common	Cardiac fibrillation (inc atrial), Arrhythmia*, Cardiac failure (inc left and right ventricular)*, Myocardial ischaemia, Ventricular dysfunction*
	Uncommon	Cardiovascular disorder (inc cardiogenic shock)
Vascular disorders	Common	Hypertension*, Hypotension*, Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Cough*, Hiccups
	Uncommon	Acute respiratory distress syndrome, Pulmonary embolism, Pneumonitis, Pulmonary hypertension, Pulmonary oedema (inc acute)
Gastrointestinal disorders	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Stomatitis*, Constipation
	Common	Gastrointestinal haemorrhage (inc mucosal)*, Abdominal distension, Dyspepsia, Oropharyngeal pain*, Gastritis*, Oral ulceration*, Abdominal discomfort, Dysphagia, Gastrointestinal inflammation*, Abdominal pain (inc gastrointestinal and splenic pain)*, Oral disorder*
	Uncommon	Colitis (inc clostridium difficile)*
Hepatobiliary disorders	Common	Hepatotoxicity (inc liver disorder)
	Uncommon	Hepatic failure
Skin and subcutaneous tissue disorders	Very Common	Hair disorder*
	Common	Pruritus*, Dermatitis*, Rash*
Musculoskeletal and connective tissue disorders	Common	Muscle spasms*, Musculoskeletal pain*, Pain in extremity
Renal and urinary disorders	Common	Urinary tract infection*
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc peripheral), Chills, Injection site reaction*, Malaise*
Investigations	Common	Hyperbilirubinaemia*, Protein analyses abnormal*, Weight decreased, Weight increased

* Grouping of more than one MedDRA preferred term.

Description of selected adverse reactions

Herpes zoster virus reactivation

Multiple Myeloma

Antiviral prophylaxis was administered to 26% of the patients in the Vc+M+P arm. The incidence of herpes zoster among patients in the Vc+M+P treatment group was 17% for patients not administered antiviral prophylaxis compared to 3% for patients administered antiviral prophylaxis.

Mantle cell lymphoma

Antiviral prophylaxis was administered to 137 of 240 patients (57%) in the VcR-CAP arm. The incidence of herpes zoster among patients in the VcR-CAP arm was 10.7% for patients not administered antiviral prophylaxis compared to 3.6% for patients administered antiviral prophylaxis (see section 4.4).

Hepatitis B Virus (HBV) reactivation and infection

Mantle cell lymphoma

HBV infection with fatal outcomes occurred in 0.8% (n=2) of patients in the non-VELCADE treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP) and 0.4% (n=1) of patients receiving VELCADE in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP). The overall incidence of hepatitis B infections was similar in patients treated with VcR-CAP or with R-CHOP (0.8% vs 1.2% respectively).

Peripheral neuropathy in combination regimens

Multiple Myeloma

In trials in which VELCADE was administered as induction treatment in combination with dexamethasone (study IFM-2005-01), and dexamethasone-thalidomide (study MMY-3010), the incidence of peripheral neuropathy in the combination regimens is presented in the table below:

Table 9: Incidence of peripheral neuropathy during induction treatment by toxicity and treatment discontinuation due to peripheral neuropathy

	IFM-2005-01		MMY-3010	
	VDDx (N=239)	VcDx (N=239)	TDx (N=126)	VcTDx (N=130)
Incidence of PN (%)				
All GradePN	3	15	12	45
≥ Grade 2 PN	1	10	2	31
≥ Grade 3 PN	< 1	5	0	5
Discontinuation due to PN (%)	< 1	2	1	5

VDDx=vincristine, doxorubicin, dexamethasone; VcDx=VELCADE, dexamethasone; TDx=thalidomide, dexamethasone; VcTDx=VELCADE, thalidomide, dexamethasone; PN=peripheral neuropathy

Note: Peripheral neuropathy included the preferred terms: neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

Mantle cell lymphoma

In study LYM-3002 in which VELCADE was administered with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CAP), the incidence of peripheral neuropathy in the combination regimens is presented in the table below:

Table 10: Incidence of peripheral neuropathy in study LYM-3002 by toxicity and treatment discontinuation due to peripheral neuropathy

	VcR-CAP (N=240)	R-CHOP (N=242)
Incidence of PN (%)		
All GradePN	30	29
≥ Grade 2 PN	18	9
≥ Grade 3 PN	8	4
Discontinuation due to PN (%)	2	< 1

VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP= rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; PN=peripheral neuropathy
Peripheral neuropathy included the preferred terms: peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

Elderly MCL patients
42.9% and 10.4% of patients in the VcR-CAP arm were in the range 65-74 years and ≥ 75 years of age, respectively. Although in patients aged ≥ 75 years, both VcR-CAP and R-CHOP were less tolerated, the serious adverse event rate in the VcR-CAP groups was 68%, compared to 42% in the R-CHOP group.

Notable differences in the safety profile of VELCADE administered subcutaneously versus intravenously as single agent
In the Phase III study patients who received VELCADE subcutaneously compared to intravenous administration had 13% lower overall incidence of treatment emergent adverse reactions that were Grade 3 or higher in toxicity, and a 5% lower incidence of discontinuation of VELCADE. The overall incidence of diarrhoea, gastrointestinal and abdominal pain, asthenic conditions, upper respiratory tract infections and peripheral neuropathies were 12%-15% lower in the subcutaneous group than in the intravenous group. In addition, the incidence of Grade 3 or higher peripheral neuropathies was 10% lower, and the discontinuation rate due to peripheral neuropathies 8% lower for the subcutaneous group as compared to the intravenous group.

Six percent of patients had an adverse local reaction to subcutaneous administration, mostly redness. Cases resolved in a median of 6 days, dose modification was required in two patients. Two (1%) of the patients had severe reactions; 1 case of pruritus and 1 case of redness.

The incidence of death on treatment was 5% in the subcutaneous treatment group and 7% in the intravenous treatment group. Incidence of death from "Progressive disease" was 18% in the subcutaneous group and 9% in the intravenous group.

Retreatment of patients with relapsed multiple myeloma
In a study in which VELCADE retreatment was administered in 130 patients with relapsed multiple myeloma, who previously had at least partial response on a VELCADE-containing regimen, the most common all-grade adverse events occurring in at least 25% of patients were thrombocytopenia (55%), neuropathy (40%), anaemia (37%), diarrhoea (35%), and constipation (28%). All grade peripheral neuropathy and grade ≥ 3 peripheral neuropathy were observed in 40% and 8.5% of patients, respectively.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In patients, overdose more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes. For preclinical cardiovascular safety pharmacology studies, see section 5.3.

There is no known specific antidote for bortezomib overdose. In the event of an overdose, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature (see sections 4.2 and 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX32.

Mechanism of action
Bortezomib is a proteasome inhibitor. It is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death.

Bortezomib is highly selective for the proteasome. At 10 μM concentrations, bortezomib does not inhibit any of a wide variety of receptors and proteases screened and is more than 1,500-fold more selective for the proteasome than for its next preferable enzyme. The kinetics of proteasome inhibition were evaluated *in vitro*, and bortezomib was shown to dissociate from the proteasome with a $t_{½}$ of 20 minutes, thus demonstrating that proteasome inhibition by bortezomib is reversible.

Bortezomib mediated proteasome inhibition affects cancer cells in a number of ways, including, but not limited to, altering regulatory proteins, which control cell cycle progression and nuclear factor kappa B (NF-kB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF-kB is a transcription factor whose activation is required for many aspects of tumourigenesis, including cell growth and survival, angiogenesis, cell-cell interactions, and metastasis. In myeloma, bortezomib affects the ability of myeloma cells to interact with the bone marrow microenvironment.

Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types and that cancer cells are more sensitive to the pro-apoptotic effects of proteasome inhibition than normal cells. Bortezomib causes reduction of tumour growth *in vivo* in many preclinical tumour models, including multiple myeloma.

Data from *in vitro*, *ex-vivo*, and animal models with bortezomib suggest that it increases osteoblast differentiation and activity and inhibits osteoclast function. These effects have been observed in patients with multiple myeloma affected by an advanced osteolytic disease and treated with bortezomib.

Clinical efficacy in previously untreated multiple myeloma
A prospective Phase III, international, randomised (1:1), open-label clinical study (MMY-3002 VISTA) of 682 patients was conducted to determine whether VELCADE (1.3 mg/m^2 injected intravenously) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in patients with previously untreated multiple myeloma. Treatment was administered for a maximum of 9 cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. The median age of the patients in the study was 71 years, 50% were male, 88% were Caucasian and the median Karnofsky performance status score for the patients was 80. Patients had IgG/IgA/Light chain myeloma in 63%/25%/8% instances, a median hemoglobin of 105 g/l, and a median platelet count of 221.5 x 10^9/l. Similar proportions of patients had creatinine clearance ≤ 30 ml/min (3% in each arm).
At the time of a pre-specified interim analysis, the primary endpoint, time to progression, was met and patients in the M+P arm were offered Vc+M+P treatment. Median follow-up was 16.3 months. The final survival update was performed with a median duration of follow-up of 60.1 months. A statistically significant survival benefit in favour of the Vc+M+P treatment group was observed (HR=0.695; p=0.00043) despite subsequent therapies including VELCADE-based regimens. Median survival for the Vc+M+P treatment group was 56.4 months compared to 43.1 for the M+P treatment group. Efficacy results are presented in Table 11:

Table 11: Efficacy results following the final survival update to VISTA study

Efficacy endpoint	**Vc+M+P n=344**	**M+P n=338**
Time to progression		
Events n (%)	101 (29)	152 (45)
Median[a] (95% CI)	20.7 mo (17.6, 24,7)	15.0 mo (14.1, 17.9)
Hazard ratio[b] (95% CI)	0.54 (0.42, 0.70)	
p-value[c]	0.000002	
Progression-free survival		
Events n (%)	135 (39)	190 (56)
Median[a] (95% CI)	18.3 mo (16.6, 21.7)	14.0 mo (11.1, 15.0)
Hazard ratio[b] (95% CI)	0.61 (0.49, 0.76)	
p-value [c]	0.00001	
Overall survival*		
Events (deaths) n (%)	176 (51.2)	211 (62.4)
Median[a] (95% CI)	56.4 mo (52.8, 60.9)	43.1 mo (35.3, 48.3)
Hazard ratio[b] (95% CI)	0.695 (0.567, 0.852)	
p-value[c]	0.00043	
Response rate population[e] n=668	n=337	n=331
CR[f] n (%)	102 (30)	12 (4)
PR[f] n (%)	136 (40)	103 (31)
nCR n (%)	5 (1)	0
CR+PR[f] n (%)	238 (71)	115 (35)
p-value[d]	$< 10^{-10}$	
Reduction in serum M-protein population[g] n=667	n=336	n=331
≥90% n (%)	151 (45)	34 (10)
Time to first response in CR + PR		
Median	1.4 mo	4.2 mo
Median[a] response duration		
CR[f]	24.0 mo	12.8 mo
CR+PR[f]	19.9 mo	13.1 mo
Time to next therapy		
Events n (%)	224 (65.1)	260 (76.9)
Median[a] (95% CI)	27.0 mo (24.7, 31.1)	19.2 mo (17.0, 21.0)
Hazard ratio[b] (95% CI)	0.557 (0.462, 0.671)	
p-value[c]	< 0.000001	

[a] Kaplan-Meier estimate.
[b] Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors: β_2-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for VMP
[c] Nominal p-value based on the stratified log-rank test adjusted for stratification factors: β_2-microglobulin, albumin, and region
[d] p-value for Response Rate (CR+PR) from the Cochran Mantel-Haenszel chi-square test adjusted for the stratification factors
[e] Response population includes patients who had measurable disease at baseline
[f] CR=Complete Response; PR=Partial Response. EBMT criteria
[g] All randomised patients with secretory disease
* Survival update based on a median duration of follow-up at 60.1 months
mo: months
CI=Confidence Interval

Patients eligible for stem cell transplantation
Two randomised, open-label, multicenter Phase III trials (IFM-2005-01, MMY-3010) were conducted to demonstrate the safety and efficacy of VELCADE in dual and triple combinations with other chemotherapeutic agents, as induction therapy prior to stem cell transplantation in patients with previously untreated multiple myeloma.

In study IFM-2005-01 VELCADE combined with dexamethasone [VcDx, n=240] was compared to vincristine- doxorubicin-dexamethasone [VDDx, n=242]. Patients in the VcDx group received four 21 day cycles, each consisting of VELCADE (1.3 mg/m^2 administered intravenously twice weekly on days 1, 4, 8, and 11), and oral dexamethasone (40 mg/day on days 1 to 4 and days 9 to 12, in Cycles 1 and 2, and on days 1 to 4 in Cycles 3 and 4).
Autologous stem cell transplants were received by 198 (82%) patients and 208 (87%) patients in the VDDx and VcDx groups respectively; the majority of patients underwent one single transplant procedure. Patient demographic and baseline disease charateristics were similar between the treatment groups. Median age of the patients in the study was 57 years, 55% were male and 48% of patients had high-risk cytogenetics. The median duration of treatment was 13 weeks for the VDDx group and 11 weeks for the VcDx group. The median number of cycles received for both groups was 4 cycles.
The primary efficacy endpoint of the study was post-induction response rate (CR+nCR). A statistically significant difference in CR+nCR was observed in favour of the VELCADE combined with dexamethasone group. Secondary efficacy endpoints included post-transplant response rates (CR+nCR, CR+nCR+VGPR+PR), Progression Free Survival and Overall Survival. Main efficacy results are presented in Table 12.

Table 12: Efficacy results from study IFM-2005-01

Endpoints	**VcDx**	**VDDx**	**OR; 95% CI; P value[a]**
IFM-2005-01	N=240 (ITT population)	N=242 (ITT population)	
RR (Post-induction)			
*CR+nCR	14.6 (10.4, 19.7)	6.2 (3.5, 10.0)	2.58 (1.37, 4.85); 0.003
CR+nCR+VGPR+PR	77.1 (71.2, 82.2)	60.7 (54.3, 66.9)	2.18 (1.46, 3.24); < 0.001
% (95% CI)			
RR (Post-transplant)[b]			
CR+nCR	37.5 (31.4, 44.0)	23.1 (18.0, 29.0)	1.98 (1.33, 2.95); 0.001
CR+nCR+VGPR+PR	79.6 (73.9, 84.5)	74.4 (68.4, 79.8)	1.34 (0.87, 2.05); 0.179
% (95% CI)			

CI=confidence interval; CR=complete response; nCR=near complete response; ITT=intent to treat; RR=response rate; Vc=VELCADE; VcDx=VELCADE, dexamethasone; VDDx=vincristine, doxorubicin, dexamethasone; VGPR=very good partial response; PR=partial response; OR=odds ratio.
* Primary endpoint
[a] OR for response rates based on Mantel-Haenszel estimate of the common odds ratio for stratified tables; p-values by Cochran Mantel-Haenszel test.
[b] Refers to response rate after second transplant for subjects who received a second transplant (42/240 [18%] in VcDx group and 52/242 [21%] in VDDx group).
Note: An OR > 1 indicates an advantage for Vc-containing induction therapy.

In study MMY-3010 induction treatment withVELCADE combined with thalidomide and dexamethasone [VcTDx, n=130] was compared to thalidomide-dexamethasone [TDx, n=127]. Patients

in the VcTDx group received six 4-week cycles, each consisting of VELCADE (1.3 mg/m^2 administered twice weekly days 1, 4, 8, and 11, followed by a 17-day rest period from day 12 to day 28), dexamethasone (40 mg administered orally on days 1 to 4 and days 8 to 11), and thalidomide (administered orally at 50 mg daily on days 1-14, increased to 100 mg on days 15-28 and thereafter to 200 mg daily).
One single autologous stem cell transplant was received by 105 (81%) patients and 78 (61%) patients in the VcTDx and TDx groups, respectively. Patient demographic and baseline disease charateristics were similar between the treatment groups. Patients in the VcTDx and TDx groups respectively had a median age of 57 versus 56 years, 99% versus 98% patients were Caucasians, and 58% versus 54% were males. In the VcTDx group 12% of patients were cytogenetically classified as high risk versus 16% of patients in the TDx group. The median duration of treatment was 24.0 weeks and the median number of treatment cycles received was 6.0, and was consistent across treatment groups.
The primary efficacy endpoints of the study were post-induction and post-transplant response rates (CR+nCR). A statistically significant difference in CR+nCR was observed in favour of the VELCADE combined with dexamethasone and thalidomide group. Secondary efficacy endpoints included Progression Free Survival and Overall Survival. Main efficacy results are presented in Table 13.

Table 13: Efficacy results from study MMY-3010

Endpoints	VcTDx	TDx	OR; 95% CI; P value[a]
MMY-3010	N=130 (ITT population)	N=127 (ITT population)	
**RR (Post-induction)*			
CR+nCR	49.2 (40.4, 58.1)	17.3 (11.2, 25.0)	4.63 (2.61, 8.22); < 0.001[a]
CR+nCR+PR % (95% CI)	84.6 (77.2, 90.3)	61.4 (52.4, 69.9)	3.46 (1.90, 6.27); < 0.001[a]
**RR (Post-transplant)*			
CR+nCR	55.4 (46.4, 64.1)	34.6 (26.4, 43.6)	2.34 (1.42, 3.87); 0.001[a]
CR+nCR+PR % (95% CI)	77.7 (69.6, 84.5)	56.7 (47.6, 65.5)	2.66 (1.55, 4.57); < 0.001[a]

CI=confidence interval; CR=complete response; nCR=near complete response; ITT=intent to treat; RR=response rate; Vc=VELCADE; VcTDx=VELCADE, thalidomide, dexamethasone; TDx=thalidomide, dexamethasone; PR=partial response; OR=odds ratio

* Primary endpoint

[a] OR for response rates based on Mantel-Haenszel estimate of the common odds ratio for stratified tables; p-values by Cochran Mantel-Haenszel test.

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

Clinical efficacy in relapsed or refractory multiple myeloma

The safety and efficacy of VELCADE (injected intravenously) were evaluated in 2 studies at the recommended dose of 1.3 mg/m^2: a Phase III randomised, comparative study (APEX), versus dexamethasone (Dex), of 669 patients with relapsed or refractory multiple myeloma who had received 1-3 prior lines of therapy, and a Phase II single-arm study of 202 patients with relapsed and refractory multiple myeloma, who had received at least 2 prior lines of treatment and who were progressing on their most recent treatment.

In the Phase III study, treatment with VELCADE led to a significantly longer time to progression, a significantly prolonged survival and a significantly higher response rate, compared to treatment with dexamethasone (see Table 14), in all patients as well as in patients who have received 1 prior line of therapy. As a result of a pre-planned interim analysis, the dexamethasone arm was halted at the recommendation of the data monitoring committee and all patients randomised to dexamethasone were then offered VELCADE, regardless of disease status. Due to this early crossover, the median duration of follow-up for surviving patients is 8.3 months. Both in patients who were refractory to their last prior therapy and those who were not refractory, overall survival was significantly longer and response rate was significantly higher on the VELCADE arm.

Of the 669 patients enrolled, 245 (37%) were 65 years of age or older. Response parameters as well as TTP remained significantly better for VELCADE independently of age. Regardless of β_2-microglobulin levels at baseline, all efficacy parameters (time to progression and overall survival, as well as response rate) were significantly improved on the VELCADE arm.

In the refractory population of the Phase II study, responses were determined by an independent review committee and the response criteria were those of the European Bone Marrow Transplant Group. The median survival of all patients enrolled was 17 months (range < 1 to 36+ months). This survival was greater than the six-to-nine month median survival anticipated by consultant clinical investigators for a similar patient population. By multivariate analysis, the response rate was independent of myeloma type, performance status, chromosome 13 deletion status, or the number or type of previous therapies. Patients who had received 2 to 3 prior therapeutic regimens had a response rate of 32% (10/32) and patients who received greater than 7 prior therapeutic regimens had a response rate of 31% (21/67).

Table 14: Summary of disease outcomes from the Phase III (APEX) and Phase II studies

	Phase III		**Phase III**		**Phase III**		**Phase II**
	All patients		**1 prior line of therapy**		**> 1 prior line of therapy**		**≥ 2 prior lines**
Time related events	**Vc n=333[a]**	**Dex n=336[a]**	**Vc n=132[a]**	**Dex n=119[a]**	**Vc n=200[a]**	**Dex n=217[a]**	**Vc n=202[a]**
TTP, days [95% CI]	189[b] [148, 211]	106[b] [86, 128]	212[d] [188, 267]	169[d] [105, 191]	148[b] [129, 192]	87[b] [84, 107]	210 [154, 281]
1 year survival, % [95% CI]	80[d] [74,85]	66[d] [59,72]	89[d] [82,95]	72[d] [62,83]	73 [64,82]	62 [53,71]	60
Best response (%)	**Vc n=315[c]**	**Dex n=312[c]**	**Vc n=128**	**Dex n=110**	**Vc n=187**	**Dex n=202**	**Vc n=193**
CR	20 (6)[b]	2 (< 1)[b]	8 (6)	2 (2)	12 (6)	0 (0)	(4)**
CR+nCR	41 (13)[b]	5 (2)[b]	16 (13)	4 (4)	25 (13)	1 (< 1)	(10)**
CR+nCR+PR	121 (38)[b]	56 (18)[b]	57 (45)[d]	29 (26)[d]	64 (34)[b]	27 (13)[b]	(27)**
CR+nCR+ PR+MR	146 (46)	108 (35)	66 (52)	45 (41)	80 (43)	63 (31)	(35)**
Median duration Days (months)	242 (8.0)	169 (5.6)	246 (8.1)	189 (6.2)	238 (7.8)	126 (4.1)	385*
Time to response CR+PR (days)	43	43	44	46	41	27	38*

[a] Intent to Treat (ITT) population

[b] p-value from the stratified log-rank test; analysis by line of therapy excludes stratification for therapeutic history; $p < 0.0001$

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

[d] p-value from the Cochran Mantel-Haenszel chi-square test adjusted for the stratification factors; analysis by line of therapy excludes stratification for therapeutic history

* CR+PR+MR **CR=CR, (IF-); nCR=CR (IF+)

NA=not applicable, NE=not estimated
TTP-Time to Progression
CI=Confidence Interval
Vc=VELCADE; Dex=dexamethasone
CR=Complete Response; nCR=near Complete response
PR=Partial Response; MR=Minimal response

In the Phase II study, patients who did not obtain an optimal response to therapy with VELCADE alone were able to receive high-dose dexamethasone in conjunction with VELCADE. The protocol allowed patients to receive dexamethasone if they had had a less than optimal response to VELCADE alone. A total of 74 evaluable patients were administered dexamethasone in combination with VELCADE. Eighteen percent of patients achieved, or had an improved response [MR (11%) or PR (7%)] with combination treatment.

Clinical efficacy with subcutaneous administration of VELCADE in patients with relapsed/refractory multiple myeloma

An open label, randomised, Phase III non-inferiority study compared the efficacy and safety of the subcutaneous administration of VELCADE versus the intravenous administration. This study included

222 patients with relapsed/refractory multiple myeloma, who were randomised in a 2:1 ratio to receive 1.3 mg/m^2 of VELCADE by either the subcutaneous or intravenous route for 8 cycles. Patients who did not obtain an optimal response (less than Complete Response [CR]) to therapy with VELCADE alone after 4 cycles were allowed to receive dexamethasone 20 mg daily on the day of and after VELCADE administration. Patients with baseline Grade ≥ 2 peripheral neuropathy or platelet counts < 50,000/µl were excluded. A total of 218 patients were evaluable for response.

This study met its primary objective of non-inferiority for response rate (CR+PR) after 4 cycles of single agent VELCADE for both the subcutaneous and intravenous routes, 42% in both groups. In addition, secondary response-related and time to event related efficacy endpoints showed consistent results for subcutaneous and intravenous administration (Table 15).

Table 15: Summary of efficacy analyses comparing subcutaneous and intravenous administrations of VELCADE

	VELCADE intravenous arm	**VELCADE subcutaneous arm**
Response Evaluable Population	**n=73**	**n=145**
Response Rate at 4 cycles n (%)		
ORR (CR+PR)	31 (42)	61 (42)
p-value[a]	0.00201	
CR n (%)	6 (8)	9 (6)
PR n (%)	25 (34)	52 (36)
nCR n (%)	4 (5)	9 (6)
Response Rate at 8 cycles n (%)		
ORR (CR+PR)	38 (52)	76 (52)
p-value[a]	0.0001	
CR n (%)	9 (12)	15 (10)
PR n (%)	29 (40)	61 (42)
nCR n (%)	7 (10)	14 (10)
Intent to Treat Population[b]	**n=74**	**n=148**
TTP, months	9.4	10.4
(95% CI)	(7.6, 10.6)	(8.5, 11.7)
Hazard ratio (95% CI)[c]	0.839 (0.564, 1.249)	
p-value[d]	0.38657	
Progression Free Survival, months	8.0	10.2
(95% CI)	(6.7, 9.8)	(8.1, 10.8)
Hazard ratio (95% CI)[c]	0.824 (0.574, 1.183)	
p-value[d]	0.295	
1-year Overall Survival (%)[e]	76.7	72.6
(95% CI)	(64.1, 85.4)	(63.1, 80.0)

[a] p-value is for the non-inferiority hypothesis that the SC arm retains at least 60% of the response rate in the IV arm.

[b] 222 subjects were enrolled into the study; 221 subjects were treated with VELCADE

[c] Hazards ratio estimate is based on a Cox model adjusted for stratification factors: ISS staging and number of prior lines.

[d] Log rank test adjusted for stratification factors: ISS staging and number of prior lines.

[e] Median duration of follow up is 11.8 months

VELCADE combination treatment with pegylated liposomal doxorubicin (study DOXIL-MMY-3001)
A Phase III randomised, parallel-group, open-label, multicentre study was conducted in 646 patients comparing the safety and efficacy of VELCADE plus pegylated liposomal doxorubicin versus VELCADE monotherapy in patients with multiple myeloma who had received at least 1 prior therapy and who did not progress while receiving anthracycline-based therapy. The primary efficacy endpoint was TTP while the secondary efficacy endpoints were OS and ORR (CR+PR), using the European Group for Blood and Marrow Transplantation (EBMT) criteria.
A protocol-defined interim analysis (based on 249 TTP events) triggered early study termination for efficacy. This interim analysis showed a TTP risk reduction of 45% (95% CI; 29-57%, p < 0.0001) for patients treated with combination therapy of VELCADE and pegylated liposomal doxorubicin. The

median TTP was 6.5 months for the VELCADE monotherapy patients compared with 9.3 months for the VELCADE plus pegylated liposomal doxorubicin combination therapy patients. These results, though not mature, constituted the protocol defined final analysis.
The final analysis for OS performed after a median follow-up of 8.6 years showed no significant difference in OS between the two treatment arms. The median OS was 30.8 months (95% CI; 25.2-36.5 months) for the VELCADE monotherapy patients and 33.0 months (95% CI; 28.9-37.1 months) for the VELCADE plus pegylated liposomal doxorubicin combination therapy patients.

VELCADE combination treatment with dexamethasone
In the absence of any direct comparison between VELCADE and VELCADE in combination with dexamethasone in patients with progressive multiple myeloma, a statistical matched-pair analysis was conducted to compare results from the non randomised arm of VELCADE in combination with dexamethasone (Phase II open-label study MMY-2045), with results obtained in the VELCADE monotherapy arms from different Phase III randomised studies (M34101-039 [APEX] and DOXIL MMY-3001) in the same indication.
The matched-pair analysis is a statistical method in which patients in the treatment group (e.g. VELCADE in combination with dexamethasone) and patients in the comparison group (e.g. VELCADE) are made comparable with respect to confounding factors by individually pairing study subjects. This minimises the effects of observed confounders when estimating treatment effects using non-randomised data.
One hundred and twenty seven matched pairs of patients were identified. The analysis demonstrated improved ORR (CR+PR) (odds ratio 3.769; 95% CI 2.045-6.947; $p < 0.001$), PFS (hazard ratio 0.511; 95% CI 0.309-0.845; p=0.008), TTP (hazard ratio 0.385; 95% CI 0.212-0.698; p=0.001) for VELCADE in combination with dexamethasone over VELCADE monotherapy.

Limited information on VELCADE retreatment in relapsed multiple myeloma is available.
Phase II study MMY-2036 (RETRIEVE), single arm, open-label study was conducted to determine the efficacy and safety of retreatment with VELCADE. One hundred and thirty patients (≥ 18 years of age) with multiple myeloma who previously had at least partial response on a VELCADE-containing regimen were retreated upon progression. At least 6 months after prior therapy, VELCADE was started at the last tolerated dose of 1.3 mg/m^2 (n=93) or ≤ 1.0 mg/m^2 (n=37) and given on days 1, 4, 8 and 11 every 3 weeks for maximum of 8 cycles either as single agent or in combination with dexamethasone in accordance with the standard of care. Dexamethasone was administered in combination with VELCADE to 83 patients in Cycle 1 with an additional 11 patients receiving dexamethasone during the course of VELCADE retreatment cycles.
The primary endpoint was best confirmed response to retreatment as assessed by EBMT criteria. The overall best response rate (CR + PR), to retreatment in 130 patients was 38.5% (95% CI: 30.1, 47.4).

<u>Clinical efficacy in previously untreated mantle cell lymphoma (MCL)</u>
Study LYM-3002 was a Phase III, randomised, open-label study comparing the efficacy and safety of the combination of VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP; n=243) to that of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; n=244) in adult patients with previously untreated MCL (Stage II, III or IV). Patients in the VcR-CAP treatment arm received VELCADE (1.3 mg/m^2; on days 1, 4, 8, 11, rest period days 12-21), rituximab 375 mg/m^2 IV on day 1; cyclophosphamide 750 mg/m^2 IV on day 1; doxorubicin 50 mg/m^2 IV on day 1; and prednisone 100 mg/m^2 orally on day 1 through day 5 of the 21 day VELCADE treatment cycle. For patients with a response first documented at cycle 6, two additional treatment cycles were given.
The primary efficacy endpoint was progression-free survival based on Independent Review Committee (IRC) assessment. Secondary endpoints included, time to progression (TTP), time to next anti-lymphoma treatment (TNT), duration of treatment free interval (TFI), overall response rate (ORR) and complete response (CR/CRu) rate, overall survival (OS) and response duration.

The demographic and baseline disease characteristics were generally well balanced between the two treatment arms: median patient age was 66 years, 74% were male, 66% were Caucasian and 32% Asian, 69% of patients had a positive bone marrow aspirate and/or a positive bone marrow biopsy for

MCL, 54% of patients had an International Prognostic Index (IPI) score of ≥ 3, and 76% had Stage IV disease. Treatment duration (median=17 weeks) and duration of follow-up (median=40 months) were comparable in both treatment arms. A median of 6 cycles was received by patients in both treatment arms with 14% of subjects in the VcR-CAP group and 17% of patients in the R-CHOP group receiving 2 additional cycles. The majority of the patients in both groups completed treatment, 80% in the VcR-CAP group and 82% in the R-CHOP group. Efficacy results are presented in Table 16:

Table 16: Efficacy results from study LYM-3002

Efficacy endpoint	**VcR-CAP**	**R-CHOP**	
n: ITT patients	243	244	
Progression free survival (IRC)[a]			
Events n (%)	133 (54.7%)	165 (67.6%)	HR[b] (95% CI)=0.63 (0.50; 0.79) p-value[d] < 0.001
Median[c](95% CI) (months)	24.7 (19.8; 31.8)	14.4 (12; 16.9)	
Response rate			
n: response-evaluable patients	229	228	
Overall complete response (CR+CRu)[f] *n(%)*	122 (53.3%)	95 (41.7%)	OR[e] (95% CI)=1.688 (1.148; 2.481) p-value[g]=0.007
Overall response (CR+CRu+PR)[h] *n(%)*	211 (92.1%)	204 (89.5%)	OR[e] (95% CI)=1.428 (0.749; 2.722) p-value[g]=0.275

[a] Based on Independent Review Committee (IRC) assessment (radiological data only).

[b] Hazard ratio estimate is based on a Cox's model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for VcR-CAP.

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

[d] Based on Log rank test stratified with IPI risk and stage of disease.

[e] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used, with IPI risk and stage of disease as stratification factors. An odds ratio (OR) > 1 indicates an advantage for VcR-CAP.

[f] Include all CR+CRu, by IRC, bone marrow and LDH.

[g] P-value from the Cochran Mantel-Haenszel chi-square test, with IPI and stage of disease as stratification factors.

[h] Include all radiological CR+CRu+PR by IRC regardless the verification by bone marrow and LDH.

CR=Complete Response; CRu=Complete Response unconfirmed; PR=Partial Response; CI=Confidence Interval, HR=Hazard Ratio; OR=Odds Ratio; ITT=Intent to Treat

Median PFS by investigator assessment was 30.7 months in the VcR-CAP group and 16.1 months in the R-CHOP group (Hazard Ratio [HR]=0.51; p < 0.001). A statistically significant benefit (p < 0.001) in favour of the VcR-CAP treatment group over the R-CHOP group was observed for TTP (median 30.5 versus 16.1 months), TNT (median 44.5 versus 24.8 months) and TFI (median 40.6 versus 20.5 months). The median duration of complete response was 42.1 months in the VcR-CAP group compared with 18 months in the R-CHOP group. The duration of overall response was 21.4 months longer in the VcR-CAP group (median 36.5 months versus 15.1 months in the R-CHOP group). The final analysis for OS was performed after a median follow-up of 82 months. Median OS was 90.7 months for the VcR-CAP group compared with 55.7 months for the R-CHOP group (HR=0.66; p=0.001). The observed final median difference in the OS between the 2 treatment groups was 35 months.

Patients with previously treated light-chain (AL) Amyloidosis

An open label non randomised Phase I/II study was conducted to determine the safety and efficacy of VELCADE in patients with previously treated light-chain (AL) Amyloidosis. No new safety concerns were observed during the study, and in particular VELCADE did not exacerbate target organ damage (heart, kidney and liver). In an exploratory efficacy analysis, a 67.3% response rate (including a 28.6% CR rate) as measured by hematologic response (M-protein) was reported in 49 evaluable patients treated with the maximum allowed doses of 1.6 mg/m^2 weekly and 1.3 mg/m^2 twice-weekly. For these dose cohorts, the combined 1-year survival rate was 88.1%.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with VELCADE in all subsets of the paediatric population in multiple myeloma and in mantle cell lymphoma (see section 4.2 for information on paediatric use).

A Phase II, single-arm activity, safety, and pharmacokinetic trial conducted by the Children's Oncology Group assessed the activity of the addition of bortezomib to multi-agent re-induction chemotherapy in paediatric and young adult patients with lymphoid malignancies (pre-B cell acute lymphoblastic leukemia [ALL], T-cell ALL, and T-cell lymphoblastic lymphoma [LL]). An effective re-induction multi-agent chemotherapy regimen was administered in 3 blocks. VELCADE was administered only in Blocks 1 and 2 to avoid potential overlapping toxicities with coadministered drugs in Block 3.

Complete response (CR) was evaluated at the end of Block 1. In B-ALL patients with relapse within 18 months of diagnosis (n = 27) the CR rate was 67% (95% CI: 46, 84); the 4-month event free survival rate was 44% (95% CI: 26, 62). In B-ALL patients with relapse 18-36 months from diagnosis (n = 33) the CR rate was 79% (95% CI: 61, 91) and the 4-month event free survival rate was 73% (95% CI: 54, 85). The CR rate in first-relapsed T-cell ALL patients (n = 22) was 68% (95% CI: 45, 86) and the 4-month event free survival rate was 67% (95% CI: 42, 83). The reported efficacy data are considered inconclusive (see section 4.2).

There were 140 patients with ALL or LL enrolled and evaluated for safety; median age was 10 years (range 1 to 26). No new safety concerns were observed when VELCADE was added to the standard pediatric pre B cell ALL chemotherapy backbone. The following adverse reactions (Grade ≥ 3) were observed at a higher incidence in the VELCADE containing treatment regimen as compared with a historical control study in which the backbone regimen was given alone: in Block 1 peripheral sensory neuropathy (3% versus 0%); ileus (2.1% versus 0%); hypoxia (8% versus 2%). No information on possible sequelae or rates of peripheral neuropathy resolution were available in this study. Higher incidences were also noted for infections with Grade ≥ 3 neutropenia (24% versus 19% in Block 1 and 22% versus 11% in Block 2), increased ALT (17% versus 8% in Block 2), hypokalaemia (18% versus 6% in Block 1 and 21% versus 12% in Block 2) and hyponatraemia (12% versus 5% in Block 1 and 4% versus 0 in Block 2).

5.2 Pharmacokinetic properties

Absorption
Following intravenous bolus administration of a 1.0 mg/m^2 and 1.3 mg/m^2 dose to 11 patients with multiple myeloma and creatinine clearance values greater than 50 ml/min, 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.

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

Distribution
The mean distribution volume (V_d) of bortezomib ranged from 1,659 l to 3,294 l following single- or repeated-dose intravenous 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. Over a bortezomib concentration range of 0.01 to 1.0 µg/ml, the *in vitro* protein binding averaged 82.9% in human plasma. The fraction of bortezomib bound to plasma proteins was not concentration-dependent.

Biotransformation
In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolised via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites

that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors.

Elimination
The mean elimination half-life ($t_{1/2}$) of bortezomib upon multiple dosing ranged from 40-193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 l/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 l/h and 18 to 32 l/h following subsequent doses for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively.

Special populations
Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed in a Phase I study during the first treatment cycle, including 61 patients primarily with solid tumors and varying degrees of hepatic impairment at bortezomib doses ranging from 0.5 to 1.3 mg/m^2.

When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalised bortezomib AUC. However, the dose-normalised mean AUC values were increased by approximately 60% in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be closely monitored (see section 4.2, Table 6).

Renal impairment
A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCL) into the following groups: Normal (CrCL $\geq$ 60 ml/min/1.73 m^2, n=12), Mild (CrCL=40-59 ml/min/1.73 m^2, n=10), Moderate (CrCL=20-39 ml/min/1.73 m^2, n=9), and Severe (CrCL < 20 ml/min/1.73 m^2, n=3). A group of dialysis patients who were dosed after dialysis was also included in the study (n=8). Patients were administered intravenous doses of 0.7 to 1.3 mg/m^2 of VELCADE twice weekly. Exposure of VELCADE (dose-normalised AUC and C_{max}) was comparable among all the groups (see section 4.2).

Age
The pharmacokinetics of bortezomib were characterized following twice weekly intravenous bolus administration of 1.3 mg/m^2 doses to 104 pediatric patients (2-16 years old) with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). Based on a population pharmacokinetic analysis, clearance of bortezomib increased with increasing body surface area (BSA). Geometric mean (%CV) clearance was 7.79 (25%) L/hr/m^2, volume of distribution at steady-state was 834 (39%) L/m^2, and the elimination half-life was 100 (44%) hours. After correcting for the BSA effect, other demographics such as age, body weight and sex did not have clinically significant effects on bortezomib clearance. BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

5.3 Preclinical safety data

Bortezomib was positive for clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary (CHO) cells at concentrations as low as 3.125 μg/ml, which was the lowest concentration evaluated. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames assay) and *in vivo* micronucleus assay in mice.

Developmental toxicity studies in the rat and rabbit have shown embryo-fetal lethality at maternally toxic doses, but no direct embryo-foetal toxicity below maternally toxic doses. Fertility studies were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6-month rat study, degenerative effects in both the testes and the ovary have been observed. It is, therefore, likely that bortezomib could have a potential effect on either male or female fertility. Peri- and postnatal development studies were not conducted.

In multi-cycle general toxicity studies conducted in the rat and monkey, the principal target organs included the gastrointestinal tract, resulting in vomiting and/or diarrhoea; haematopoietic and lymphatic tissues, resulting in peripheral blood cytopenias, lymphoid tissue atrophy and haematopoietic bone marrow hypocellularity; peripheral neuropathy (observed in monkeys, mice and dogs) involving sensory nerve axons; and mild changes in the kidneys. All these target organs have shown partial to full recovery following discontinuation of treatment.

Based on animal studies, the penetration of bortezomib through the blood-brain barrier appears to be limited, if any and the relevance to humans is unknown.

Cardiovascular safety pharmacology studies in monkeys and dogs show that intravenous 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 death. In dogs, the decreased cardiac contractility and hypotension responded to acute intervention with positive inotropic or pressor agents. Moreover, in dog studies, a slight increase in the corrected QT interval was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E 421)
Nitrogen

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
3 years

Reconstituted solution
The reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. However, the chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 25°C stored in the original vial and/or a syringe. The total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration.

6.4 Special precautions for storage

Do not store above 30°C.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type 1 glass 10 ml-vial with a grey bromobutyl stopper and an aluminium seal, with a royal blue cap containing 3.5 mg bortezomib.

The vial is contained in a transparent blister pack consisting of a tray with a lid. Each pack contains 1 single-use vial.

6.6 Special precautions for disposal and other handling

General precautions
Bortezomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation of VELCADE. Use of gloves and other protective clothing to prevent skin contact is recommended.

Aseptic technique must be strictly observed throughout the handling of VELCADE, since it contains no preservative.

There have been fatal cases of inadvertent intrathecal administration of VELCADE. VELCADE 1 mg powder for solution for injection is for intravenous use only, while VELCADE 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. VELCADE should not be administered intrathecally.

Instructions for reconstitution
VELCADE must be reconstituted by a healthcare professional.

Intravenous injection
Each 10 ml vial of VELCADE must be carefully reconstituted with 3.5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.
After reconstitution, each ml solution contains 1 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7.
The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

Subcutaneous injection
Each 10 ml vial of VELCADE must be carefully reconstituted with 1.4 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.
After reconstitution, each ml solution contains 2.5 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

Disposal
VELCADE is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

JANSSEN-CILAG INTERNATIONAL NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER

EU/1/04/274/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 April 2004

Date of latest renewal: 10 January 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON, VELCADE 1 mg

1. NAME OF THE MEDICINAL PRODUCT

VELCADE 1 mg powder for solution for injection
bortezomib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 1 mg bortezomib (as a mannitol boronic ester).

3. LIST OF EXCIPIENTS

Mannitol (E421), nitrogen

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use only.
For single use only.
Do not give by other routes.
Intravenous use: Add 1 ml 0.9% Sodium Chloride to make 1 mg/ml final concentration.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

CYTOTOXIC. Special handling instructions

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

JANSSEN-CILAG INTERNATIONAL NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/274/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL VELCADE 1 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VELCADE 1 mg powder for solution for injection
bortezomib
Intravenous use only.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON, VELCADE 3.5 mg

1. NAME OF THE MEDICINAL PRODUCT

VELCADE 3.5 mg powder for solution for injection
bortezomib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 3.5 mg bortezomib (as a mannitol boronic ester).

3. LIST OF EXCIPIENTS

Mannitol (E421), nitrogen

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous or Intravenous use only.
For single use only.
Do not give by other routes.
Subcutaneous use: Add 1.4 ml 0.9% Sodium Chloride to make 2.5 mg/ml final concentration.
Intravenous use: Add 3.5 ml 0.9% Sodium Chloride to make 1 mg/ml final concentration.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

CYTOTOXIC. Special handling instructions

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

JANSSEN-CILAG INTERNATIONAL NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/274/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL VELCADE 3.5 mg FLAG LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VELCADE 3.5 mg powder for solution for injection
bortezomib
Subcutaneous or Intravenous use only.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3.5 mg

6. OTHER

For single use only
Do not give by other routes.

Subcutaneous use: Add 1.4 ml 0.9% Sodium Chloride to make 2.5 mg/ml final concentration.
Intravenous use: Add 3.5 ml 0.9% Sodium Chloride to make 1 mg/ml final concentration.

Do not store above 30^{o}C. Keep the vial in the outer carton in order to protect from light.

Peel here

B. PACKAGE LEAFLET

Package leaflet: Information for the user

VELCADE 1 mg powder for solution for injection
bortezomib

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What VELCADE is and what it is used for
2. What you need to know before you use VELCADE
3. How to use VELCADE
4. Possible side effects
5. How to store VELCADE
6. Contents of the pack and other information

1. What VELCADE is and what it is used for

VELCADE contains the active substance bortezomib, a so-called 'proteasome inhibitor'. Proteasomes play an important role in controlling cell function and growth. By interfering with their function, bortezomib can kill cancer cells.

VELCADE is used for the treatment of multiple myeloma (a cancer of the bone marrow) in patients older than 18 years:
- alone or together with the medicines pegylated liposomal doxorubicin or dexamethasone, for patients whose disease is worsening (progressive) after receiving at least one prior treatment and for whom blood stem cell transplantation was not successful or is unsuitable.
- in combination with the medicines melphalan and prednisone, for patients whose disease has not been previously treated and are unsuitable for high-dose chemotherapy with blood stem cell transplantation.
- in combination with the medicines dexamethasone or dexamethasone together with thalidomide, for patients whose disease has not been previously treated and before receiving high-dose chemotherapy with blood stem cell transplantation (induction treatment).

VELCADE is used for the treatment of mantle cell lymphoma (a type of cancer affecting the lymph nodes) in patients 18 years or older in combination with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone, for patients whose disease has not been previously treated and for whom blood stem cell transplantation is unsuitable.

2. What you need to know before you use VELCADE

Do not use VELCADE
- if you are allergic to bortezomib, boron or to any of the other ingredients of this medicine (listed in section 6)
- if you have certain severe lung or heart problems.

Warnings and precautions
You should tell your doctor if you have any of the following:
- low numbers of red or white blood cells
- bleeding problems and/or low number of platelets in your blood
- diarrhoea, constipation, nausea or vomiting

- fainting, dizziness or light-headedness in the past
- kidney problems
- moderate to severe liver problems
- numbness, tingling, or pain in the hands or feet (neuropathy) in the past
- heart or blood pressure problems
- shortness of breath or cough
- seizures
- shingles (localised including around the eyes or spread across the body)
- symptoms of tumor lysis syndrome such as muscle cramping, muscle weakness, confusion, visual loss or disturbances and shortness of breath
- memory loss, trouble thinking, difficulty with walking or loss of vision. These may be signs of a serious brain infection and your doctor may suggest further testing and follow-up.

You will have to take regular blood tests before and during your treatment with VELCADE, to check your blood cell counts regularly.

If you have mantle cell lymphoma and are given the medicine rituximab with VELCADE you should tell your doctor:
- if you think you have hepatitis infection now or have had it in the past. In a few cases, patients who have had hepatitis B might have a repeated attack of hepatitis, which can be fatal. If you have a history of hepatitis B infection you will be carefully checked by your doctor for signs of active hepatitis B.

You must read the package leaflets of all medicinal products to be taken in combination with VELCADE for information related to these medicines before starting treatment with VELCADE. When thalidomide is used, particular attention to pregnancy testing and prevention requirements is needed (see Pregnancy and breast-feeding in this section).

Children and adolescents
VELCADE should not be used in children and adolescents because it is not known how the medicine will affect them.

Other medicines and VELCADE
Please tell your doctor, or pharmacist if you are taking, have recently taken or might take any other medicines.
In particular, tell your doctor if you are using medicines containing any of the following active substances:
- ketoconazole, used to treat fungal infections
  ritonavir, used to treat HIV infection
- rifampicin, an antibiotic used to treat bacterial infections
- carbamazepine, phenytoin or phenobarbital used to treat epilepsy
- St. John's Wort (*Hypericum perforatum*), used for depression or other conditions
- oral antidiabetics

Pregnancy and breast-feeding
You should not use VELCADE if you are pregnant, unless clearly necessary.

Both men and women receiving VELCADE must use effective contraception during and for up to 3 months after treatment. If, despite these measures, pregnancy occurs, tell your doctor immediately.

You should not breast-feed while using VELCADE. Discuss with your doctor when it is safe to restart breast-feeding after finishing your treatment.

Thalidomide causes birth defects and foetal death. When VELCADE is given in combination with thalidomide you must follow the pregnancy prevention programme for thalidomide (see package leaflet for thalidomide).

Driving and using machines
VELCADE might cause tiredness, dizziness, fainting, or blurred vision. Do not drive or operate tools or machines if you experience such side effects; even if you do not, you should still be cautious.

3. How to use VELCADE

Your doctor will work out your dose of VELCADE according to your height and weight (body surface area). The usual starting dose of VELCADE is 1.3 mg/m^2 body surface area twice a week.
Your doctor may change the dose and total number of treatment cycles, depending on your response to the treatment on the occurrence of certain side effects and on your underlying conditions (e.g. liver problems).

Progressive multiple myeloma
When VELCADE is given alone, you will receive 4 doses of VELCADE intravenously on days 1, 4, 8 and 11, followed by a 10-day 'rest period' without treatment. This 21-day period (3 weeks) corresponds to one treatment cycle. You might receive up to 8 cycles (24 weeks).

You may also be given VELCADE together with the medicines pegylated liposomal doxorubicin or dexamethasone.

When VELCADE is given together with pegylated liposomal doxorubicin, you will receive VELCADE intravenously as a 21-day treatment cycle and pegylated liposomal doxorubicin 30 mg/m^2 is given on day 4 of the VELCADE 21-day treatment cycle as an intravenous infusion after the VELCADE injection.
You might receive up to 8 cycles (24 weeks).

When VELCADE is given together with dexamethasone, you will receive VELCADE intravenously as a 21-day treatment cycle and dexamethasone 20 mg is given orally on days 1, 2, 4, 5, 8, 9, 11, and 12, of the VELCADE, 21-day treatment cycle.
You might receive up to 8 cycles (24 weeks).

Previously untreated multiple myeloma
If you have not been treated before for multiple myeloma, and **you are not** suitable for blood stem cell transplantation you will receive VELCADE intravenously together with two other medicines; melphalan and prednisone.
In this case, the duration of a treatment cycle is 42 days (6 weeks). You will receive 9 cycles (54 weeks).
- In cycles 1 to 4, VELCADE is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32.
- In cycles 5 to 9, VELCADE is administered once weekly on days 1, 8, 22 and 29.

Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) are both given orally on days 1, 2, 3 and 4 of the first week of each cycle.

If you have not been treated before for multiple myeloma, and **you are** suitable for blood stem cell transplantation you will receive VELCADE intravenously together with the medicines dexamethasone, or dexamethasone and thalidomide, as induction treatment.

When VELCADE is given together with dexamethasone, you will receive VELCADE intravenously as a 21-day treatment cycle and dexamethasone 40 mg is given orally on days 1, 2, 3, 4, 8, 9, 10 and 11 of the VELCADE 21-day treatment cycle.
You will receive 4 cycles (12 weeks).

When VELCADE is given together with thalidomide and dexamethasone, the duration of a treatment cycle is 28 days (4 weeks).
Dexamethasone 40 mg is given orally on days 1, 2, 3, 4, 8, 9, 10 and 11 of the VELCADE 28-day treatment cycle and thalidomide is given orally daily at 50 mg up to day 14 of the first cycle, and if

tolerated the thalidomide dose is increased to 100 mg on days 15-28 and may be further increased to 200 mg daily from the second cycle onwards.
You might receive up to 6 cycles (24 weeks).

Previously untreated mantle cell lymphoma
If you have not been treated before for mantle cell lymphoma you will receive VELCADE intravenously together with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone. VELCADE is given intravenously on days 1, 4, 8 and 11, followed by a 'rest period' without treatment. The duration of a treatment cycle is 21 days (3 weeks). You might receive up to 8 cycles (24 weeks).
The following medicinal products are given on day 1 of each VELCADE 21-day treatment cycle as intravenous infusions:
Rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2 and doxorubicin at 50 mg/m^2.
Prednisone is given orally at 100 mg/m^2 on days 1, 2, 3, 4 and 5 of the VELCADE treatment cycle.

How VELCADE is given
This medicine is for intravenous use only. VELCADE will be administered by a health care professional experienced in the use of cytotoxic medicines.
VELCADE powder has to be dissolved before administration. This will be done by a healthcare professional. The resulting solution is then injected into a vein rapidly, over 3 to 5 seconds.

If you are given too much VELCADE
As this medicine is being given by your doctor or nurse, it is unlikely that you will be given too much. In the unlikely event of an overdose, your doctor will monitor you for side effects.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these effects may be serious.

If you are given VELCADE for multiple myeloma or mantle cell lymphoma, tell your doctor straight away if you notice any of the following symptoms:
- muscle cramping, muscle weakness
- confusion, visual loss or disturbances, blindness, seizures, headaches
- shortness of breath, swelling of your feet or changes in your heart beat, high blood pressure, tiredness, fainting
- coughing and breathing difficulties or tightness in the chest.

Treatment with VELCADE can very commonly cause a decrease in the numbers of red and white blood cells and platelets in your blood. Therefore, you will have to take regular blood tests before and during your treatment with VELCADE, to check your blood cell counts regularly. You may experience a reduction in the number of:
- platelets, which may make you be more prone to bruising, or to bleeding without obvious injury (e.g., bleeding from your bowels, stomach, mouth and gum or bleeding in the brain or bleeding from the liver)
- red blood cells, which can cause anaemia, with symptoms such as tiredness and paleness
- white blood cells may make you more prone to infections or flu-like symptoms.

If you are given VELCADE for the treatment of multiple myeloma the side effects you may get are listed below:

Very common side effects (may affect more than 1 in 10 people)
- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage
- Reduction in the number of red blood cells and or white blood cells (see above)
- Fever

- Feeling sick (nausea) or vomiting, loss of appetite
- Constipation with or without bloating (can be severe)
- Diarrhoea: if this happens, it is important that you drink more water than usual. Your doctor may give you another medicine to control diarrhoea
- Tiredness (fatigue), feeling weak
- Muscle pain, bone pain

Common side effects (may affect up to 1 in 10 people)
- Low blood pressure, sudden fall of blood pressure on standing which may lead to fainting
- High blood pressure
- Reduced functioning of your kidneys
- Headache
- General ill feeling, pain, vertigo, light-headedness, a feeling of weakness or loss of consciousness
- Shivering
- Infections, including pneumonia, respiratory infections, bronchitis, fungal infections, coughing with phlegm, flu like illness
- Shingles (localised including around the eyes or spread across the body)
- Chest pains or shortness of breath with exercise
- Different types of rash
- Itching of the skin, lumps on the skin or dry skin
- Facial blushing or tiny broken capillaries
- Redness of the skin
- Dehydration
- Heartburn, bloating, belching, wind, stomach pain, bleeding from your bowels or stomach
- Alteration of liver functioning
- A sore mouth or lip, dry mouth, mouth ulcers or throat pain
- Weight loss, loss of taste
- Muscle cramps, muscle spasms, muscle weakness, pain in your limbs
- Blurred vision
- Infection of the outermost layer of the eye and the inner surface of the eyelids (conjunctivitis)
- Nose bleeds
- Difficulty or problems in sleeping, sweating, anxiety, mood swings, depressed mood, restlessness or agitation, changes in your mental status, disorientation
- Swelling of body, to include around eyes and other parts of the body

Uncommon side effects (may affect up to 1 in 100 people)
- Heart failure, heart attack, chest pain, chest discomfort, increased or reduced heart rate
- Failing of your kidneys
- Inflammation of a vein, blood clots in your veins and lungs
- Problems with blood clotting
- Insufficient circulation
- Inflammation of the lining around your heart or fluid around your heart
- Infections including urinary tract infections, the flu, herpes virus infections, ear infection and cellulitis
- Bloody stools, or bleeding from mucosal membranes, e.g., mouth, vagina
- Cerebrovascular disorders
- Paralysis, seizures, falling, movement disorders, abnormal or change in, or reduced sensation (feeling, hearing, tasting, smelling), attention disturbance, trembling, twitching
- Arthritis, including inflammation of the joints in the fingers, toes, and the jaw
- Disorders that affect your lungs, preventing your body from getting enough oxygen. Some of these include difficulty breathing, shortness of breath, shortness of breath without exercise, breathing that becomes shallow, difficult or stops, wheezing
- Hiccups, speech disorders

- Increased or decreased urine production (due to kidney damage), painful passing of urine or blood/proteins in the urine, fluid retention
- Altered levels of consciousness, confusion, memory impairment or loss
- Hypersensitivity
- Hearing loss, deafness or ringing in the ears, ear discomfort
- Hormone abnormality which may affect salt and water absorption
- Overactive thyroid gland
- Inability to produce enough insulin or resistance to normal levels of insulin
- Irritated or inflamed eyes, excessively wet eyes, painful eyes, dry eyes, eye infections, lump in the eyelid (chalazion), red and swollen eyelids, discharge from the eyes, abnormal vision, bleeding of the eye
- Swelling of your lymph glands
- Joint or muscle stiffness, sense of heaviness, pain in your groin
- Hair loss and abnormal hair texture
- Allergic reactions
- Redness or pain at the injection site
- Mouth pain
- Infections or inflammation of the mouth, mouth ulcers, oesophagus, stomach and intestines, sometimes associated with pain or bleeding, poor movement of the intestines (including blockage), abdominal or oesophageal discomfort, difficulty swallowing, vomiting of blood
- Skin infections
- Bacterial and viral infections
- Tooth infection
- Inflammation of the pancreas, obstruction of the bile duct
- Genital pain, problem having an erection
- Weight increase
- Thirst
- Hepatitis
- Injection site or injection device related disorders
- Skin reactions and disorders (which may be severe and life threatening), skin ulcers
- Bruises, falls and injuries
- Inflammation or haemorrhage of the blood vessels that can appear as small red or purple dots (usually on the legs) to large bruise-like patches under the skin or tissue
- Benign cysts
- A severe reversible brain condition which includes seizures, high blood pressure, headaches, tiredness, confusion, blindness or other vision problems.

Rare side effects (may affect up to 1 in 1,000 people)
- Heart problems to include heart attack, angina
- Flushing
- Discoloration of the veins
- Inflammation of the spinal nerve
- Problems with your ear, bleeding from your ear
- Underactivity of your thyroid gland
- Budd–Chiari syndrome (the clinical symptoms caused by blockage of the hepatic veins)
- Changes in or abnormal bowel function
- Bleeding in the brain
- Yellow discolouration of eyes and skin (jaundice)
- Serious allergic reaction (anaphylactic shock) signs of which may include difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse
- Breast disorders
- Vaginal tears

- Genital swelling
- Inability to tolerate alcohol consumption
- Wasting, or loss of body mass
- Increased appetite
- Fistula
- Joint effusion
- Cysts in the lining of joints (synovial cysts)
- Fracture
- Breakdown of muscle fibers leading to other complications
- Swelling of the liver, bleeding from the liver
- Cancer of the kidney
- Psoriasis like skin condition
- Cancer of the skin
- Paleness of the skin
- Increase of platelets or plasma cells (a type of white cell) in the blood
- Blood clot in small blood vessels (thrombotic microangiopathy)
- Abnormal reaction to blood transfusions
- Partial or total loss of vision
- Decreased sex drive
- Drooling
- Bulging eyes
- Sensitivity to light
- Rapid breathing
- Rectal pain
- Gallstones
- Hernia
- Injuries
- Brittle or weak nails
- Abnormal protein deposits in your vital organs
- Coma
- Intestinal ulcers
- Multi-organ failure
- Death

If you are given VELCADE together with other medicines for the treatment of mantle cell lymphoma the side effects you may get are listed below:

Very common side effects (may affect more than 1 in 10 people)
- Pneumonia
- Loss of appetite
- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage
- Nausea and vomiting
- Diarrhoea
- Mouth ulcers
- Constipation
- Muscle pain, bone pain
- Hair loss and abnormal hair texture
- Tiredness, feeling weak
- Fever

Common side effects (may affect up to 1 in 10 people)
- Shingles (localized including around the eyes or spread across the body)
- Herpes virus infections

- Bacterial and viral infections
- Respiratory infections, bronchitis, coughing with phlegm, flu like illness
- Fungal infections
- Hypersensitivity (allergic reaction)
- Inability to produce enough insulin or resistance to normal levels of insulin
- Fluid retention
- Difficulty or problems in sleeping
- Loss of conciousness
- Altered level of consciousness, confusion
- Feeling dizzy
- Increased heartbeat, high blood pressure, sweating,
- Abnormal vision, blurred vision
- Heart failure, heart attack, chest pain, chest discomfort, increased or reduced heart rate
- High or low blood pressure
- Sudden fall of blood pressure upon standing which may lead to fainting
- Shortness of breath with exercise
- Cough
- Hiccups
- Ringing in the ears, ear discomfort
- Bleeding from your bowels or stomach
- Heartburn
- Stomach pain, bloating
- Difficulty swallowing
- Infection or inflammation of the stomach and intentines
- Stomach pain
- Sore mouth or lip, throat pain
- Alteration of liver function
- Itching of skin
- Redness of skin
- Rash
- Muscle spasms
- Infection of the urinary tract
- Pain in limbs
- Swelling of body, to include eyes and other parts of the body
- Shivering
- Redness and pain at injection site
- General ill feeling
- Weight loss
- Weight increase

Uncommon side effects (may affect up to 1 in 100 people)
- Hepatitis
- Severe allergic reaction (anaphylactic reaction) signs of which may include difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse
- Movement disorders, paralysis, twitching
- Vertigo
- Hearing loss, deafness
- Disorders that affect your lungs, preventing your body from getting enough oxygen. Some of these include difficulty breathing, shortness of breath, shortness of breath without exercise, breathing that becomes shallow, difficult or stops, wheezing
- Blood clots in your lungs
- Yellow discoloration of the eyes and skin (jaundice)

- Lump in the eyelid (chalazion), red and swollen eyelids

Rare side effects (may affect up to 1 in 1,000 people)
- Blood clot in small blood vessels (thrombotic microangiopathy)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VELCADE

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the vial and the carton after EXP.

Do not store above 30°C. Keep the vial in the outer carton in order to protect from light.

The reconstituted solution should be used immediately after preparation. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. However, the reconstituted solution is stable for 8 hours at 25°C stored in the original vial and/or a syringe, with a total storage time for the reconstituted medicine not exceeding 8 hours prior to administration.

VELCADE is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What VELCADE contains
- The active substance is bortezomib. Each vial contains 1 mg of bortezomib (as a mannitol boronic ester). After reconstitution, 1 ml of solution for injection contains 1 mg bortezomib.
- The other ingredients are mannitol (E421) and nitrogen.

What VELCADE looks like and contents of the pack
VELCADE powder for solution for injection is a white to off-white cake or powder.

Each carton of VELCADE 1 mg powder for solution for injection contains a glass vial with a green cap, in a transparent blister pack.

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Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

1. RECONSTITUTION FOR INTRAVENOUS INJECTION

Note: VELCADE is a cytotoxic agent. Therefore, caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.

ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF VELCADE SINCE NO PRESERVATIVE IS PRESENT.

1.1 **Preparation of the 1 mg vial: carefully add 1.0 ml** of sterile, 9 mg/ml (0.9%) sodium chloride solution for injection to the vial containing the VELCADE powder by using a 1 ml syringe without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

The concentration of the resulting solution will be 1 mg/ml. The solution will be clear and colourless, with a final pH of 4 to 7. You do not need to check the pH of the solution.

1.2 Before administration, visually inspect the solution for particulate matter and discolouration. If any discolouration or particulate matter is observed, the solution should be discarded. Confirm concentration on vial to ensure that the correct dose is being given for the intravenous route of administration (1 mg/ml).

1.3 The reconstituted solution is preservative free and should be used immediately after preparation. However, the chemical and physical in-use stability has been demonstrated for 8 hours at 25°C stored in the original vial and/or a syringe. The total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

It is not necessary to protect the reconstituted medicinal product from light.

2. ADMINISTRATION

- Once dissolved, withdraw the appropriate amount of the reconstituted solution according to calculated dose based upon the patient´s Body Surface Area.
- Confirm the dose and concentration in the syringe prior to use (check that the syringe is marked as intravenous administration).
- Inject the solution as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter into a vein.
- Flush the peripheral or intravenous catheter with sterile, 9 mg/ml (0.9%) sodium chloride solution.

VELCADE 1 mg powder for solution for injection IS FOR INTRAVENOUS USE ONLY. Do not give by other routes. Intrathecal administration has resulted in death.

3. DISPOSAL

A vial is for single use only and the remaining solution must be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

VELCADE 3.5 mg powder for solution for injection
bortezomib

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What VELCADE is and what it is used for
2. What you need to know before you use VELCADE
3. How to use VELCADE
4. Possible side effects
5. How to store VELCADE
6. Contents of the pack and other information

1. What VELCADE is and what it is used for

VELCADE contains the active substance bortezomib, a so-called 'proteasome inhibitor'. Proteasomes play an important role in controlling cell function and growth. By interfering with their function, bortezomib can kill cancer cells.

VELCADE is used for the treatment of multiple myeloma (a cancer of the bone marrow) in patients older than 18 years:
- alone or together with the medicines pegylated liposomal doxorubicin or dexamethasone, for patients whose disease is worsening (progressive) after receiving at least one prior treatment and for whom blood stem cell transplantation was not successful or is unsuitable.
- in combination with the medicines melphalan and prednisone, for patients whose disease has not been previously treated and are unsuitable for high-dose chemotherapy with blood stem cell transplantation.
- in combination with the medicines dexamethasone or dexamethasone together with thalidomide, for patients whose disease has not been previously treated and before receiving high-dose chemotherapy with blood stem cell transplantation (induction treatment).

VELCADE is used for the treatment of mantle cell lymphoma (a type of cancer affecting the lymph nodes) in patients 18 years or older in combination with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone, for patients whose disease has not been previously treated and for whom blood stem cell transplantation is unsuitable.

2. What you need to know before you use VELCADE

Do not use VELCADE
- if you are allergic to bortezomib, boron or to any of the other ingredients of this medicine (listed in section 6)
- if you have certain severe lung or heart problems.

Warnings and precautions
You should tell your doctor if you have any of the following:
- low numbers of red or white blood cells
- bleeding problems and/or low number of platelets in your blood
- diarrhoea, constipation, nausea or vomiting

- fainting, dizziness or light-headedness in the past
- kidney problems
- moderate to severe liver problems
- numbness, tingling, or pain in the hands or feet (neuropathy) in the past
- heart or blood pressure problems
- shortness of breath or cough
- seizures
- shingles (localised including around the eyes or spread across the body)
- symptoms of tumor lysis syndrome such as muscle cramping, muscle weakness, confusion, visual loss or disturbances and shortness of breath
- memory loss, trouble thinking, difficulty with walking or loss of vision. These may be signs of a serious brain infection and your doctor may suggest further testing and follow-up.

You will have to take regular blood tests before and during your treatment with VELCADE, to check your blood cell counts regularly.

If you have mantle cell lymphoma and are given the medicine rituximab with VELCADE you should tell your doctor:
- if you think you have hepatitis infection now or have had it in the past. In a few cases, patients who have had hepatitis B might have a repeated attack of hepatitis, which can be fatal. If you have a history of hepatitis B infection you will be carefully checked by your doctor for signs of active hepatitis B.

You must read the package leaflets of all medicinal products to be taken in combination with VELCADE for information related to these medicines before starting treatment with VELCADE. When thalidomide is used, particular attention to pregnancy testing and prevention requirements is needed (see Pregnancy and breast-feeding in this section).

Children and adolescents
VELCADE should not be used in children and adolescents because it is not known how the medicine will affect them.

Other medicines and VELCADE
Please tell your doctor, or pharmacist if you are taking, have recently taken or might take any other medicines.
In particular, tell your doctor if you are using medicines containing any of the following active substances:
- ketoconazole, used to treat fungal infections
  ritonavir, used to treat HIV infection
- rifampicin, an antibiotic used to treat bacterial infections
- carbamazepine, phenytoin or phenobarbital used to treat epilepsy
- St. John's Wort (*Hypericum perforatum*), used for depression or other conditions
- oral antidiabetics

Pregnancy and breast-feeding
You should not use VELCADE if you are pregnant, unless clearly necessary.

Both men and women receiving VELCADE must use effective contraception during and for up to 3 months after treatment. If, despite these measures, pregnancy occurs, tell your doctor immediately.

You should not breast-feed while using VELCADE. Discuss with your doctor when it is safe to restart breast-feeding after finishing your treatment.

Thalidomide causes birth defects and foetal death. When VELCADE is given in combination with thalidomide you must follow the pregnancy prevention programme for thalidomide (see package leaflet for thalidomide).

Driving and using machines
VELCADE might cause tiredness, dizziness, fainting, or blurred vision. Do not drive or operate tools or machines if you experience such side effects; even if you do not, you should still be cautious.

3. How to use VELCADE

Your doctor will work out your dose of VELCADE according to your height and weight (body surface area). The usual starting dose of VELCADE is 1.3 mg/m^2 body surface area twice a week.
Your doctor may change the dose and total number of treatment cycles, depending on your response to the treatment on the occurrence of certain side effects and on your underlying conditions (e.g. liver problems).

Progressive multiple myeloma
When VELCADE is given alone, you will receive 4 doses of VELCADE intravenously or subcutaneously on days 1, 4, 8 and 11, followed by a 10-day 'rest period' without treatment. This 21-day period (3 weeks) corresponds to one treatment cycle. You might receive up to 8 cycles (24 weeks).

You may also be given VELCADE together with the medicines pegylated liposomal doxorubicin or dexamethasone.

When VELCADE is given together with pegylated liposomal doxorubicin, you will receive VELCADE intravenously or subcutaneously as a 21-day treatment cycle and pegylated liposomal doxorubicin 30 mg/m^2 is given on day 4 of the VELCADE 21-day treatment cycle as an intravenous infusion after the VELCADE injection.
You might receive up to 8 cycles (24 weeks).

When VELCADE is given together with dexamethasone, you will receive VELCADE intravenously or subcutaneously as a 21-day treatment cycle and dexamethasone 20 mg is given orally on days 1, 2, 4, 5, 8, 9, 11, and 12, of the VELCADE, 21-day treatment cycle.
You might receive up to 8 cycles (24 weeks).

Previously untreated multiple myeloma
If you have not been treated before for multiple myeloma, and **you are not** suitable for blood stem cell transplantation you will receive VELCADE together with two other medicines; melphalan and prednisone.
In this case, the duration of a treatment cycle is 42 days (6 weeks). You will receive 9 cycles (54 weeks).
- In cycles 1 to 4, VELCADE is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32.
- In cycles 5 to 9, VELCADE is administered once weekly on days 1, 8, 22 and 29.

Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) are both given orally on days 1, 2, 3 and 4 of the first week of each cycle.

If you have not been treated before for multiple myeloma, and **you are** suitable for blood stem cell transplantation you will receive VELCADE intravenously or subcutaneously together with the medicines dexamethasone, or dexamethasone and thalidomide, as induction treatment.

When VELCADE is given together with dexamethasone, you will receive VELCADE intravenously or subcutaneously as a 21-day treatment cycle and dexamethasone 40 mg is given orally on days 1, 2, 3, 4, 8, 9, 10 and 11 of the VELCADE 21-day treatment cycle.
You will receive 4 cycles (12 weeks).

When VELCADE is given together with thalidomide and dexamethasone, the duration of a treatment cycle is 28 days (4 weeks).

Dexamethasone 40 mg is given orally on days 1, 2, 3, 4, 8, 9, 10 and 11 of the VELCADE 28-day treatment cycle and thalidomide is given orally daily at 50 mg up to day 14 of the first cycle, and if tolerated the thalidomide dose is increased to 100 mg on days 15-28 and may be further increased to 200 mg daily from the second cycle onwards.
You might receive up to 6 cycles (24 weeks).

Previously untreated mantle cell lymphoma
If you have not been treated before for mantle cell lymphoma you will receive VELCADE intravenously or subcutaneously together with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone.
VELCADE is given intravenously or subcutaneously on days 1, 4, 8 and 11, followed by a 'rest period' without treatment. The duration of a treatment cycle is 21 days (3 weeks). You might receive up to 8 cycles (24 weeks).
The following medicinal products are given on day 1 of each VELCADE 21-day treatment cycle as intravenous infusions:
Rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2 and doxorubicin at 50 mg/m^2.
Prednisone is given orally at 100 mg/m^2 on days 1, 2, 3, 4 and 5 of the VELCADE treatment cycle.

How VELCADE is given
This medicine is for intravenous or subcutaneous use. VELCADE will be administered by a health care professional experienced in the use of cytotoxic medicines.
VELCADE powder has to be dissolved before administration. This will be done by a healthcare professional. The resulting solution is then either injected into a vein or under the skin. Injection into a vein is rapid, taking 3 to 5 seconds. Injection under the skin is in either the thighs or the abdomen.

If you are given too much VELCADE
As this medicine is being given by your doctor or nurse, it is unlikely that you will be given too much. In the unlikely event of an overdose, your doctor will monitor you for side effects.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these effects may be serious.

If you are given VELCADE for multiple myeloma or mantle cell lymphoma, tell your doctor straight away if you notice any of the following symptoms:
- muscle cramping, muscle weakness
- confusion, visual loss or disturbances, blindness, seizures, headaches
- shortness of breath, swelling of your feet or changes in your heart beat, high blood pressure, tiredness, fainting
- coughing and breathing difficulties or tightness in the chest.

Treatment with VELCADE can very commonly cause a decrease in the numbers of red and white blood cells and platelets in your blood. Therefore, you will have to take regular blood tests before and during your treatment with VELCADE, to check your blood cell counts regularly. You may experience a reduction in the number of:
- platelets, which may make you be more prone to bruising, or to bleeding without obvious injury (e.g., bleeding from your bowels, stomach, mouth and gum or bleeding in the brain or bleeding from the liver)
- red blood cells, which can cause anaemia, with symptoms such as tiredness and paleness
- white blood cells may make you more prone to infections or flu-like symptoms.

If you are given VELCADE for the treatment of multiple myeloma the side effects you may get are listed below:

Very common side effects (may affect more than 1 in 10 people)
- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage
- Reduction in the number of red blood cells and or white blood cells (see above)
- Fever
- Feeling sick (nausea) or vomiting, loss of appetite
- Constipation with or without bloating (can be severe)
- Diarrhoea: if this happens, it is important that you drink more water than usual. Your doctor may give you another medicine to control diarrhoea
- Tiredness (fatigue), feeling weak
- Muscle pain, bone pain

Common side effects (may affect up to 1 in 10 people)
- Low blood pressure, sudden fall of blood pressure on standing which may lead to fainting
- High blood pressure
- Reduced functioning of your kidneys
- Headache
- General ill feeling, pain, vertigo, light-headedness, a feeling of weakness or loss of consciousness
- Shivering
- Infections, including pneumonia, respiratory infections, bronchitis, fungal infections, coughing with phlegm, flu like illness
- Shingles (localised including around the eyes or spread across the body)
- Chest pains or shortness of breath with exercise
- Different types of rash
- Itching of the skin, lumps on the skin or dry skin
- Facial blushing or tiny broken capillaries
- Redness of the skin
- Dehydration
- Heartburn, bloating, belching, wind, stomach pain, bleeding from your bowels or stomach
- Alteration of liver functioning
- A sore mouth or lip, dry mouth, mouth ulcers or throat pain
- Weight loss, loss of taste
- Muscle cramps, muscle spasms, muscle weakness, pain in your limbs
- Blurred vision
- Infection of the outermost layer of the eye and the inner surface of the eyelids (conjunctivitis)
- Nose bleeds
- Difficulty or problems in sleeping, sweating, anxiety, mood swings, depressed mood, restlessness or agitation, changes in your mental status, disorientation
- Swelling of body, to include around eyes and other parts of the body

Uncommon side effects (may affect up to 1 in 100 people)
- Heart failure, heart attack, chest pain, chest discomfort, increased or reduced heart rate
- Failing of your kidneys
- Inflammation of a vein, blood clots in your veins and lungs
- Problems with blood clotting
- Insufficient circulation
- Inflammation of the lining around your heart or fluid around your heart
- Infections including urinary tract infections, the flu, herpes virus infections, ear infection and cellulitis
- Bloody stools, or bleeding from mucosal membranes, e.g., mouth, vagina
- Cerebrovascular disorders
- Paralysis, seizures, falling, movement disorders, abnormal or change in, or reduced sensation (feeling, hearing, tasting, smelling), attention disturbance, trembling, twitching

- Arthritis, including inflammation of the joints in the fingers, toes, and the jaw
- Disorders that affect your lungs, preventing your body from getting enough oxygen. Some of these include difficulty breathing, shortness of breath, shortness of breath without exercise, breathing that becomes shallow, difficult or stops, wheezing
- Hiccups, speech disorders
- Increased or decreased urine production (due to kidney damage), painful passing of urine or blood/proteins in the urine, fluid retention
- Altered levels of consciousness, confusion, memory impairment or loss
- Hypersensitivity
- Hearing loss, deafness or ringing in the ears, ear discomfort
- Hormone abnormality which may affect salt and water absorption
- Overactive thyroid gland
- Inability to produce enough insulin or resistance to normal levels of insulin
- Irritated or inflamed eyes, excessively wet eyes, painful eyes, dry eyes, eye infections, lump in the eyelid (chalazion), red and swollen eyelids, discharge from the eyes, abnormal vision, bleeding of the eye
- Swelling of your lymph glands
- Joint or muscle stiffness, sense of heaviness, pain in your groin
- Hair loss and abnormal hair texture
- Allergic reactions
- Redness or pain at the injection site
- Mouth pain
- Infections or inflammation of the mouth, mouth ulcers, oesophagus, stomach and intestines, sometimes associated with pain or bleeding, poor movement of the intestines (including blockage), abdominal or oesophageal discomfort, difficulty swallowing, vomiting of blood
- Skin infections
- Bacterial and viral infections
- Tooth infection
- Inflammation of the pancreas, obstruction of the bile duct
- Genital pain, problem having an erection
- Weight increase
- Thirst
- Hepatitis
- Injection site or injection device related disorders
- Skin reactions and disorders (which may be severe and life threatening), skin ulcers
- Bruises, falls and injuries
- Inflammation or haemorrhage of the blood vessels that can appear as small red or purple dots (usually on the legs) to large bruise-like patches under the skin or tissue
- Benign cysts
- A severe reversible brain condition which includes seizures, high blood pressure, headaches, tiredness, confusion, blindness or other vision problems.

Rare side effects (may affect up to 1 in 1,000 people)
- Heart problems to include heart attack, angina
- Flushing
- Discoloration of the veins
- Inflammation of the spinal nerve
- Problems with your ear, bleeding from your ear
- Underactivity of your thyroid gland
- Budd–Chiari syndrome (the clinical symptoms caused by blockage of the hepatic veins)
- Changes in or abnormal bowel function
- Bleeding in the brain
- Yellow discolouration of eyes and skin (jaundice)

- Serious allergic reaction (anaphylactic shock) signs of which may include difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse
- Breast disorders
- Vaginal tears
- Genital swelling
- Inability to tolerate alcohol consumption
- Wasting, or loss of body mass
- Increased appetite
- Fistula
- Joint effusion
- Cysts in the lining of joints (synovial cysts)
- Fracture
- Breakdown of muscle fibers leading to other complications
- Swelling of the liver, bleeding from the liver
- Cancer of the kidney
- Psoriasis like skin condition
- Cancer of the skin
- Paleness of the skin
- Increase of platelets or plasma cells (a type of white cell) in the blood
- Blood clot in small blood vessels (thrombotic microangiopathy)
- Abnormal reaction to blood transfusions
- Partial or total loss of vision
- Decreased sex drive
- Drooling
- Bulging eyes
- Sensitivity to light
- Rapid breathing
- Rectal pain
- Gallstones
- Hernia
- Injuries
- Brittle or weak nails
- Abnormal protein deposits in your vital organs
- Coma
- Intestinal ulcers
- Multi-organ failure
- Death

If you are given VELCADE together with other medicines for the treatment of mantle cell lymphoma the side effects you may get are listed below:

Very common side effects (may affect more than 1 in 10 people)
- Pneumonia
- Loss of appetite
- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage
- Nausea and vomiting
- Diarrhoea
- Mouth ulcers
- Constipation
- Muscle pain, bone pain
- Hair loss and abnormal hair texture

- Tiredness, feeling weak
- Fever

Common side effects (may affect up to 1 in 10 people)
- Shingles (localized including around the eyes or spread across the body)
- Herpes virus infections
- Bacterial and viral infections
- Respiratory infections, bronchitis, coughing with phlegm, flu like illness
- Fungal infections
- Hypersensitivity (allergic reaction)
- Inability to produce enough insulin or resistance to normal levels of insulin
- Fluid retention
- Difficulty or problems in sleeping
- Loss of conciousness
- Altered level of consciousness, confusion
- Feeling dizzy
- Increased heartbeat, high blood pressure, sweating,
- Abnormal vision, blurred vision
- Heart failure, heart attack, chest pain, chest discomfort, increased or reduced heart rate
- High or low blood pressure
- Sudden fall of blood pressure upon standing which may lead to fainting
- Shortness of breath with exercise
- Cough
- Hiccups
- Ringing in the ears, ear discomfort
- Bleeding from your bowels or stomach
- Heartburn
- Stomach pain, bloating
- Difficulty swallowing
- Infection or inflammation of the stomach and intentines
- Stomach pain
- Sore mouth or lip, throat pain
- Alteration of liver function
- Itching of skin
- Redness of skin
- Rash
- Muscle spasms
- Infection of the urinary tract
- Pain in limbs
- Swelling of body, to include eyes and other parts of the body
- Shivering
- Redness and pain at injection site
- General ill feeling
- Weight loss
- Weight increase

Uncommon side effects (may affect up to 1 in 100 people)
- Hepatitis
- Severe allergic reaction (anaphylactic reaction) signs of which may include difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse
- Movement disorders, paralysis, twitching
- Vertigo

- Hearing loss, deafness
- Disorders that affect your lungs, preventing your body from getting enough oxygen. Some of these include difficulty breathing, shortness of breath, shortness of breath without exercise, breathing that becomes shallow, difficult or stops, wheezing
- Blood clots in your lungs
- Yellow discoloration of the eyes and skin (jaundice)
- Lump in the eyelid (chalazion), red and swollen eyelids

Rare side effects (may affect up to 1 in 1,000 people)
- Blood clot in small blood vessels (thrombotic microangiopathy)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VELCADE

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the vial and the carton after EXP.

Do not store above 30°C. Keep the vial in the outer carton in order to protect from light.

The reconstituted solution should be used immediately after preparation. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. However, the reconstituted solution is stable for 8 hours at 25°C stored in the original vial and/or a syringe, with a total storage time for the reconstituted medicine not exceeding 8 hours prior to administration.

VELCADE is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What VELCADE contains
- The active substance is bortezomib. Each vial contains 3.5 mg of bortezomib (as a mannitol boronic ester).
- The other ingredients are mannitol (E421) and nitrogen.

Intravenous reconstitution:
After reconstitution, 1 ml of solution for intravenous injection contains 1 mg bortezomib.

Subcutaneous reconstitution:
After reconstitution, 1 ml of solution for subcutaneous injection contains 2.5 mg bortezomib.

What VELCADE looks like and contents of the pack
VELCADE powder for solution for injection is a white to off-white cake or powder.

Each carton of VELCADE 3.5 mg powder for solution for injection contains a glass 10 ml vial with a royal blue cap, in a transparent blister pack.

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This leaflet was last revised in

Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

1. RECONSTITUTION FOR INTRAVENOUS INJECTION

Note: VELCADE is a cytotoxic agent. Therefore, caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.

ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF VELCADE SINCE NO PRESERVATIVE IS PRESENT.

1.1 **Preparation of the 3.5 mg vial: carefully add 3.5 ml** of sterile, 9 mg/ml (0.9%) sodium chloride solution for injection to the vial containing the VELCADE powder by using a syringe of the appropriate size without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

The concentration of the resulting solution will be 1 mg/ml. The solution will be clear and colourless, with a final pH of 4 to 7. You do not need to check the pH of the solution.

1.2 Before administration, visually inspect the solution for particulate matter and discolouration. If any discolouration or particulate matter is observed, the solution should be discarded. Be sure that the correct dose is being given for the **intravenous route** of administration (1 mg/ml).

1.3 The reconstituted solution is preservative free and should be used immediately after preparation. However, the chemical and physical in-use stability has been demonstrated for 8 hours at 25°C stored in the original vial and/or a syringe. The total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

It is not necessary to protect the reconstituted medicinal product from light.

2. ADMINISTRATION

- Once dissolved, withdraw the appropriate amount of the reconstituted solution according to calculated dose based upon the patient´s Body Surface Area.
- Confirm the dose and concentration in the syringe prior to use (check that the syringe is marked as intravenous administration).
- Inject the solution as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter into a vein.
- Flush the peripheral or intravenous catheter with sterile, 9 mg/ml (0.9%) sodium chloride solution.

VELCADE 3.5 mg powder for solution for injection IS FOR SUBCUTANEOUS OR INTRAVENOUS USE. Do not give by other routes. Intrathecal administration has resulted in death.

3. DISPOSAL

A vial is for single use only and the remaining solution must be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

The following information is intended for healthcare professionals only:

Only the 3.5 mg vial can be administered subcutaneously, as described below.

1. RECONSTITUTION FOR SUBCUTANEOUS INJECTION

Note: VELCADE is a cytotoxic agent. Therefore, caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.

ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF VELCADE SINCE NO PRESERVATIVE IS PRESENT.

1.1 **Preparation of the 3.5 mg vial: carefully add 1.4 ml** of sterile, 9 mg/ml (0.9%) sodium chloride solution for injection to the vial containing the VELCADE powder by using a syringe of the appropriate size without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

The concentration of the resulting solution will be 2.5 mg/ml. The solution will be clear and colourless, with a final pH of 4 to 7. You do not need to check the pH of the solution.

1.2 Before administration, visually inspect the solution for particulate matter and discolouration. If any discolouration or particulate matter is observed, the solution should be discarded. Be sure that the correct dose is being given for the **subcutaneous** route of administration (2.5 mg/ml).

1.3 The reconstituted product is preservative free and should be used immediately after preparation. However, the chemical and physical in-use stability has been demonstrated for 8 hours at 25°C stored in the original vial and/or a syringe. The total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

It is not necessary to protect the reconstituted medicinal product from light.

2. ADMINISTRATION

- Once dissolved, withdraw the appropriate amount of the reconstituted solution according to calculated dose based upon the patient´s Body Surface Area.
- Confirm the dose and concentration in the syringe prior to use. (check that the syringe is marked as subcutaneous administration).
- Inject the solution subcutaneously, under a 45-90°angle.
- The reconstituted solution is administered subcutaneously through the thighs (right or left) or abdomen (right or left).
- Injection sites should be rotated for successive injections.
- If local injection site reactions occur following VELCADE injection subcutaneously, either a less concentrated VELCADE solution (1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously or a switch to intravenous injection is recommended.

VELCADE 3.5 mg powder for solution for injection IS FOR SUBCUTANEOUS OR INTRAVENOUS USE. Do not give by other routes. Intrathecal administration has resulted in death.

3. DISPOSAL

A vial is for single use only and the remaining solution must be discarded.

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

1.7　同種同効品一覧表

該当なし

201x 年 x 月改訂（第 1 版）
貯　　法：室温保存
有効期間：36 ヵ月

日本標準商品分類番号
874291

抗悪性腫瘍剤（プロテアソーム阻害剤）

毒薬
処方箋医薬品※

注射用ボルテゾミブ

ベルケイド®注射用 3mg

VELCADE® Injection

※注意－医師等の処方箋により使用すること

承認番号	21800AMX10868000
販売開始	2006 年 12 月

1. 警告

1.1 本剤の投与は、緊急時に十分対応できる医療施設において、造血器悪性腫瘍又は全身性 AL アミロイドーシスの治療に対して十分な知識・経験を持つ医師のもとで、本剤の投与が適切と判断される症例のみに行うこと。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分に説明し、同意を得てから投与を開始すること。

1.2 治療初期は入院環境で医師の管理下にて適切な処置を行うこと。

1.3 国内の臨床試験において、本剤との因果関係の否定できない肺障害（間質性肺炎）による死亡例が認められている。海外ではまれであるが、国内では本剤との因果関係の否定できない肺障害（間質性肺炎、肺水腫、急性呼吸窮迫症候群、胸水等）がより高頻度に発生する可能性があるため、特に以下の事項に十分注意すること。［8.1、9.1.1、11.1.1 参照］

1.3.1 本剤による治療を開始するにあたり、胸部 X 線検査、胸部 CT 検査等を実施し、異常の有無を確認した上で、治療開始の可否を慎重に判断すること。

1.3.2 本剤による治療中及び治療後、特に治療開始後早期は、息切れ、呼吸困難、咳、発熱等の自覚症状や、胸部聴診所見、呼吸数等での異常の有無を慎重に観察すること。必要に応じて動脈血酸素飽和度や胸部 CT 検査等を適切に実施し、経過を観察すること。本剤による肺障害が疑われた場合には、投与中止も含め適切な処置を行うこと。

2. 禁忌（次の患者には投与しないこと）

ボルテゾミブ、マンニトール又はホウ素に対して過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

販売名	ベルケイド注射用 3mg
有効成分	（1 バイアル中） ボルテゾミブ 3mg 含有
添加剤	D-マンニトール 30 mg

3.2 製剤の性状

剤形	凍結乾燥注射剤
色・性状	白色～微黄白色の塊又は粉末
pH	4.0～7.0 （本剤 1 バイアルを生理食塩液 3mL 又は 1.2mL に溶解したとき）

4. 効能又は効果

○多発性骨髄腫
○マントル細胞リンパ腫
○原発性マクログロブリン血症及びリンパ形質細胞リンパ腫
○全身性 AL アミロイドーシス

5. 効能又は効果に関連する注意

〈多発性骨髄腫、マントル細胞リンパ腫及び全身性 AL アミロイドーシス〉

「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。

6. 用法及び用量

〈多発性骨髄腫〉

通常、成人に1日1回、ボルテゾミブとして1.3mg/m²（体表面積）を以下のA法又はB法で静脈内投与又は皮下投与する。本剤は最低72時間空けて投与すること。

A法：

他の抗悪性腫瘍剤との併用において、週 2 回、2 週間（1、4、8、11 日目）投与した後、10 日間休薬（12～21 日目）する。この 3 週間を 1 サイクルとし、2 又は 8 サイクルまで投与を繰り返す。3 又は 9 サイクル以降は、週 1 回、2 週間（1、8 日目）投与し、13 日間休薬（9～21 日目）する。この 3 週間を 1 サイクルとし、18 サイクルまで投与を繰り返す。週 1 回投与への移行時期は併用する抗悪性腫瘍剤を考慮して選択すること。

B 法（再発又は難治性の場合に限る）：

週 2 回、2 週間（1、4、8、11 日目）投与した後、10 日間休薬（12～21 日目）する。この 3 週間を 1 サイクルとし、投与を繰り返す。8サイクルを超えて継続投与する場合には上記の用法・用量で投与を継続するか、又は維持療法として週1回、4週間（1、8、15、22日目）投与した後、13日間休薬（23～35日目）する。この5週間を1サイクルとし、投与を繰り返す。

〈マントル細胞リンパ腫〉

他の抗悪性腫瘍剤との併用において、通常、成人に1日1回、ボルテゾミブとして1.3mg/m²（体表面積）を1、4、8、11日目に静脈内投与した後、10日間休薬（12～21日目）する。この3週間を1サイクルとし、6サイクルまで（6サイクル目に初めて奏効が認められた場合は8サイクルまで）投与を繰り返す。本剤は最低72時間空けて投与すること。なお、静脈内投与が困難な場合には、皮下投与することもできる。

〈原発性マクログロブリン血症及びリンパ形質細胞リンパ腫〉

通常、成人に1日1回、ボルテゾミブとして1.3mg/m²（体表面積）を1、4、8、11日目に静脈内投与又は皮下投与した後、10日間休薬（12～21日目）する。この3週間を1サイクルとし、投与を繰り返す。本剤は最低72時間空けて投与すること。

〈全身性ALアミロイドーシス〉

他の薬剤との併用において、通常、成人に1日1回、ボルテゾミブとして1.3 mg/m²（体表面積）を1、8、15、22日目に皮下投与する。28日間を1サイクルとし、6サイクルまで投与を繰り返す。注射部位反応が発現した場合には、静脈内投与することもできる。

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 未治療の多発性骨髄腫、マントル細胞リンパ腫及び全身性 AL アミロイドーシスに対し、本剤単独投与での有効性及び安全性は確立していない。

〈多発性骨髄腫〉

7.2 週1回投与への移行時期、本剤と併用する抗悪性腫瘍剤等について、「17. 臨床成績」の項の内容を熟知した上で選択すること。

〈全身性 AL アミロイドーシス〉

7.3 本剤と併用する薬剤等について、「17. 臨床成績」の項の内容を熟知した上で選択すること。

〈マントル細胞リンパ腫〉

7.4 本剤を含むがん化学療法については、「17. 臨床成績」の項の内容を熟知した上で、患者の状態や化学療法歴に応じて選択をすること。

7.5 皮下投与の臨床試験成績は得られていない。

7.6 本剤の投与については、以下の記載に従って、適切に減量、休薬又は投与中止の判断を行うこと。

〈多発性骨髄腫、原発性マクログロブリン血症、リンパ形質細胞リンパ腫及び全身性ALアミロイドーシス〉

・Grade 3/4※の副作用の場合（末梢性ニューロパチー又は神経障害性疼痛を除く）

Grade 3以上の非血液毒性（末梢性ニューロパチー・神経障害性疼痛を除く）又はGrade 4の血液毒性に該当する副作用が発現した場合は、回復するまで休薬する。投与を再開する場合には、本剤の投与による有益性と危険性を慎重に検討した上で、下表を目安として減量等を考慮する。副作用が回復しない場合又は最低投与量（0.7mg/m²）でも再発する場合は、本剤の投与中止を考慮する。

最新の添付文書を参照すること

Grade 3/4 の副作用（末梢性ニューロパチー又は神経障害性疼痛を除く）に対する減量の目安

副作用発現時の投与量	減量の目安
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	投与中止

・末梢性ニューロパチー又は神経障害性疼痛について

本剤に起因すると考えられる末梢性ニューロパチー又は神経障害性疼痛が発現した場合は、以下に示す用法及び用量変更の目安に従って減量、休薬又は中止すること。[8.4、11.1.3 参照]

末梢性ニューロパチー又は神経障害性疼痛に対する用法及び用量変更の目安

NCI-CTCAE Grade※（症状）	用法及び用量変更の目安
疼痛又は機能消失を伴わないGrade 1（症状がない；深部腱反射の低下又は知覚異常）	なし
疼痛を伴うGrade 1又はGrade 2（中等度の症状がある；身の回り以外の日常生活動作の制限）	1.3mg/m^2 の場合1.0mg/m^{2}へ減量又は1.0mg/m^2 の場合0.7mg/m^{2}へ減量
疼痛を伴うGrade 2又はGrade 3（高度の症状がある；身の回りの日常生活動作の制限）	回復するまで休薬。症状が回復した場合は、0.7mg/m^{2}に減量した上で週1回投与に変更
Grade 4（生命を脅かす；緊急処置を要する）	投与中止

〈マントル細胞リンパ腫〉

新たなサイクルを開始する前に以下を確認すること。

- 血小板数が100,000/μL以上、好中球数が1,500/μL以上及びヘモグロビン値が8g/dL以上であること。[8.6参照]
- 非血液毒性がGrade 1※又は投与前値に回復していること。

副作用発現時の用法及び用量変更の目安

副作用	用法及び用量変更の目安
発熱を伴うGrade 3以上の好中球減少症、7日間を超えて持続するGrade 4の好中球減少症、血小板数10,000/μL未満が発現した場合	好中球数が750/μL以上、血小板数が25,000/μL以上に回復するまで最長2週間本剤を休薬する。 ・本剤休薬後も副作用が上記の基準まで回復しない場合には、本剤の投与を中止すること。 ・副作用が上記の基準まで回復した場合には、本剤の投与量を1段階減量して投与する。（1.3mg/m^{2}の場合1.0mg/m^{2}へ減量、1.0mg/m^{2}の場合0.7mg/m^{2}へ減量）
本剤投与日（各サイクルの第1日目以外）に血小板数が25,000/μL未満又は好中球数が750/μL未満の場合	本剤の投与を最長2日間延期し、2日を越える延期を要する場合は本剤を休薬する。
Grade 3以上の非血液毒性が発現した場合（末梢性ニューロパチー又は神経障害性疼痛を除く）	Grade 2以下に回復するまで本剤を休薬する。回復した場合は本剤の投与量を1段階減量して投与する。（1.3mg/m^{2}の場合1.0mg/m^{2}へ減量、1.0mg/m^{2}の場合0.7mg/m^{2}へ減量）
末梢性ニューロパチー又は神経障害性疼痛が発現した場合	「7.6 末梢性ニューロパチー又は神経障害性疼痛について」に従うこと。

※NCI-CTCAE v4.0

8. 重要な基本的注意

〈効能共通〉

8.1 肺障害があらわれることがあるので、息切れ、呼吸困難、胸水、咳、及び発熱等の自覚症状や、胸部聴診所見、呼吸数等での異常の有無を慎重に観察すること。また、必要に応じて動脈血酸素飽和度や胸部CT等の検査を適切に実施し、慎重に経過を観察すること。肺障害の危険因子は現時点では明確でないため、肺障害の既往歴のない患者においても、慎重な経過観察を行う必要がある。[1.3.1、1.3.2、9.1.1、11.1.1 参照]

8.2 心障害による死亡例、うっ血性心不全の急性発現又は増悪、心嚢液貯留、左室駆出率低下が報告されているため、心障害の既往や症状の危険因子がある場合には、患者の状態には十分に注意すること。[11.1.2 参照]

8.3 本剤の投与により B 型肝炎ウイルスの再活性化による肝炎があらわれることがあるので、本剤投与に先立って肝炎ウイルス感染の有無を確認し、本剤投与前に適切な処置を行うこと。[9.1.2、11.1.6 参照]

8.4 末梢神経障害があらわれることがあるので、灼熱感、知覚過敏、感覚減退、錯感覚、不快感、神経障害性疼痛等のニューロパチーの症状について観察すること。また、末梢性ニューロパチーが発現する可能性のある薬剤を併用する場合には注意すること。[7.6、9.1.3、11.1.3 参照]

8.5 国内臨床試験では重度の発熱性好中球減少症、好中球減少症（好中球数減少）及び貧血（ヘモグロビン減少）が認められているため、頻回に臨床検査（血液検査等）を行うなど、患者の状態を十分に観察すること。[11.1.4 参照]

8.6 本剤は血小板減少症を引き起こすことが認められている。本剤の投与前に毎回血小板数を確認すること。本剤投与により発現した血小板減少に伴う胃腸出血及び脳出血の報告例があるので、必要に応じ輸血を考慮すること。[7.6、11.1.4 参照]

8.7 本剤の投与により悪心、下痢、便秘及び嘔吐の発現が認められており、制吐剤又は止痢剤による処置を要することがある。脱水症状を予防するため、必要に応じ補液及び電解質補充を行うこと。本剤の投与期間中は嘔吐又は下痢がみられるため、患者には脱水症状を避ける適切な対処方法を指導すること。浮動性めまい、頭部ふらふら感又は失神発作があらわれた場合には、医師の診察を受けるよう患者を指導すること。
また、イレウスが報告されているため、便秘を認めた患者は慎重に観察すること。[11.1.5 参照]

8.8 肝機能障害があらわれることがあるので、定期的に肝機能検査を行うこと。[11.1.6 参照]

8.9 低血圧（起立性低血圧を含む）の管理には、必要に応じて降圧剤の調節、水分補給、ミネラルコルチコイド又は交感神経作動薬の投与等の支持療法を行うこと。[9.1.4、11.1.7 参照]

8.10 疲労、浮動性めまい、失神、起立性低血圧、霧視が起こることがあるので、本剤投与中の患者には自動車の運転等危険を伴う機械の操作に従事させないよう注意すること。

8.11 腫瘍量の急激な減少に伴い、腫瘍崩壊症候群（tumor lysis syndrome）があらわれることがあるため、予防措置として、高尿酸血症治療剤の投与及び適切な水分補給等を考慮すること。急激に腫瘍量が減少した患者においては血清中電解質濃度及び腎機能検査を行うなど、患者の状態を十分に観察すること。[11.1.8 参照]

〈原発性マクログロブリン血症及びリンパ形質細胞リンパ腫〉

8.12 本剤を使用する際には、関連文献（「医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書」等）[3] を熟読すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 間質性肺炎、肺線維症等の肺障害の既往歴のある患者

投与前に間質性陰影を認めた患者で致死的な急性肺障害の経過をたどる例が報告されている。[1.3.1、1.3.2、8.1、11.1.1 参照]

9.1.2 B 型肝炎ウイルスキャリアの患者又は HBs 抗原陰性で HBc 抗体陽性若しくは HBs 抗体陽性の患者

本剤の投与開始後は継続して肝機能検査や肝炎ウイルスマーカーのモニタリングを行うなど、B 型肝炎ウイルスの再活性化の徴候や症状の発現に注意すること。本剤の投与により B 型肝炎ウイルスの再活性化による肝炎があらわれることがある。[8.3、11.1.6 参照]

9.1.3 末梢性ニューロパチーの症状（足又は手のしびれ、疼痛又は灼熱感）や徴候のある患者

本剤の投与期間中に症状が増悪（Grade 3 以上を含む）するおそれがある。[8.4、11.1.3 参照]

9.1.4 失神の既往や症状がある患者、低血圧が発現する可能性のある薬剤を投与中の患者及び脱水状態にある患者

患者の状態を十分に観察すること。低血圧（起立性低血圧を含む）が投与期間を通じ報告されている。[8.9、11.1.7 参照]

9.1.5 経口血糖降下剤を併用した糖尿病患者

血糖値を注意深く観察し、経口血糖降下剤の用量に留意して慎重に投与すること。海外臨床試験において、低血糖及び高血糖が報告されている。

9.3 肝機能障害患者

本剤のクリアランスが低下し、副作用が強くあらわれるおそれがある。[16.6.2 参照]

9.4 生殖能を有する者

妊娠可能年齢にある女性においては本剤投与中及び投与終了後一定期間は避妊するよう指導すること。

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、原則として投与し

最新の添付文書を参照すること

ないこと。動物実験では、妊娠ウサギの器官形成期にボルテゾミブを 0.05mg/kg(0.6mg/m²) 投与したところ、有意な着床後死亡の増加とそれに伴う生存胎児数の減少が認められた。これらの生存胎児は有意な体重の減少も示した。

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。

9.7 小児等

小児等を対象とした臨床試験は実施していない。

9.8 高齢者

患者の状態を観察しながら慎重に投与すること。海外臨床試験において、65 歳以上と 65 歳未満の患者で安全性及び有効性に差は認められなかったが、高齢者では一般に生理機能が低下している。

なお、年齢別での Grade 3 以上の有害事象の発現頻度は、再発又は難治性の多発性骨髄腫を対象とした海外第Ⅲ相試験(039 試験)の本剤群においては 50 歳以下で 64%(27/42 例)、51～64 歳で 78%(128/165 例)、65 歳以上で 75%(93/124 例)であった。また、海外第Ⅱ相試験(024 試験及び 025 試験)においては 50 歳以下で 74%(29/39 例)、51～65 歳で 80%(104/130 例)、66 歳以上で 85%(74/87 例)であった。

10. 相互作用

ヒト肝ミクロソームを用いた *in vitro* 試験より、ボルテゾミブがチトクローム P450 3A4、2C19 及び 1A2 の基質であることが示されている。本剤と CYP3A4 の基質、阻害剤又は誘導剤を併用している患者においては、副作用又は効果の減弱について注意深く観察すること。

10.2 併用注意(併用に注意すること)

薬剤名等	臨床症状・措置方法	機序・危険因子
CYP3A4 阻害剤 ケトコナゾール[注)] 等	ケトコナゾール(400mg/日を 4 日間反復経口投与)と併用したとき、ボルテゾミブの AUC は 35%増加した。[4)]	これらの薬剤の CYP3A4 に対する阻害作用により、本剤の代謝が阻害される。
CYP3A4 誘導剤 リファンピシン等	リファンピシン(600mg/日を 7 日間反復経口投与)と併用したとき、ボルテゾミブの AUC は 45%低下した。[5)]	これらの薬剤の CYP3A4 に対する誘導作用により、本剤の代謝が促進される。

注) 国内では外用剤のみ発売

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 肺障害

間質性肺炎(0.2%、2.5%[注 1)])、急性肺水腫(0.5%、0.4%[注 1)])、胸水(0.1%、1.8%[注 1)])、急性呼吸窮迫症候群(0.1%、頻度不明[注 1)])があらわれることがある。国内の臨床試験及び市販後の報告において、本剤との因果関係の否定できない肺障害(間質性肺炎)による死亡例が認められており[1)、2)]、海外と比較して肺障害の発生頻度が高い可能性がある。なお、肺障害の対処方法及び可能性のあるリスク因子について臨床試験では確認されていない。急性骨髄性白血病に対し、本剤、ダウノルビシン塩酸塩及び高用量シタラビンの 24 時間持続点滴(2000mg/m²/日)を併用した海外の臨床試験において、本剤との因果関係を否定できない急性呼吸窮迫症候群による死亡が報告されている。[1.3.1、1.3.2、8.1、9.1.1 参照]

11.1.2 心障害

うっ血性心不全(1.3%)、心嚢液貯留(0.1%)、心原性ショック(0.1%)、心停止(0.1%)、心肺停止(頻度不明)があらわれることがある。また、投与前の左室駆出率に異常の無い患者においても左室駆出率低下が報告されている。海外臨床試験において QT 間隔延長の報告があるが、薬剤との関連性については明らかになっていない。再発又は難治性の多発性骨髄腫を対象とした海外第Ⅲ相試験において、本剤群及びデキサメタゾン群で発現した心障害の発現頻度はそれぞれ 14%及び 12%であった。そのうち心不全等(急性肺水腫、心不全、うっ血性心不全、心原性ショック、肺水腫)の発現頻度はそれぞれ 5%及び 4%であった。[8.2 参照]

11.1.3 末梢神経障害

末梢性感覚ニューロパチー(28.2%)、神経障害性疼痛(14.8%)、錯感覚(8.6%)、末梢性ニューロパチー(8.1%)、感覚減退(3.6%)、末梢性運動ニューロパチー(2.3%)、灼熱感(0.4%)があらわれることがあり、重症の感覚性ニューロパチーも報告されている。本剤の投与により、感覚障害による末梢性ニューロパチーが主に認められるが、感覚障害と運動障害が混在するニューロパチーの発現例も報告されている。末梢性ニューロパチーに加えて、起立性低血圧やイレウスを伴う重度の便秘等、一部の有害事象に自律神経ニューロパチーが関与している可能性があるが、十分な情報は得られていない。また、本剤の投与により糖尿病性ニューロパチー等の基礎疾患を悪化させる可能性がある。再発又は難治性の多発性骨髄腫を対象とした海外第Ⅲ相試験において Grade 2 以上の末梢性ニューロパチーを認めた患者では用量調整により末梢性ニューロパチーの改善あるいは回復が 51%で認められた。また、海外第Ⅱ相試験において Grade 3 以上の末梢性ニューロパチーを発現した患者又は Grade 2 のニューロパチーを呈し、投与を中止した患者では、末梢性ニューロパチーの改善あるいは回復が 73%で認められた。[7.6、8.4、9.1.3 参照]

11.1.4 骨髄抑制

血小板減少(39.0%)、好中球減少(34.8%)、貧血(21.9%)、白血球減少(17.9%)、リンパ球減少(10.9%)、発熱性好中球減少症(2.8%)、汎血球減少(0.1%)があらわれることがある。骨髄機能が抑制された結果、感染症(敗血症性ショック等)や出血等の重篤な副作用が発現することがある。再発又は難治性の多発性骨髄腫を対象とした海外第Ⅲ相試験における重症の出血(Grade 3 以上)の発現率は本剤群で 4%、デキサメタゾン群で 5%であった。血小板数は各サイクルの 11 日目に最低値に達し、通常は次サイクル開始前までに回復した。血小板数の減少と回復のパターンは週 2 回投与の 8 サイクルにわたり一貫しており、蓄積性の血小板減少症は認められなかった。再発又は難治性の多発性骨髄腫を対象とした海外第Ⅲ相試験において血小板数の最低値の平均は、投与開始前の約 40%であった。再発又は難治性の多発性骨髄腫を対象とした海外第Ⅲ相試験における投与開始前の血小板数と血小板減少症の重症度との関係を以下の表に示す。[8.5、8.6 参照]

再発又は難治性の多発性骨髄腫を対象とした海外第Ⅲ相試験における投与開始前の血小板数と血小板減少症の重症度との関係

投与開始前の血小板数[注 2)]	患者数(n=331)[注 3)]	10,000/μL 未満の患者数(%)	10,000～25,000/μL の患者数(%)
75,000/μL 以上	309	8(3%)	36(12%)
50,000/μL 以上 75,000/μL 未満	14	2(14%)	11(79%)
10,000/μL 以上 50,000/μL 未満	7	1(14%)	5(71%)

注 2) 投与開始前の血小板数として 50,000/μL 以上を臨床試験の選択基準とした。

注 3) 投与開始前のデータが 1 例で不明

11.1.5 イレウス(0.7%)

食欲不振、嘔吐、便秘、腹部膨満感等の症状があらわれた場合には適切な処置を行うこと。[8.7 参照]

11.1.6 肝機能障害

AST の増加(0.7%)、ALT の増加(0.7%)、γ-GTP の増加(0.6%)、ALP の増加(0.5%)及び血中ビリルビンの増加(0.6%)等を伴う肝機能障害(B 型肝炎ウイルスの再活性化によるものを含む)があらわれることがある。[8.3、8.8、9.1.2 参照]

11.1.7 低血圧

低血圧(3.0%)、起立性低血圧(2.2%)があらわれることがある。低血圧の機序は不明であるが、一部は自律神経ニューロパチーが関与している可能性がある。[8.9、9.1.4 参照]

11.1.8 腫瘍崩壊症候群(0.3%)[8.11 参照]

11.1.9 皮膚粘膜眼症候群(Stevens-Johnson 症候群)、中毒性表皮壊死症(Toxic Epidermal Necrolysis:TEN)(頻度不明)

11.1.10 発熱(12.4%)

本剤の投与日から翌日にかけて高頻度に Grade 1～2 の薬剤性の発熱があらわれることがあるので、患者の状態を観察し、必要に応じて解熱剤等による処置を考慮すること。また発熱が持続する場合や呼吸器症状を伴う場合には、肺障害の可能性について注意すること。

11.1.11 可逆性後白質脳症症候群(頻度不明)

痙攣、血圧上昇、頭痛、意識障害、錯乱、視覚障害等があらわれることがある。

11.1.12 進行性多巣性白質脳症(頻度不明)

本剤の治療期間中及び治療終了後は患者の状態を十分に観察し、意識障害、認知障害、麻痺症状(片麻痺、四肢麻痺)、言語障害等の症状があらわれた場合は、MRI による画像診断及び脳脊髄液検査を行うとともに、投与を中止し、適切な処置を行うこと。

最新の添付文書を参照すること

注 1）日本人における発現率（多発性骨髄腫を対象とした静脈内投与における国内臨床試験、特定使用成績調査及び使用成績調査、並びにマントル細胞リンパ腫、多発性骨髄腫及び全身性 AL アミロイドーシスを対象とした国際共同試験（日本人症例のみ）の集計）

11.2 その他の副作用

	10%以上	10%未満 5%以上	5%未満	頻度不明
感染症	感染	帯状疱疹、肺炎	単純ヘルペス、鼻咽頭炎、敗血症、口腔カンジダ症、麦粒腫、感染性腸炎、膀胱炎、中耳炎、蜂巣炎、毛包炎	気管支肺炎、白癬感染、外耳炎
血液			出血、白血球数増加、好中球数増加、単球数増加	
免疫系障害			過敏症	
代謝・栄養	食欲不振		体重減少、脱水、高血糖、高尿酸血症、低アルブミン血症、低血糖症、高アミラーゼ血症	高コレステロール血症
電解質			低カリウム血症、低ナトリウム血症、高カリウム血症、高カルシウム血症	高ナトリウム血症
精神神経系		頭痛、不眠症	浮動性めまい、うつ病、失神、味覚異常、嗜眠、神経痛、不安、痙攣、傾眠、体位性めまい	嗅覚錯誤
眼			霧視、結膜炎、眼瞼炎、眼部腫脹、ドライアイ、霰粒腫	角膜びらん、眼瞼出血、後天性涙腺炎
循環器			高血圧、心房細動、動悸、頻脈、期外収縮、不整脈、心房粗動、徐脈	心電図 QT 延長
呼吸器			呼吸困難、咳嗽、鼻出血、咽喉頭疼痛、鼻漏、肺高血圧症	喀血、上気道の炎症、咽頭不快感、無気肺、胸膜炎、気胸
消化器	下痢、悪心、便秘、嘔吐	腹痛	消化不良、口内炎、腹部膨満、胃炎、鼓腸、胃腸出血、歯肉炎、嚥下障害、胃食道逆流、腸炎、過敏性腸症候群、歯周炎、レッチング、舌潰瘍、おくび、齲歯	口唇炎、耳下腺腫大
肝臓			肝機能異常	肝障害
皮膚		発疹	そう痒症、脱毛症、紅斑、多汗症、蕁麻疹、点状出血、顔面腫脹、紫斑、多形紅斑、薬疹、紅色汗疹、皮膚出血	好中球浸潤・有痛性紅斑・発熱を伴う皮膚障害（Sweet 症候群）、丘疹、水疱性皮膚炎
筋骨格		筋骨格痛	筋痙縮、筋痛、筋力低下、骨痛、筋骨格硬直、関節炎	
腎臓・泌尿器			腎機能障害、排尿障害（尿閉、神経因性膀胱等）、尿中血陽性	蛋白尿、β_2 ミクログロブリン増加、尿沈渣異常
全身	疲労、無力症	浮腫	悪寒、疼痛、倦怠感、口渇、胸痛、顔面浮腫	
その他			注射部位反応、静脈炎、潮紅、血中クレアチニン増加、総蛋白減少、ほてり、PO_2 低下、末梢冷感、血中重炭酸塩減少、血中尿酸減少	LDH 増加、CRP 増加、腫瘍熱、PO_2 上昇、血中クレアチニン減少、総蛋白増加、血中重炭酸塩増加

13. 過量投与

13.1 徴候、症状

推奨用量の 2 倍を超えた過量投与により、致命的な転帰を伴う急性の症候性低血圧及び血小板減少症が報告されている。

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 静脈内投与

1 バイアルを日局生理食塩液 3.0mL で溶解して使用すること。

14.1.2 皮下投与

1 バイアルを日局生理食塩液 1.2mL で溶解して使用すること。

注射液の調製法

投与経路	ボルテゾミブ（mg/バイアル）	日局生理食塩液	ボルテゾミブ最終濃度
静脈内投与	3.0mg	3.0mL	1.0mg/mL
皮下投与	3.0mg	1.2mL	2.5mg/mL

14.1.3 本剤の取り扱い及び調製にあたっては、手袋を使用するなど慎重に行うこと。本剤が皮膚又は粘液に触れた場合には、直ちに石鹸でよく洗うこと。

14.2 薬剤投与時の注意

本剤のバイアルは 1 回使い切りである。溶解後は 8 時間以内に使用すること。バイアル中の未使用残液は適切に廃棄すること。

14.2.1 静脈内投与

他の薬剤の混入を避けるため、本剤投与のためのルートを留置して実施すること。他の薬剤が投与されているルートを用いての投与は行わないこと。また、延長チューブを使用した際は、投与後速やかに日局生理食塩液でフラッシングを行うこと。

14.2.2 皮下投与

繰り返し皮下投与する場合には、左右の大腿部、腹部等に交互に投与するなど同一注射部位を避けること。

15. その他の注意

15.2 非臨床試験に基づく情報

15.2.1 動物（サル及びイヌ）を用いた試験において、ボルテゾミブを体表面積換算で臨床推奨用量の約 2～3 倍量を静脈内投与することにより、心拍数増加、心筋収縮力減弱及び低血圧が認められ、死に至った。この心筋収縮力減弱及び低血圧の状態においても、陽性変力作用を示す薬剤あるいは昇圧剤投与に対する反応は認められた。イヌの試験において、致死用量では QTc 間隔の軽度な延長が認められた。[6)]

15.2.2 動物実験（ラット）において、0.20 及び 0.15mg/kg（1.20 及び 0.90mg/m^2）群で精巣-精上皮の変性/萎縮及び低用量から卵巣黄体の単細胞壊死が認められた[7)]。

15.2.3 チャイニーズハムスター卵巣細胞を用いた *in vitro* 染色体異常試験で、評価を行った最低用量である 3.125μg/mL 以上で染色体異常誘発性（構造的染色体異常）を示した[8)]。

16. 薬物動態

16.1 血中濃度

16.1.1 単独投与

再発又は難治性の多発性骨髄腫患者に、本剤 0.7、1.0 又は 1.3mg/m^2（各 n=3、6 又は 5～7）を単独で、1 日 1 回、週 2 回、2 週間（1、4、8、11 日目）静脈内投与したときの 1 日目及び 11 日目における血漿中ボルテゾミブ濃度を検討した。

各用量群の血漿中濃度推移は類似しており、速やかな分布相とそれに続く緩やかな長い消失相を特徴とする二相性の低下を示した。また、最終消失相における分布容積（V_z）より、ボルテゾミブの組織移行性が良好であることが示唆された。投与日間での比較の結果、1 日目と比較し、11 日目において、消失半減期（$t_{1/2}$）の延長、全身クリアランス（CL）の低下が各用量群で見られた。このことに伴い、投与終了時の血漿中濃度（C_0）並びに血漿中濃度-時間曲線下面積（AUC）も 1 日目より 11 日目で高値を示した。一方、用量間での比較の結果、C_0 に用量相関性は認められなかったが、AUC に関しては各試験日において、個体間でのばらつきは大きいが、

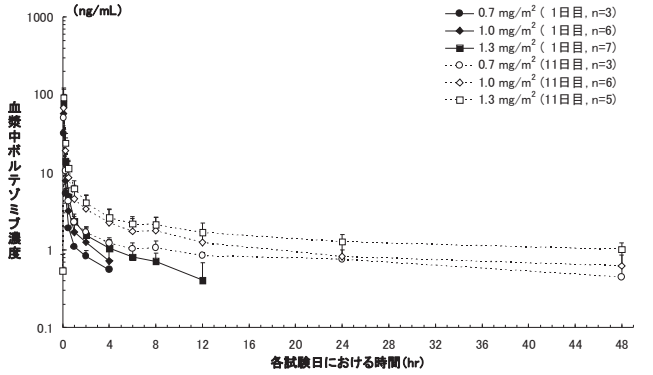
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用量相関性が認められた。[9)、10)]

再発又は難治性の多発性骨髄腫患者に本剤を 0.7、1.0 又は 1.3 mg/m² で静脈内投与したときの各試験日における血漿中ボルテゾミブの薬物動態パラメータ（解析法：ノンコンパートメントモデル）

薬物動態パラメータ	試験日	0.7mg/m²(n=3)		1.0mg/m²(n=6)		1.3mg/m²(n=5～7)[注]	
		平均値	SD	平均値	SD	平均値	SD
C_0(ng/mL)	1	73.75	7.89	144.92	179.31	185.84	57.65
	11	130.68	71.97	147.19	72.33	187.03	54.31
AUC(ng･hr/mL)	1	14.04	0.70	28.58	24.86	46.50	19.89
	11	112.01	47.74	108.39	52.32	186.60	49.79
$t_{1/2}$(hr)	1	3.31	0.88	6.81	8.81	16.11	20.75
	11	64.59	30.29	32.46	12.91	57.39	24.92
CL(L/hr)	1	83.35	10.52	105.41	75.66	51.97	18.99
	11	11.77	4.67	19.63	14.50	12.10	3.73
V_z(L)	1	406.92	154.03	520.08	349.87	894.41	682.35
	11	978.51	263.13	731.69	242.35	957.81	350.40

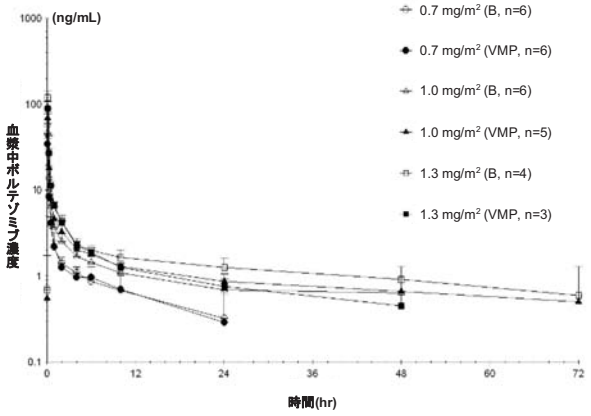
注）1 日目：n=7、11 日目：n=5



再発又は難治性の多発性骨髄腫患者に本剤を 0.7、1.0 又は 1.3mg/m² で静脈内投与したときの各試験日における血漿中ボルテゾミブ濃度推移（平均値+SD）

16.1.2 単独又は併用投与

造血幹細胞移植の適応とならない未治療の多発性骨髄腫患者に、本剤 0.7、1.0 又は 1.3mg/m²（各 n=6、5～6 又は 3～4）を単独又はメルファラン及びプレドニゾロン併用で静脈内投与したときの血漿中ボルテゾミブ濃度を検討した。その結果、血漿中ボルテゾミブの薬物動態は本剤単独投与時とメルファラン及びプレドニゾロン併用で大きく異ならなかった。



造血幹細胞移植の適応とならない未治療の多発性骨髄腫患者に本剤 0.7、1.0 又は 1.3 mg/m² を単独（B）又はメルファラン及びプレドニゾロン併用（VMP）で静脈内投与したときの血漿中ボルテゾミブ濃度推移（平均値+SD）

造血幹細胞移植の適応とならない未治療の多発性骨髄腫患者に本剤 0.7、1.0 又は 1.3 mg/m² を単独又はメルファラン及びプレドニゾロン併用で静脈内投与したときの血漿中ボルテゾミブの薬物動態パラメータ（解析法：ノンコンパートメントモデル）

薬物動態パラメータ	投与法	0.7mg/m²(n=6)		1.0mg/m²(n=5～6)[注1)]		1.3mg/m²(n=3～4)[注2)]	
		平均値	SD	平均値	SD	平均値	SD
$C_{0.08h}$ (ng/mL)	単独	45.43	10.09	59.42	18.89	120.3	24.53
	併用	34.40	5.799	69.50	19.46	88.87	19.57
AUC_{last} (ng･hr/mL)	単独	28.82	14.64	62.56	24.80	115.0	28.67
	併用	26.69	12.87	82.77	13.83	75.59	20.43

注 1）本剤単独投与時：n=6、メルファラン及びプレドニゾロン併用時：n=5
注 2）本剤単独投与時：n=4、メルファラン及びプレドニゾロン併用時：n=3

16.1.3 単独投与

前治療歴のある多発性骨髄腫患者に、本剤 1.3mg/m² を単独で、1 日 1 回、週 2 回、2 週間（1、4、8、11 日目）皮下投与（n=17）及び静脈内投与（n=14）したとき 11 日目における血漿中ボルテゾミブ濃度を検討した。その結果、本剤皮下投与時の C_{max} は静脈内投与時の約 1/10 であったが、AUC_{last} は両投与間で大きく異ならなかった。[11)]（外国人データ）

前治療歴のある多発性骨髄腫患者に本剤 1.3mg/m² を皮下投与及び静脈内投与したときの血漿中ボルテゾミブの薬物動態パラメータ（解析法：ノンコンパートメントモデル）

薬物動態パラメータ	皮下投与（n=17）		静脈内投与（n=14）	
	平均値	SD	平均値	SD
C_{max}(ng/mL)	20.4	8.87	223	101
t_{max}(hr)[注]	0.50	(0.08～1.00)	0.03	(0.03～0.08)
AUC_{last}(ng･hr/mL)	155	56.8	151	42.9

注）中央値（最小値～最大値）

16.2 吸収

16.2.1 血漿蛋白結合率

ヒトにおけるボルテゾミブの血漿蛋白結合率は 78.9～85.7%であった（*in vitro*、限外ろ過法、10～1000ng/mL）[12)]。

16.4 代謝

ヒトにおけるボルテゾミブの主な代謝経路は脱ホウ素化であり、ヒト肝ミクロソームを用いた *in vitro* 試験より、ボルテゾミブが主にチトクローム P450 3A4、2C19 及び 1A2 の基質であることが示されている。チトクローム P450 2D6 及び 2C9 の寄与は小さい。また、ヒト肝ミクロソームを用いた *in vitro* 試験より、ボルテゾミブによるチトクローム P450 1A2、2C9、2D6 及び 3A4 への阻害能は弱いが（IC_{50}=>30μmol/L、>11.5 μg/mL）、チトクローム P450 2C19 に対する阻害能（IC_{50}=18μmol/L、6.9μg/mL）が示されているため、本酵素の基質である薬剤の血中濃度を上昇させる可能性がある。初代培養ヒト肝細胞を用いた *in vitro* 試験より、ボルテゾミブによるチトクローム P450 1A2 及び 3A4 の明確な誘導能は認められなかった。[13)、14)]

代謝物の活性の有無：脱ホウ素化された代謝物は活性を示さない。

16.5 排泄

ヒトにおけるボルテゾミブの排泄経路は特定されていない。

16.6 特定の背景を有する患者

16.6.1 腎機能障害

クレアチニンクリアランス値（CrCL）で分類した様々な程度の腎機能を有する患者を対象に、本剤の薬物動態試験を実施した。また、透析後に本剤を投与した透析患者も本試験に組み入れた。本剤 0.7～1.3mg/m² を週 2 回静脈内投与したときの 8 日目のボルテゾミブのクリアランス（CL）は以下の通りであった。[15)]（外国人データ）

腎機能の程度別の血漿中ボルテゾミブの CL（8 日目）

腎機能の程度（CrCL）	≧60 mL/min/1.73m²	40～59 mL/min/1.73m²	20～39 mL/min/1.73m²	＜20 mL/min/1.73m²	透析群
n[注]	12	9	9	3	8
平均値	30.5	29.6	28.9	27.7	24.7
SD	10.0	18.5	13.5	13.4	10.1

注）薬物動態評価対象例数

16.6.2 肝機能障害

ビリルビン値で分類した様々な程度の肝機能を有する患者を対象に、本剤 0.5～1.3 mg/m² を週 2 回静脈内投与したときのボルテゾミブの用量で規格化した AUC は以下の通りであった[16)]。（外国人データ）［9.3 参照］

肝機能の程度別の血漿中ボルテゾミブの用量で規格化した AUC（8 日目）

肝機能の程度（ビリルビン値）	施設基準値以下	施設基準値の＞1.0～1.5 倍	施設基準値の＞1.5～3 倍	施設基準値の＞3 倍
n[注]	11	9	8	14
幾何平均値	52.2	51.9	85.0	83.2
変動係数（%）	25.7	90.7	26.6	57.1

注）薬物動態評価対象例数

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈多発性骨髄腫〉

17.1.1 海外第Ⅲ相比較試験（039 試験）

再発又は難治性の多発性骨髄腫に対する海外第Ⅲ相比較試験（039 試験）における成績概要は以下のとおりであった[17)]。

1～3 回の前治療歴を有する患者を対象とする無作為化非盲検群間比較試験の本剤群では 1.3mg/m² を静脈内投与した。腫瘍増殖抑制期間（TTP）は、デキサメタゾン群の 3.5 ヵ月（中央値）に対して、本剤群で 6.2 ヵ月（中央値）であった。生存期間のハザード比は、0.57（95%信頼区間 0.40，0.81；p<0.05）であった。なお、生存期間中央値は、全患者の本剤群で 16.6 ヵ月であった以外は、追跡期間が短くすべて評価不能であった。

海外第Ⅲ相比較試験（039 試験）における有効性解析の要約

	全患者		前治療回数 1 回のみ		前治療回数 ＞1 回	
評価項目	本剤 n=333	デキサメタゾン n=336	本剤 n=132	デキサメタゾン n=119	本剤 n=200	デキサメタゾン n=217
TTP						
イベント数（%）	147(44)	196(58)	55(42)	64(54)	92(46)	132(61)
中央値（月）（95%信頼区間）	6.2 (4.9,	3.5 (2.9,	7.0 (6.2, 8.8)	5.6 (3.4,	4.9 (4.2,	2.9 (2.8,

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	6.9)	4.2)		6.3)	6.3)	3.5)
ハザード比	0.55		0.55		0.54	
(95%信頼区間)	(0.44, 0.69)		(0.38, 0.81)		(0.41, 0.72)	
p値[注1)]	<0.0001		0.0019		<0.0001	
生存期間						
死亡患者数(%)	51(15)	84(25)	12(9)	24(20)	39(20)	60(28)
ハザード比	0.57		0.39		0.65	
(95%信頼区間)	(0.40, 0.81)		(0.19, 0.81)		(0.43, 0.97)	
p値[注1)]	<0.05		<0.05		<0.05	

注1) 無作為化の層別因子により調整したLog-rank検定でのp値

331例中324例(97.9%)に副作用が認められた。主な副作用[10%以上を記載]は、下痢[173例52.3%]、悪心[172例52.0%]、疲労[131例39.6%]、血小板減少[109例32.9%]、食欲不振[100例30.2%]、便秘[99例29.9%]、嘔吐[96例29.0%]、末梢性ニューロパチー[93例28.1%]、発熱[67例20.2%]、錯感覚[65例19.6%]、無力症[64例19.3%]、貧血[63例19.0%]、頭痛[62例18.7%]、発疹[61例18.4%]、筋骨格痛[61例18.4%]、好中球減少[59例17.8%]、腹痛[54例16.3%]、呼吸困難[42例12.7%]、感染[39例11.8%]、末梢性感覚ニューロパチー[38例11.5%]であった。

17.1.2 海外第Ⅲ相試験(MMY3002試験)

造血幹細胞移植の適応とならない未治療の多発性骨髄腫に対する海外第Ⅲ相試験(MMY3002試験)における成績概要は以下のとおりであった[18)、19)]。

造血幹細胞移植の適応とならない未治療の多発性骨髄腫患者を対象とする無作為化非盲検群間比較試験において、メルファラン9mg/m^{2}とprednisone※60mg/m^{2}の併用療法(MP療法)とMP療法に本剤[注1)](静脈内投与)1.3mg/m^{2}を上乗せしたMPB療法を比較した。腫瘍増殖抑制期間(TTP)は、MP群の15.0ヵ月(中央値)に対して、MPB群で20.7ヵ月(中央値)であった。生存期間は、MP群の43.1ヵ月(中央値)に対して、MPB群では未到達であった。

海外第Ⅲ相試験(MMY3002試験)における有効性解析の要約

	MPB n=344	MP n=338
TTP		
イベント数(%)	101(29)	152(45)
中央値(月)(95%信頼区間)	20.7(17.6, 24.7)	15.0(14.1, 17.9)
ハザード比(95%信頼区間)	0.54(0.42, 0.70)	
p値[注2)]	0.000002	
生存期間		
死亡患者数(%)	109(32)	148(44)
中央値(月)(95%信頼区間)	NE(46.2, NE)	43.1(34.8, NE)
ハザード比(95%信頼区間)	0.65(0.51, 0.84)	
p値[注2)]	0.00084	

注1) 1サイクルを21日間として、本剤1.3mg/m^{2}を、第1～8サイクルの第1、4、8及び11日目、第9～18サイクルの第1及び8日目に静脈内投与。
注2) 無作為化の層別因子により調整したLog-rank検定でのp値

340例中331例(97.4%)に副作用が認められた。主な副作用[10%以上を記載]は、血小板減少[164例48.2%]、好中球減少[163例47.9%]、末梢性感覚ニューロパチー[148例43.5%]、悪心[134例39.4%]、下痢[119例35.0%]、神経障害性疼痛[117例34.4%]、貧血[109例32.1%]、白血球減少[108例31.8%]、嘔吐[87例25.6%]、疲労[85例25.0%]、リンパ球減少[78例22.9%]、便秘[77例22.7%]、食欲不振[70例20.6%]、腹痛[63例18.5%]、感染[59例17.4%]、発熱[55例16.2%]、無力症[54例15.9%]、発疹[48例14.1%]、錯感覚[41例12.1%]、筋骨格痛[41例12.1%]、帯状疱疹[40例11.8%]、不眠症[35例10.3%]であった。

※:国内未承認

17.1.3 国際共同第Ⅲ相試験(MMY3007試験)

造血幹細胞移植の適応とならない未治療の多発性骨髄腫に対する国際共同第Ⅲ相試験(MMY3007試験)における成績概要は以下のとおりであった[20)]。

造血幹細胞移植の適応とならない未治療の多発性骨髄腫患者680例(日本人患者24例を含む)を対象とする無作為化非盲検群間比較試験において、本剤[注1)]1.3mg/m^2(皮下又は静脈内投与)、メルファラン9mg/m^{2}及びプレドニゾロン又はprednisone※60mg/m^{2}の併用療法(MPB療法)とMPB療法にダラツムマブ(遺伝子組換え)16mg/kgを上乗せしたDMPB療法を比較した。主要評価項目である無増悪生存期間(PFS)は、DMPB群では未到達、MPB群で17.9ヵ月(中央値)(95%信頼区間:16.1～19.8)であり、DMPB群で統計学的に有意な延長を示した[ハザード比:0.51、95%信頼区間:0.39～0.67、p<0.0001[注2)]]。

注1) 1サイクルを21日間として、本剤1.3 mg/m^{2}を、第1～2サイクルの第1、4、8及び11日目、第3～18サイクルの第1及び8日目に皮下又は静脈内投与。
注2) 無作為化の層別因子により調整したLog-rank検定でのp値

※:国内未承認

333例(日本人11例を含む)中250例(75.1%)に副作用が認められた。主な副作用[10%以上を記載]は、血小板減少[115例34.5%]、好中球減少[104例31.2%]、末梢性感覚ニューロパチー[92例27.6%]、貧血[39例11.7%]であった。

17.1.4 海外第Ⅲ相試験(MMY3021試験)

前治療歴のある多発性骨髄腫患者に対する海外第Ⅲ相試験(MMY3021試験)における成績概要は以下のとおりであった[11)]。

1～3回の前治療歴を有する患者を対象とする無作為化非盲検非劣性試験の皮下投与群及び静脈内投与群では本剤1.3mg/m^{2}を投与した。主要評価項目であるサイクル4までの全奏効率(ORR)は、皮下投与群、静脈内投与群ともに42%であり、非劣性が検証された。副次評価項目である腫瘍増殖抑制期間(TTP)及び1年生存率は、静脈内投与群で9.4ヵ月(中央値)及び76.7%、皮下投与群で10.4ヵ月(中央値)及び72.6%であった。

海外第Ⅲ相試験(MMY3021試験)における有効性解析の要約

	本剤静脈内投与	本剤皮下投与
サイクル4までの全奏効率(ORR[注1)])		
評価例数	73	145
全奏効例数	31	61
ORR(%)	42	42
p値[注2)]	0.00201	
ORR比(95%信頼区間)	0.99(0.71, 1.37)	
TTP		
評価例数	74	148
中央値(月)(95%信頼区間)	9.4(7.6, 10.6)	10.4(8.5, 11.7)
ハザード比(95%信頼区間)	0.839(0.564, 1.249)	
p値[注3)]	0.38657	
1年生存率(%)(95%信頼区間)	76.7(64.1, 85.4)	72.6(63.1, 80.0)

注1) CR+PR
注2) 非劣性検定でのp値
注3) 無作為化の層別因子により調整したLog-rank検定でのp値

本剤を皮下投与した症例において、147例中124例(84%)に副作用が認められた。主な副作用[10%以上を記載]は、末梢性感覚ニューロパチー[51例35%]、血小板減少[44例30%]、好中球減少[34例23%]、神経痛[34例23%]、貧血[28例19%]、下痢[28例19%]、白血球減少[26例18%]、悪心[24例16%]、発熱[18例12%]であった。なお、皮下投与による局所注射部位反応は85例(58%)に認められた。

〈マントル細胞リンパ腫〉

17.1.5 国際共同第Ⅲ相試験(LYM3002試験)

造血幹細胞移植の適応とならない未治療のマントル細胞リンパ腫に対する国際共同第Ⅲ相試験(LYM3002試験)の成績概要は以下のとおりであった[21)]。

造血幹細胞移植の適応とならない未治療のマントル細胞リンパ腫患者を対象とする無作為化非盲検群間比較試験において、リツキシマブ(遺伝子組換え)375mg/m^2、シクロホスファミド750mg/m^2、ドキソルビシン50mg/m^2、ビンクリスチン1.4mg/m^{2}及びprednisone※100 mg/m^{2}の併用療法(R-CHOP療法[注1)])と、R-CHOP療法のビンクリスチンを本剤に置き換えたVcR-CAP療法[注2)](本剤[静脈内投与]1.3mg/m^2、リツキシマブ(遺伝子組換え)375mg/m^2、シクロホスファミド750mg/m^2、ドキソルビシン50mg/m^{2}及びprednisone※100mg/m^2)を比較した。無増悪生存期間(PFS)は、R-CHOP群の14.4ヵ月(中央値)に対して、VcR-CAP群で24.7ヵ月(中央値)であった。生存期間は、R-CHOP群の56.3ヵ月(中央値)に対して、VcR-CAP群では未到達であった。

国際共同第Ⅲ相試験(LYM3002試験)における有効性解析の要約

	VcR-CAP n=243	R-CHOP n=244
PFS		
イベント数(%)	133(55)	165(68)
中央値(月)(95%信頼区間)	24.7(19.8, 31.8)	14.4(12.0, 16.9)
ハザード比(95%信頼区間)	0.63(0.50, 0.79)	
p値[注3)]	<0.001	
生存期間		
死亡患者数(%)	71(29)	87(36)
中央値(月)(95%信頼区間)	NE(56.0, NE)	56.3(47.2, NE)
ハザード比(95%信頼区間)	0.80(0.59, 1.10)	
p値[注3)]	0.173	

注1) 21日間を1サイクルとして、リツキシマブ(遺伝子組換え)375mg/m^2、シクロホスファミド750mg/m^2、ドキソルビシン50mg/m^{2}及びビンクリ

最新の添付文書を参照すること

スチン 1.4mg/m²（最大 2mg）を 1 日目に静脈内投与並びに prednisone ※100mg/m²を 1～5 日目に経口投与

注 2）21 日間を 1 サイクルとして、本剤 1.3mg/m²を 1、4、8 及び 11 日目に静脈内投与、リツキシマブ（遺伝子組換え）375mg/m²、シクロホスファミド 750mg/m²及びドキソルビシン 50mg/m²を 1 日目に静脈内投与並びに prednisone※100mg/m²を 1～5 日目に経口投与

注 3）無作為化の層別因子により調整した Log-rank 検定での p 値

※：国内未承認

240 例（日本人 7 例を含む）中 227 例（94.6%）に副作用が認められた。主な副作用［10%以上を記載］は、好中球減少［190 例 79.2%］、血小板減少［163 例 67.9%］、白血球減少［100 例 41.7%］、貧血［86 例 35.8%］、下痢［57 例 23.8%］、末梢性感覚ニューロパチー［52 例 21.7%］、リンパ球減少［48 例 20.0%］、悪心［44 例 18.3%］、疲労［42 例 17.5%］、便秘［41 例 17.1%］、発熱性好中球減少症［36 例 15.0%］、発熱［33 例 13.8%］、食欲不振［31 例 12.9%］、無力症［29 例 12.1%］、神経痛［25 例 10.4%］であった。

〈全身性 AL アミロイドーシス〉

17.1.6 国際共同第Ⅲ相試験（AMY3001 試験）

未治療の全身性 AL アミロイドーシスに対する国際共同第Ⅲ相試験（AMY3001 試験）の成績概要は以下のとおりであった。

未治療の全身性 AL アミロイドーシス患者を対象とする無作為化非盲検群間比較試験において、本剤[注 1)]1.3mg/m²、シクロホスファミド水和物[注 2)]300mg/m²（無水物換算）及びデキサメタゾン[注 3)]40mg の併用療法（CyBorD 療法）と CyBorD 療法にダラツムマブ（遺伝子組換え）1,800mg・ボルヒアルロニダーゼ アルファ（遺伝子組換え）30,000 単位[注 4)]を上乗せした DCyBorD 療法を比較した。主要評価項目である血液学的完全奏効(CR)率は、DCyBorD 群では 53.3%、CyBorD 群では 18.1%であり、DCyBorD 群で統計学的に有意な改善を示した。[22)]

国際共同第Ⅲ相試験（AMY3001 試験）における有効性解析の要約

	CyBorD n=193	DCyBorD n=195
血液学的 CR 率		
CR 例数(%)	35(18.1)	104(53.3)
オッズ比(95%信頼区間)	5.13(3.22, 8.16)	
p 値[注 5)]	<0.0001	

注 1）28 日間を 1 サイクルとし、本剤 1.3mg/m²を 1 週間間隔で 6 サイクルまで皮下投与。なお、本剤の投与により注射部位反応が発現した場合、静脈内投与を可とした。

注 2）28 日間を 1 サイクルとし、シクロホスファミド水和物 300mg/m²（最大 500mg）（無水物換算）を 1 週間間隔で 6 サイクルまで経口又は静脈内投与。

注 3）28 日間を 1 サイクルとし、デキサメタゾン 40mg を 1 週間間隔で 6 サイクルまで経口投与。

注 4）28 日間を 1 サイクルとし、ダラツムマブ（遺伝子組換え）として 1 回 1,800mg（ボルヒアルロニダーゼ アルファ 30,000 単位を含む）を、1 週間間隔（1～8 週目）、2 週間間隔（9～24 週目）及び 4 週間間隔（25 週目以降）で 24 サイクルまで皮下投与。

注 5）層別 Cochran-Mantel-Haenszel 検定での p 値，有意水準：0.04999

193 例（日本人 15 例を含む）中 156 例（80.8%）に副作用が認められた。主な副作用［10%以上を記載］は、末梢性感覚ニューロパチー［52 例 26.9%］、便秘［37 例 19.2%］、下痢［34 例 17.6%］、血小板減少［26 例 13.5%］、リンパ球減少［22 例 11.4%］、貧血［21 例 10.9%］、疲労［21 例 10.9%］、感染［20 例 10.4%］であった。DCyBorD 群の 72.5%がベースライン時に全身性 AL アミロイドーシスに関連する心臓障害を有していた。心臓障害関連の有害事象は、心不全 8.3%、動悸 5.7%、心房細動 5.7%であり、重篤又は致死的な心臓障害関連の有害事象は、心不全 6.2%，心停止 3.6%、心房細動 2.1%であった。重篤又は致死的な心臓障害を発現した患者はベースライン時に全身性 AL アミロイドーシスに関連する心臓障害を有していた。なお、臨床試験では Mayo Clinic Cardiac Staging System に基づく心臓病期 stageIIIb(NT-proBNP>8,500pg/mL)、NYHA 分類クラス IIIB 又は IV の患者は除外された。

〈マントル細胞リンパ腫〉

17.2 製造販売後調査等

再発又は難治性の多発性骨髄腫及び未治療の多発性骨髄腫患者を対象に本剤を静脈内投与した特定使用成績調査及び使用成績調査において、1186 例中 1060 例（89.4%）に副作用が認められた。主な副作用［10%以上を記載］は、血小板減少［691 例 58.3%］、白血球減少［332 例 28.0%］、発熱［299 例 25.2%］、貧血［216 例 18.2%］、感覚減退［199 例 16.8%］、好中球減少［184 例 15.5%］、便秘［183 例 15.4%］、下痢［181 例 15.3%］、末梢性ニューロパチー［170 例 14.3%］、LDH 増加［139 例 11.7%］、帯状疱疹［134 例 11.3%］、CRP 増加［129 例 10.9%］、発疹［126 例 10.6%］であった。

17.3 その他

再発又は難治性の多発性骨髄腫患者を対象に本剤を静脈内投与した国内臨床試験、及び未治療の多発性骨髄腫患者を対象にメルファラン及びプレドニゾロンとの併用で本剤を静脈内投与した国内臨床試験の安全性評価症例において、133 例中 133 例(100%)に副作用が認められた。主な副作用［30%以上を記載］は、リンパ球減少［131 例 98.5%］、白血球減少［128 例 96.2%］、好中球減少［127 例 95.5%］、血小板減少［126 例 94.7%］、貧血［88 例 66.2%］、食欲不振［75 例 56.4%］、下痢［75 例 56.4%］、発疹［75 例 56.4%］、便秘［69 例 51.9%］、悪心［67 例 50.4%］、LDH 増加［67 例 50.4%］、CRP 増加［66 例 49.6%］、発熱［52 例 39.1%］、体重減少［52 例 39.1%］、末梢性ニューロパチー［52 例 39.1%］、低ナトリウム血症［51 例 38.3%］、Al-P 増加［51 例 38.3%］、倦怠感［50 例 37.6%］、嘔吐［47 例 35.3%］、肝機能異常［47 例 35.3%］、高血糖［44 例 33.1%］、高カリウム血症［41 例 30.8%］であった。

18. 薬効薬理

18.1 作用機序

18.1.1 ボルテゾミブは、腫瘍細胞のプロテアソームを阻害することにより、その増殖を抑制しアポトーシスを誘導する[23)]。

18.1.2 ボルテゾミブは、細胞の増殖やアポトーシスを制御する転写因子 NF-κB の活性化を阻害する[25)]。

18.1.3 ボルテゾミブは、NF-κB の活性化を阻害することにより、骨髄腫細胞と骨髄ストローマ細胞の接着を阻害し、IL-6 等のサイトカインの分泌を抑制し、骨髄腫細胞の増殖を抑制する[26)、27)]。

18.2 薬理作用

18.2.1 ボルテゾミブは、*in vitro* 試験において、ヒト骨髄腫由来 RPMI8226 及び U266 細胞株、ヒトマントル細胞リンパ腫由来 SP53、MINO、Grant 519 及び Jeko-1 細胞株並びに多発性骨髄腫及びマントル細胞リンパ腫患者から分離した腫瘍細胞の増殖を抑制し、アポトーシスを誘導した。また、ドキソルビシン、ミトキサントロン、メルファラン又はデキサメタゾンに耐性となった骨髄腫細胞株に対しても増殖抑制作用を示した。[23)、27)]

18.2.2 ボルテゾミブは、RPMI8226 細胞株を移植した担癌マウスにおいて、腫瘍の増大を抑制し、延命効果を示した[24)、25)]。

19. 有効成分に関する理化学的知見

一般的名称：ボルテゾミブ（Bortezomib）

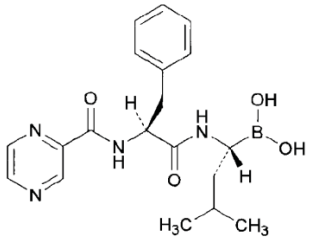
化学名：{(1*R*)-3-Methyl-1-[(2*S*)-3-phenyl-2-(pyrazine-2-carboxamido) propanamido]butyl}boronic acid

分子式：$C_{19}H_{25}BN_4O_4$

分子量：384.24

性状：白色～微黄白色の粉末又は塊

化学構造式：



分配係数：k_0=100.87（pH 1～8）

k_1<0.1（pH 8.5 以上）

（1-オクタノール/水）

溶解性：2-プロパノール又はアセトニトリルに溶けにくい。

20. 取扱い上の注意

包装開封後もバイアルを箱に入れて遮光保存すること。

21. 承認条件

医薬品リスク管理計画を策定の上、適切に実施すること。

22. 包装

3mg［1 バイアル］

23. 主要文献

最新の添付文書を参照すること

1) ヤンセンファーマ株式会社.：ベルケイド適正使用ガイド（肺障害発現例の情報含む）；2016
2) 向井陽美，他：臨床血液. 2011；52：1859-1869
3) 独立行政法人 医薬品医療機器総合機構.：医療上の必要性の高い未承認薬・適応外薬検討会議 公知申請への該当性に係る報告書（ボルテゾミブ：原発性マクログロブリン血症及びリンパ形質細胞リンパ腫）. 2017；1-52
4) Venkatakrishnan K, et al.：Clin Ther. 2009；31：2444-2458
5) Hellmann A, et al.：Clin Pharmacokinet. 2011；50：781-791
6) 社内資料：ボルテゾミブの毒性試験（2006年10月20日承認、CTD2.6.2.4）
7) 社内資料：ボルテゾミブの毒性試験（2006年10月20日承認、CTD2.6.6.3、2012年12月21日承認、CTD2.6.6.3）
8) 社内資料：ボルテゾミブの染色体異常試験（2006年10月20日承認、CTD2.6.6.4）
9) Ogawa Y, et al.：Cancer Sci. 2008；99：140-144
10) 社内資料：ボルテゾミブの国内第Ⅰ/Ⅱ相臨床試験（JPN-101）（2006年10月20日承認、CTD2.7.6.2.7）
11) Moreau P, et al.：Lancet Oncol. 2011；12：431-440
12) 社内資料：ボルテゾミブの蛋白結合率の検討（2006年10月20日承認、CTD2.6.4.4）
13) 社内資料：ボルテゾミブの代謝の検討（2006年10月20日承認、CTD2.6.4.5）
14) 社内資料：ボルテゾミブ代謝物の活性の検討（2006年10月20日承認）
15) 社内資料：腎機能障害患者におけるボルテゾミブの薬物動態試験（2006年10月20日承認）
16) LoRusso P M, et al.：Clin Cancer Res. 2012；18：2954-2963
17) Richardson P G, et al.：N Engl J Med. 2005；352：2487-2498
18) San Miguel J F, et al.：N Engl J Med. 2008；359：906-917
19) Mateos M V, et al.：J Clin Oncol. 2010；28：2259-2266
20) 社内資料：DMPB療法を検討した国際共同第Ⅲ相試験（MMY3007試験）（2019年8月22日承認、CTD 2.7.6.1）
21) Robak T, et al.：N Engl J Med. 2015；372：944-953
22) 社内資料：多発性骨髄腫患者に対する臨床成績（AMY3001試験）（2021年MM月DD日承認、CTDX.X.X.X）
23) Hideshima T, et al.：Cancer Res. 2001；61：3071-3076
24) 社内資料：ボルテゾミブの薬理作用（2006年10月20日承認、CTD2.6.2.2）
25) LeBlanc R, et al.：Cancer Res. 2002；62：4996-5000
26) 社内資料：ボルテゾミブの薬理作用（2006年10月20日承認、CTD2.6.2.2）
27) Wang M, et al.：Leukemia. 2008；22：179-185

24. 文献請求先及び問い合わせ先

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26. 製造販売業者等

26.1 製造販売元

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1.8 添付文書（案）

1.8.1 効能・効果（案），用法・用量（案）及びその設定根拠

1.8.1.1 効能・効果（案）及び用法・用量（案）

(1) 効能・効果（案）（下線部追記）

多発性骨髄腫

マントル細胞リンパ腫

原発性マクログロブリン血症及びリンパ形質細胞リンパ腫

全身性 AL アミロイドーシス

(2) 用法・用量（案）（下線部追記）

〈多発性骨髄腫〉

通常，成人に 1 日 1 回，ボルテゾミブとして 1.3 mg/m^2（体表面積）を以下の A 法又は B 法で静脈内投与又は皮下投与する。本剤は最低 72 時間空けて投与すること。

A 法：

他の抗悪性腫瘍剤との併用において，週 2 回，2 週間（1，4，8，11 日目）投与した後，10 日間休薬（12～21 日目）する。この 3 週間を 1 サイクルとし，2 又は 8 サイクルまで投与を繰り返す。3 又は 9 サイクル以降は，週 1 回，2 週間（1，8 日目）投与し，13 日間休薬（9～21 日目）する。この 3 週間を 1 サイクルとし，18 サイクルまで投与を繰り返す。週 1 回投与への移行時期は併用する抗悪性腫瘍剤を考慮して選択すること。

B 法（再発又は難治性の場合に限る）：

週 2 回，2 週間（1，4，8，11 日目）投与した後，10 日間休薬（12～21 日目）する。この 3 週間を 1 サイクルとし，投与を繰り返す。

8 サイクルを超えて継続投与する場合には上記の用法・用量で投与を継続するか，又は維持療法として週 1 回，4 週間（1，8，15，22 日目）投与した後，13 日間休薬（23～35 日目）する。この 5 週間を 1 サイクルとし，投与を繰り返す。

〈マントル細胞リンパ腫〉

他の抗悪性腫瘍剤との併用において，通常，成人に 1 日 1 回，ボルテゾミブとして 1.3 mg/m^2（体表面積）を 1，4，8，11 日目に静脈内投与した後，10 日間休薬（12～21 日目）する。この 3 週間を 1 サイクルとし，6 サイクルまで（6 サイクル目に初めて奏効が認められた場合は 8 サイクルまで）投与を繰り返す。本剤は最低 72 時間空けて投与すること。なお，静脈内投与が困難な場合には，皮下投与することもできる。

〈原発性マクログロブリン血症及びリンパ形質細胞リンパ腫〉

通常，成人に 1 日 1 回，ボルテゾミブとして 1.3 mg/m^2（体表面積）を 1，4，8，11 日目に静脈内投与又は皮下投与した後，10 日間休薬（12～21 日目）する。この 3 週間を 1 サイクルとし，投与を繰り返す。本剤は最低 72 時間空けて投与すること。

〈全身性 AL アミロイドーシス〉

他の薬剤との併用において，通常，成人に 1 日 1 回，ボルテゾミブ 1.3 mg/m^2（体表面積）を 1，8，15，22 日目に皮下投与する。28 日間を 1 サイクルとし，6 サイクルまで投与を繰り返す。注射部位反応が発現した場合には，静脈内投与することもできる。

1.8.1.2　設定根拠

全身性免疫グロブリン軽鎖（AL）アミロイドーシス患者に対するボルテゾミブの効能・効果（案）及び用法・用量（案）は，国際共同第Ⅲ相試験である 54767414AMY3001 試験（以下 AMY3001 試験）の結果に基づき設定した。

1.8.1.2.1　AMY3001 試験でのボルテゾミブの用法・用量の設定根拠

AMY3001 試験では，シクロホスファミド水和物，ボルテゾミブ及びデキサメタゾン（CyBorD）療法にダラツムマブ皮下注製剤［ダラツムマブ 1800 mg 及びボルヒアルロニダーゼアルファ（遺伝子組換え）30,000 U］を併用した DCyBorD 療法と CyBorD 療法の有効性及び安全性を比較した。

CyBorD 療法は，海外のガイドラインで未治療の全身性 AL アミロイドーシスに対する標準治療の 1 つとして推奨され[1) 2) 3)]，汎用されている。全身性 AL アミロイドーシスに対する CyBorD 療法を評価したガイドラインで引用されている主要な公表論文の用法・用量を表 1.8.1.2.1-1 に示す。CyBorD 療法の用法・用量はこれらの公表論文に基づき決定した。ボルテゾミブについては以下に詳細を記載する。

表 1.8.1.2.1-1 全身性 AL アミロイドーシス患者に対する CyBorD 療法を評価した主要な公表論文の用法・用量

公表論文	Venner et al. 2012[4)]	Mikhael et al. 2012[5)]	Palladini et al. 2015[6)]	Jaccard et al. 2014[7)]
対象患者及び研究手法	未治療又は再発の患者 43 例を対象とした後ろ向き研究	未治療及び既治療の患者 17 例を対象とした後ろ向き研究	未治療の患者 230 例を対象とした後ろ向き研究	未治療の患者 60 例を対象とした後ろ向き研究
ボルテゾミブの用法・用量	1.0 mg/m^2 週 2 回静脈内投与（忍容性が良好であれば 1.3 mg/m^2 まで増量可）	1.5 mg/m^2 週 1 回投与又は 1.3 mg/m^2 週 2 回投与（投与経路の記載なし）	Full dose 1.3 mg/m^2 週 2 回投与又は 1.6 mg/m^2 週 1 回投与 Intermediate dose 1.0 mg/m^2 週 2 回投与又は 1.3 mg/m^2 週 1 回投与 Low dose 1.0 mg/m^2 未満週 2 回投与又は 1.3 mg/m^2 週 1 回投与 （投与経路の記載なし）	4-5 週間投与 1.0-1.5 mg/m^2 週 1 回静脈内又は皮下投与 3 週間投与 1.0-1.5 mg/m^2 週 2 回静脈内又は皮下投与
シクロホスファミドの用法・用量	350 mg/m^2 週 1 回経口投与	300 mg/m^2 週 1 回経口投与	300 mg/m^2 週 1 回経口投与	300 mg/m^2 週 1 回経口投与（最大 500 mg）

デキサメタゾンの用法・用量	20 mg 週 2 回経口投与（1, 4, 8 及び 11 日目）（忍容性が良好であれば 20 mg を 2 日間まで増量可）	40 mg 週 1 回投与（投与経路の記載なし）	Full dose 1 サイクルにつき 160 mg 以上 Intermediate dose 1 サイクルにつき 160 mg 未満，80 mg 以上 Low dose 1 サイクルにつき 80 mg 未満（投与経路の記載なし）	10 又は 20 mg を 4-8 回経口投与
サイクル数	最長 8 サイクル（1 サイクルの定義記載なし）	1 サイクル 28 日で，最長 6 サイクル	1 サイクルの定義及び最長サイクル数の定義記載なし	患者の忍容性に応じて 1 サイクル 21-35 日で，最長 8 サイクル
有効性及び安全性の結果	血液学的奏効（PR 以上）は 35 例（81.4%）に認められ，18 例（41.9%）が CR を達成した。CyBorD 療法の忍容性は良好であった。	血液学的奏効（PR 以上）は 16 例（94%）に認められ，12 例（71%）が CR を達成した。末梢性ニューロパチーが 2 例/17 例に認められたが，いずれも Grade 1 又は 2 であった。このうち 1 例は，ボルテゾミブを 1.5 mg/m^2 週 1 回投与されていた。	血液学的奏効（PR 以上）は 138 例（60%）に認められ，54 例（23%）が CR を達成した。CyBorD 療法の忍容性は良好であった。	血液学的奏効（PR 以上）は 41 例（68%）に認められ，10 例（17%）が CR を達成した。ニューロパチーが 11 例（18%）に認められ，4 例が投与中止した。ボルテゾミブを週 1 回投与された患者で 21%であったのに対し，週 2 回投与された患者で 17%に認められた。

CR：complete response，CyBorD：シクロホスファミド水和物，ボルテゾミブ及びデキサメタゾン，dFLC ：involved 及び uninvolved 遊離軽鎖の差，PR：partial response ， VGPR：very good partial response

これらの論文でボルテゾミブの用法・用量は 1.0～1.6 mg/m^2 を週 1 又は 2 回投与であった。全身性 AL アミロイドーシス患者は，末梢神経系におけるアミロイド沈着による著しい末梢性ニューロパチーを発症するリスクが高い。また，ボルテゾミブの重大な副作用に末梢神経障害があり，全身性 AL アミロイドーシス患者にボルテゾミブを投与することで末梢性ニューロパチーの症状が増悪する可能性がある。以上を踏まえて，AMY3001 試験のボルテゾミブの用法・用量は，28 日間を 1 サイクルとし，1 週間隔で 1.3 mg/m^2 を週 1 回投与と設定した。

投与経路は，前治療歴を有する多発性骨髄腫患者を対象とし，全奏効率（ORR）を主要評価項目とした，ボルテゾミブの静脈内投与に対する皮下投与の非劣性の検証を目的とした海外第 III 相試験（26866138-MMY3021 試験，以下 MMY3021 試験）の結果をもとに設定した。MMY3021 試験では，ORR に関して静脈内投与に対する皮下投与の非劣性が確認され，薬物動態，薬力学，安全性及び有効性は，両投与経路で顕著な差は認められなかったが，ボルテゾミブの用量調節に至ることが多い Grade 2 以上の末梢性ニューロパチーNEC の発現率は，静脈内投与群に比べ皮下投与群の方が低かった。また，皮下投与による局所注射部位反応の発現リスクが加わるものの，局所注射部位反応の多くは軽度又は中等度であり，すべて可逆性であった。そのため，AMY3001 試験ではボルテゾミブの皮下注製剤を使用したが，注射部位反応が発現した被験者ではボルテゾミブを静脈内投与できることとした。

1.8.1.2.2 AMY3001 試験結果に基づく設定根拠

AMY3001 試験の DCyBorD 群では，いずれの治験薬投与も 28 日間を 1 サイクルとし，疾患進行又は全身性 AL アミロイドーシスに対する次治療開始まで，ダラツムマブは最長 24 サイクル

（約 2 年），ボルテゾミブ，シクロホスファミド水和物及びデキサメタゾンは最長 6 サイクル投与することとした。ダラツムマブはサイクル 1～2 は 1 週間隔，サイクル 3～6 は 2 週間隔，サイクル 7 以降は 4 週間隔で 1800 mg を皮下投与した。ボルテゾミブは 1 週間隔で 1.3 mg/m^2 を皮下投与した。なお，ボルテゾミブの投与により注射部位反応が発現した被験者では，ボルテゾミブの静脈内投与を可とした。シクロホスファミド水和物は 1 週間隔で 300 mg/m^2（無水物換算）を経口又は静脈内投与した。ただし，週間投与量は，体表面積にかかわらず 500 mg（無水物換算）までとした。デキサメタゾンは 1 週間隔で 40 mg を経口投与した。ダラツムマブ投与日にデキサメタゾンを投与する場合は前投薬として 20 mg を経口又は静脈内投与し，その翌日にも 20 mg を投与した。なお，ダラツムマブ投与日以外（サイクル 3～6 の Day 8，Day 22）にデキサメタゾンを投与する場合でも，40 mg を 20 mg ずつに分割して 2 日間にわたる投与を可とした。また，70 歳超，体格指数（BMI）18.5 未満，血液量増加症，コントロール不良の糖尿病，又はステロイドに対する不耐症／有害事象の既往のある被験者に対しては，1 週間隔で 20 mg のデキサメタゾン投与を可とした。CyBorD 群では，DCyBorD 群で投与した治験薬のうち，ボルテゾミブ，シクロホスファミド水和物及びデキサメタゾンを同一の用法・用量で投与した。

有効性

主要評価項目である complete response（CR）率は，CyBorD 群（18.1%）と比較して DCyBorD 群（53.3%）で統計学的に有意な改善が認められ［オッズ比（95% 信頼区間）：5.13（3.22, 8.16），p<0.0001］，CyBorD 療法に対するダラツムマブの上乗せ効果が示された。主な副次評価項目である，主要な臓器機能低下－無増悪生存期間（MOD-PFS）は，CyBorD 群と比較して DCyBorD 群で延長傾向がみられた。CR 率及び MOD-PFS の結果は，感度分析及び補足的解析でも一貫しており，いずれの部分集団でも CyBorD 群と比較して DCyBorD 群で改善が認められた。また，CR までの期間及び very good partial response（VGPR）以上までの期間は CyBorD 群と比較して DCyBorD 群でいずれも短縮傾向がみられ，VGPR 以上の奏効が認められた被験者の割合及び臓器奏効（心臓及び腎臓）でも CR 率及び MOD-PFS と同様，DCyBorD 群で良好な結果であった。

日本人集団に対する有効性については，主要評価項目である CR 率で全体集団との一貫性が示された。主な副次評価項目も全体集団と同様の結果であった。DCyBorD 群の MOD-PFS は CyBorD 群と比較して延長傾向がみられ，DCyBorD 群の CR までの期間及び VGPR 以上までの期間は CyBorD 群と比較して短縮傾向が示された。

安全性

DCyBorD 群の安全性プロファイルは，原疾患である全身性 AL アミロイドーシスの合併症に関連するものが含まれており，その他はダラツムマブ，ボルテゾミブ，シクロホスファミド水和物及びデキサメタゾンの既知の安全性プロファイルと比較したときと大きな差はみられず，忍容性は良好であった。DCyBorD 群の日本人集団の安全性プロファイルは，全体集団と同様であった。

以上のとおり，AMY3001 試験の結果，DCyBorD 療法は未治療の全身性 AL アミロイドーシス患者に対して臨床的に有用であることが示され，かつ外国人と日本人との間に薬物動態，安全性及び有効性のいずれについても臨床的に意義のある差は認められなかった。また，海外のガイド

ラインでは再発した全身性 AL アミロイドーシス患者に対しては，初回治療レジメンでの再治療，又はこれまでに投与していない代替併用レジメンでの治療が選択肢となるため[1) 2) 3)]，未治療の全身性 AL アミロイドーシス患者で有用性が検証された治療レジメンは，再発した全身性 AL アミロイドーシス患者での治療選択肢の 1 つとなると考える。

以上より，効能・効果（案）を全身性 AL アミロイドーシスと設定し，AMY3001 試験で用いたボルテゾミブの用法・用量を全身性 AL アミロイドーシス患者に対する推奨用法・用量（案）として設定した。

1.8.2 使用上の注意（案）及びその設定根拠

使用上の注意（案） 新記載要領に基づく改訂案(2020 年 3 月合意案)からの変更箇所 （下線：追記箇所，取消線：削除箇所）	設定根拠
1. 警告 1.1 本剤の投与は、緊急時に十分対応できる医療施設において、造血器悪性腫瘍又は全身性 AL アミロイドーシスの治療に対して十分な知識・経験を持つ医師のもとで、本剤の投与が適切と判断される症例のみに行うこと。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分に説明し、同意を得てから投与を開始すること。 1.2 治療初期は入院環境で医師の管理下にて適切な処置を行うこと。 1.3 国内の臨床試験において、本剤との因果関係の否定できない肺障害（間質性肺炎）による死亡例が認められている。海外ではまれであるが、国内では本剤との因果関係の否定できない肺障害（間質性肺炎、肺水腫、急性呼吸窮迫症候群、胸水等）がより高頻度に発生する可能性があるため、特に以下の事項に十分注意すること。［8.1、9.1.1、11.1.1 参照］ 1.3.1 本剤による治療を開始するにあたり、胸部 X 線検査、胸部 CT 検査等を実施し、異常の有無を確認した上で、治療開始の可否を慎重に判断すること。 1.3.2 本剤による治療中及び治療後、特に治療開始後早期は、息切れ、呼吸困難、咳、発熱等の自覚症状や、胸部聴診所見、呼吸数等での異常の有無を慎重に観察すること。必要に応じて動脈血酸素飽和度や胸部 CT 検査等を適切に実施し、経過を観察すること。本剤による肺障害が疑われた場合には、投与中止も含め適切な処置を行うこと。	本剤の効能又は効果へ全身性 AL アミロイドーシスが追加されることによる記載整備。
5. 効能又は効果に関連する注意 〈多発性骨髄腫、マントル細胞リンパ腫及び全身性 AL アミロイドーシス〉	本剤の効能又は効果へ全身性 AL アミロイドーシスが追加されることによる記載整備。

<table>
<tr><td>「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。</td><td></td></tr>
<tr><td>7. 用法及び用量に関連する注意
〈効能共通〉
7.1 未治療の多発性骨髄腫、マントル細胞リンパ腫及び全身性 AL アミロイドーシスに対し、本剤単独投与での有効性及び安全性は確立していない。
〈多発性骨髄腫〉
7.2 週 1 回投与への移行時期、本剤と併用する抗悪性腫瘍剤等について、「17. 臨床成績」の項の内容を熟知した上で選択すること。
〈全身性 AL アミロイドーシス〉
7.3 本剤と併用する薬剤等について、「17. 臨床成績」の項の内容を熟知した上で選択すること。
〈マントル細胞リンパ腫〉
7.4 本剤を含むがん化学療法については、「17. 臨床成績」の項の内容を熟知した上で、患者の状態や化学療法歴に応じて選択をすること。
7.5 皮下投与の臨床試験成績は得られていない。
7.6 本剤の投与については、以下の記載に従って、適切に減量、休薬又は投与中止の判断を行うこと。
〈多発性骨髄腫、原発性マクログロブリン血症、リンパ形質細胞リンパ腫及び全身性 AL アミロイドーシス〉
・Grade 3/4※の副作用の場合（末梢性ニューロパチー又は神経障害性疼痛を除く）
Grade 3 以上の非血液毒性（末梢性ニューロパチー・神経障害性疼痛を除く）又は Grade 4 の血液毒性に該当する副作用が発現した場合は、回復するまで休薬する。投与を再開する場合には、本剤の投与による有益性と危険性を慎重に検討した上で、下表を目安として減量等を考慮する。副作用が回復しない場合又は最低投与量（0.7mg/m^2）でも再発する場合は、本剤の投与中止を考慮する。
Grade 3/4 の副作用（末梢性ニューロパチー又は神経障害性疼痛を除く）に対する減量の目安
<table>
<tr><th>副作用発現時の投与量</th><th>減量の目安</th></tr>
<tr><td>1.3 mg/m^2</td><td>1.0 mg/m^2</td></tr>
<tr><td>1.0 mg/m^2</td><td>0.7 mg/m^2</td></tr>
<tr><td>0.7 mg/m^2</td><td>投与中止</td></tr>
</table>
・末梢性ニューロパチー又は神経障害性疼痛について
本剤に起因すると考えられる末梢性ニューロパチー又は神経障害性疼痛が発現した場合は、以下に示す</td><td>本剤の効能又は効果へ全身性 AL アミロイドーシスが追加されることによる記載整備。</td></tr>
</table>

用法及び用量変更の目安に従って減量、休薬又は中止すること。［8.4、11.1.3 参照］ **末梢性ニューロパチー又は神経障害性疼痛に対する用法及び用量変更の目安** NCI-CTCAE Grade※（症状）／用法及び用量変更の目安 疼痛又は機能消失を伴わないGrade 1（症状がない；深部腱反射の低下又は知覚異常）／なし 疼痛を伴うGrade 1又はGrade 2（中等度の症状がある；身の回り以外の日常生活動作の制限）／1.3mg/m²の場合1.0mg/m²へ減量又は1.0mg/m²の場合0.7mg/m²へ減量 疼痛を伴うGrade 2又はGrade 3（高度の症状がある；身の回りの日常生活動作の制限）／回復するまで休薬。症状が回復した場合は、0.7mg/m²に減量した上で週1回投与に変更 Grade 4（生命を脅かす；緊急処置を要する）／投与中止 〈マントル細胞リンパ腫〉 新たなサイクルを開始する前に以下を確認すること。 ・血小板数が100,000/μL以上、好中球数が1,500/μL以上及びヘモグロビン値が8g/dL以上であること。［8.6 参照］ ・非血液毒性がGrade 1※又は投与前値に回復していること。 **副作用発現時の用法及び用量変更の目安** 副作用／用法及び用量変更の目安 発熱を伴うGrade 3以上の好中球減少症、7日間を超えて持続するGrade 4の好中球減少症、血小板数10,000/μL未満が発現した場合／好中球数が750/μL以上、血小板数が25,000/μL以上に回復するまで最長2週間本剤を休薬する。 ・本剤休薬後も副作用が上記の基準まで回復しない場合には、本剤の投与を中止すること。 ・副作用が上記の基準まで回復した場合には、本剤の投与量を1段階減量して投与する。（1.3mg/m²の場合1.0mg/m²へ減量、1.0mg/m²の場合0.7mg/m²へ減量） 本剤投与日（各サイクルの第1日目以外）に血小板数が25,000/μL未満又は好中球数が750/μL未満の場合／本剤の投与を最長2日間延期し、2日を越える延期を要する場合は本剤を休薬する。 Grade 3以上の非血液毒性が発現した場合（末梢性ニューロパチー又は神経障害性疼痛を除く）／Grade 2以下に回復するまで本剤を休薬する。回復した場合は本剤の投与量を1段階減量して投与する。（1.3mg/m²の場合1.0mg/m²へ減量、1.0mg/m²の場合0.7mg/m²へ減量） 末梢性ニューロパチー又は神経障害性疼痛が発現した場合／「7.6 末梢性ニューロパチー又は神経障害性疼痛について」に従うこと。 ※NCI-CTCAE v4.0	
11. 副作用 次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。 11.1 重大な副作用 11.1.1 肺障害 間質性肺炎（0.2%、2.5%[注1)]）、急性肺水腫（0.5%、0.4%[注1)]）、胸水（0.1%、1.8%[注1)]）、急性呼吸窮迫症候	M34101-039 試験，MMY3002 試験，MMY3021 試験，LYM3002 試験，MMY3007 試験の DMPB 群と AMY3001 試験の DCyBorD 群においてボルテゾミブとの関連性ありとされた事象の集計結果に基づく。

群（0.1%、頻度不明[注1)]）があらわれることがある。国内の臨床試験及び市販後の報告において、本剤との因果関係の否定できない肺障害（間質性肺炎）による死亡例が認められており、海外と比較して肺障害の発生頻度が高い可能性がある。なお、肺障害の対処方法及び可能性のあるリスク因子について臨床試験では確認されていない。急性骨髄性白血病に対し、本剤、ダウノルビシン塩酸塩及び高用量シタラビンの 24 時間持続点滴（2000mg/m^2/日）を併用した海外の臨床試験において、本剤との因果関係を否定できない急性呼吸窮迫症候群による死亡が報告されている。[1.3.1、1.3.2、8.1、9.1.1 参照] 11.1.2 心障害 うっ血性心不全（1.3%）、心嚢液貯留（0.1%）、心原性ショック（0.1%）、心停止（0.1%）、心肺停止（頻度不明）があらわれることがある。また、投与前の左室駆出率に異常の無い患者においても左室駆出率低下が報告されている。海外臨床試験において QT 間隔延長の報告があるが、薬剤との関連性については明らかになっていない。再発又は難治性の多発性骨髄腫を対象とした海外第Ⅲ相試験において、本剤群及びデキサメタゾン群で発現した心障害の発現頻度はそれぞれ 14%及び 12%であった。そのうち心不全等（急性肺水腫、心不全、うっ血性心不全、心原性ショック、肺水腫）の発現頻度はそれぞれ 5%及び 4%であった。[8.2 参照] 11.1.3　末梢神経障害 末梢性感覚ニューロパチー（28.2%）、神経障害性疼痛（14.8%）、錯感覚（8.6%）、末梢性ニューロパチー（8.1%）、感覚減退（3.6%）、末梢性運動ニューロパチー（2.3%）、灼熱感（0.4%）があらわれることがあり、重症の感覚性ニューロパチーも報告されている。本剤の投与により、感覚障害による末梢性ニューロパチーが主に認められるが、感覚障害と運動障害が混在するニューロパチーの発現例も報告されている。末梢性ニューロパチーに加えて、起立性低血圧やイレウスを伴う重度の便秘等、一部の有害事象に自律神経ニューロパチーが関与している可能性があるが、十分な情報は得られていない。また、本剤の投与により糖尿病性ニューロパチー等の基礎疾患を悪化させる可能性がある。再発又は難治性の多発性骨髄腫を対象とした海外第Ⅲ相試験において Grade 2 以上の末梢性ニューロパチーを認めた患者では用量調整により末梢性ニューロパチーの改善あるいは回復が 51%で認められた。また、海外第Ⅱ相試験において Grade 3 以上の末梢性ニューロパチーを発現した患者又は Grade 2 のニューロパチーを呈し、投与を中止した患者では、末梢性ニューロパチーの改善あるいは回復が 73%で認められた。[7.6、8.4、9.1.3 参照] 11.1.4 骨髄抑制 血小板減少（39.0%）、好中球減少（34.8%）、貧血	

（21.9%）、白血球減少（17.9%）、リンパ球減少（10.9%）、発熱性好中球減少症（2.8%）、汎血球減少（0.1%）があらわれることがある。骨髄機能が抑制された結果、感染症（敗血症性ショック等）や出血等の重篤な副作用が発現することがある。再発又は難治性の多発性骨髄腫を対象とした海外第Ⅲ相試験における重症の出血（Grade 3 以上）の発現率は本剤群で 4%、デキサメタゾン群で 5%であった。血小板数は各サイクルの 11 日目に最低値に達し、通常は次サイクル開始前までに回復した。血小板数の減少と回復のパターンは週 2 回投与の 8 サイクルにわたり一貫しており、蓄積性の血小板減少症は認められなかった。再発又は難治性の多発性骨髄腫を対象とした海外第Ⅲ相試験において血小板数の最低値の平均は、投与開始前の約 40%であった。再発又は難治性の多発性骨髄腫を対象とした海外第Ⅲ相試験における投与開始前の血小板数と血小板減少症の重症度との関係を以下の表に示す。［8.5、8.6 参照］

再発又は難治性の多発性骨髄腫を対象とした海外第Ⅲ相試験における投与開始前の血小板数と血小板減少症の重症度との関係

投与開始前の血小板数[注2)]	患者数（n=331）[注3)]	10,000/μL 未満の患者数（%）	10,000～25,000/μL の患者数（%）
75,000/μL 以上	309	8（ 3%）	36（12%）
50,000/μL 以上 75,000/μL 未満	14	2（14%）	11（79%）
10,000/μL 以上 50,000/μL 未満	7	1（14%）	5（71%）

注 2）投与開始前の血小板数として 50,000/μL 以上を臨床試験の選択基準とした。
注 3）投与開始前のデータが 1 例で不明

11.1.5 イレウス（0.7%）
食欲不振、嘔吐、便秘、腹部膨満感等の症状があらわれた場合には適切な処置を行うこと。［8.7 参照］

11.1.6 肝機能障害
AST の増加（0.7%）、ALT の増加（0.7%）、γ-GTP の増加（0.6%）、ALP の増加（0.5%）及び血中ビリルビンの増加（0.6%）等を伴う肝機能障害（B 型肝炎ウイルスの再活性化によるものを含む）があらわれることがある。［8.3、8.8、9.1.2 参照］
11.1.7 低血圧
低血圧（3.0%）、起立性低血圧（2.2%）があらわれることがある。低血圧の機序は不明であるが、一部は自律神経ニューロパチーが関与している可能性がある。［8.9、9.1.4 参照］
11.1.8 腫瘍崩壊症候群（0.3%）［8.11 参照］
11.1.9 皮膚粘膜眼症候群（Stevens-Johnson 症候群）、中毒性表皮壊死症（Toxic Epidermal Necrolysis：TEN）（頻度不明）
11.1.10 発熱（12.4%）
本剤の投与日から翌日にかけて高頻度に Grade 1～2 の薬剤性の発熱があらわれることがあるので、患者の状態を観察し、必要に応じて解熱剤等による処置

を考慮すること。また発熱が持続する場合や呼吸器症状を伴う場合には、肺障害の可能性について注意すること。
11.1.11 可逆性後白質脳症症候群（頻度不明）
痙攣、血圧上昇、頭痛、意識障害、錯乱、視覚障害等があらわれることがある。
11.1.12 進行性多巣性白質脳症（頻度不明）
本剤の治療期間中及び治療終了後は患者の状態を十分に観察し、意識障害、認知障害、麻痺症状（片麻痺、四肢麻痺）、言語障害等の症状があらわれた場合は、MRI による画像診断及び脳脊髄液検査を行うとともに、投与を中止し、適切な処置を行うこと。
注 1）日本人における発現率（多発性骨髄腫を対象とした静脈内投与における国内臨床試験、特定使用成績調査及び使用成績調査、並びにマントル細胞リンパ腫、多発性骨髄腫及び全身性 AL アミロイドーシスを対象とした国際共同試験（日本人症例のみ）の集計）

11.2 その他の副作用

	10%以上	10%未満 5%以上	5%未満	頻度不明
感染症	感染	帯状疱疹、肺炎	単純ヘルペス、鼻咽頭炎、敗血症、口腔カンジダ症、麦粒腫、感染性腸炎、膀胱炎、中耳炎、蜂巣炎、毛包炎	気管支肺炎、白癬感染、外耳炎
血液			出血、白血球数増加、好中球数増加、単球数増加	
免疫系障害			過敏症	
代謝・栄養	食欲不振		体重減少、脱水、高血糖、高尿酸血症、低アルブミン血症、低血糖症、高アミラーゼ血症	高コレステロール血症
電解質			低カリウム血症、低ナトリウム血症、高カリウム血症、高カルシウム血症	高ナトリウム血症
精神神経系		頭痛、不眠症	浮動性めまい、うつ病、失神、味覚異常、嗜眠、神経痛、不安、痙攣、傾眠、体位性めまい	嗅覚錯誤
眼			霧視、結膜炎、眼瞼炎、眼部腫脹、ドライアイ、霰粒腫	角膜びらん、眼瞼出血、後天性涙腺炎
循環器			高血圧、心房細動、動悸、頻脈、期外収縮、不整脈、心房粗動、徐脈	心電図 QT 延長
呼吸器			呼吸困難、咳嗽、鼻出血、咽喉頭疼痛、鼻漏、肺高血圧症	喀血、上気道の炎症、咽頭不快感、無気肺、胸膜炎、気胸
消化器	下痢、悪心、便秘、嘔吐	腹痛	消化不良、口内炎、腹部膨満、胃炎、鼓腸、胃腸出血、歯肉炎、嚥下障害、胃食道逆流、腸炎、過敏性腸症候群、歯周炎、レッチング、舌潰瘍、おくび、齲歯	口唇炎、耳下腺腫大
肝臓			肝機能異常	肝障害

皮膚		発疹	そう痒症、脱毛症、紅斑、多汗症、蕁麻疹、点状出血、顔面腫脹、紫斑、多形紅斑、薬疹、紅色汗疹、皮膚出血	好中球浸潤・有痛性紅斑・発熱を伴う皮膚障害（Sweet症候群）、丘疹、水疱性皮膚炎
筋骨格		筋骨格痛	筋痙縮、筋痛、筋力低下、骨痛、筋骨格硬直、関節炎	
腎臓・泌尿器			腎機能障害、排尿障害（尿閉、神経因性膀胱等）、尿中血陽性	蛋白尿、β_2ミクログロブリン増加、尿沈渣異常
全身	疲労、無力症	浮腫	悪寒、疼痛、倦怠感、口渇、胸痛、顔面浮腫	
その他			注射部位反応、静脈炎、潮紅、血中クレアチニン増加、総蛋白減少、ほてり、PO_2低下、末梢冷感、血中重炭酸塩減少、血中尿酸減少	LDH増加、CRP増加、腫瘍熱、PO_2上昇、血中クレアチニン減少、総蛋白増加、血中重炭酸塩増加

上記以外の項目は変更なし

参考文献

1） National Comprehensive Cancer Network. NCCN guidelines version 1.2020. Systemic light chain amyloidosis. 2019.

2） Wechalekar AD, Gillmore JD, Bird J, et al. Guidelines on the management of AL amyloidosis. Br J Haematol. 2015;168:186-206

3） The Risk Adapted Approach to Management of Multiple Myeloma and Related Disorders [homepage on the Internet]. Mayo clinic; [update 2019 August]. Treatment Guidelines: Amyloidosis. Available from: https://static1.squarespace.com/static/5b44f08ac258b493a25098a3/t/5d7fd7bd27708631a437368f/156865939

4） Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood. 2012;119(19):4387-90.

5） Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood. 2012;119(19):4391-94.

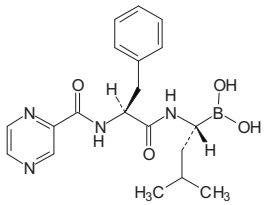
6） Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood. 2015;126(5):612-5.

7） Jaccard A, Comenzo RL, Hari P, et al. Efficacy of bortezomib, cyclophosphamide and dexamethasone in treatment-naïve patients with high-risk cardiac AL amyloidosis (Mayo Clinic stage III). Haematologica. 2014;99(9):1479-85.

1.10　毒薬・劇薬等の指定審査資料のまとめ

毒薬・劇薬等の指定審査に係る資料について，【現行】内容と併せて本申請に係る【変更】内容を次ページより示す。

【現行】

化学名・別名	{(1R)-3-Methyl-1-［(2S)-3-phenyl-2-(pyrazine-2-carboxamido)propanamido]butyl} boronic acid
構造式	
効能・効果	多発性骨髄腫 マントル細胞リンパ腫 原発性マクログロブリン血症及びリンパ形質細胞リンパ腫
用法・用量	1.　未治療の多発性骨髄腫 他の抗悪性腫瘍剤との併用において，通常，成人に1日1回，ボルテゾミブとして1.3 mg/m^2（体表面積）を1，4，8，11，22，25，29，32日目に静脈内投与又は皮下投与し，10日間休薬（33～42日目）する。この6週間を1サイクルとし，4サイクルまで投与を繰り返す。5サイクル以降は，1日1回，1，8，22，29日目に静脈内投与又は皮下投与し，13日間休薬（30～42日目）する。この6週間を1サイクルとし，9サイクルまで投与を繰り返す。本剤は最低72時間空けて投与すること。 2.　再発又は難治性の多発性骨髄腫 通常，成人に1日1回，ボルテゾミブとして1.3mg/m^2（体表面積）を週2回，2週間（1，4，8，11日目）静脈内投与又は皮下投与した後，10日間休薬（12～21日目）する。この3週間を1サイクルとし，投与を繰り返す。本剤は最低72時間空けて投与すること。 8サイクルを超えて継続投与する場合には上記の用法・用量で投与を継続するか，又は維持療法として週1回，4週間（1，8，15，22日目）静脈内投与又は皮下投与した後，13日間休薬（23～35日目）する。この5週間を1サイクルとし，投与を繰り返す。 3.　マントル細胞リンパ腫 他の抗悪性腫瘍剤との併用において，通常，成人に1日1回，ボルテゾミブとして1.3 mg/m^2（体表面積）を1，4，8，11日目に静脈内投与した後，10日間休薬（12～21日目）する。この3週間を1サイクルとし，6サイクルまで（6サイクル目に初めて奏効が認められた場合は8サイクルまで）投与を繰り返す。本剤は最低72時間空けて投与すること。なお，静脈内投与が困難な場合には，皮下投与することもできる。 4.　原発性マクログロブリン血症及びリンパ形質細胞リンパ腫 通常、成人に1日1回、ボルテゾミブとして1.3mg/m^2（体表面積）を1、4、8、11日目に静脈内投与又は皮下投与した後、10日間休薬（12～21日目）する。この3週間を1サイクルとし、投与を繰り返す。本剤は最低72時間空けて投与すること。
劇薬等の指定	原薬及び製剤：毒薬
市販名及び有効成分・分量	原薬：ボルテゾミブ 製剤：ベルケイド注射用 3mg （1 バイアル中にボルテゾミブ を 3.0 mg 含有する）
毒性	**単回投与毒性** 概略の致死量（mg/kg） 静脈内 ラット　0.30 サル　0.30 **反復投与毒性**

動物種	投与期間，投与経路	性別	投与量	最大耐量	主な所見

	ラット	2 週間（週 2 回）静脈内投与	♂, ♀	0, 0.10, 0.20, 0.25 mg/kg/回	0.25 mg/kg/回	全投薬群で腎尿細管の病理組織学的変化。0.20 mg/kg/回群以上で好中球増加。全投薬群の雄及び 0.25 mg/kg/回群の雌で血小板減少。
	ラット	26 週間（9 サイクル）静脈内投与 1 サイクル：週 2 回 2 週間投与後 1 週間休薬	♂, ♀	0, 0.05, 0.10, 0.20/0.15 mg/kg/回	0.10 mg/kg/回	0.20/0.15 mg/kg/回群で死亡。全群で血小板及び赤血球の減少，肝細胞の肥大及び空胞化。0.05 mg/kg/回群の雌及び 0.10 mg/kg/回群以上の雌雄で消化管粘膜過形成。0.10 mg/kg/回群以上でリンパ系組織萎縮及び腎尿細管拡張。0.10 mg/kg/回群の雄及び 0.20/0.15 mg/kg/回群の雌雄で骨髄の造血細胞密度低下。
	サル	4 週間（週 2 回投与），静脈内投与	♂, ♀	0, 0.045, 0.067, 0.100 mg/kg/回	0.067 mg/kg/回	0.100 mg/kg/回群で切迫屠殺。0.100 mg/kg/回群の雄で嘔吐及び下痢，体重減少，腎尿細管変性（雌雄）。0.067 mg/kg/回群の雄及び 0.100 mg/kg/回群でリンパ球減少。
	サル	38 週（13 サイクル），静脈内投与 1 サイクル：週 2 回 2 週間投与後，1 週間休薬	♂, ♀	0, 0.050, 0.075, 0.100 mg/kg/回	0.050 mg/kg/回	0.075 mg/kg/回群以上で切迫屠殺，嘔吐，消化管の膜過形成（雄）及びリンパ系組織の萎縮/単細胞壊死。0.075 mg/kg/回群の雄及び 0.100 mg/kg/回群で腎尿細管変性。0.050 mg/kg/回群の雌及び 0.075 mg/kg/回群以上の雄に末梢神経系の神経線維変性。0.100 mg/kg/回群で血小板減少。
	サル	12 週間（4 サイクル），皮下投与 1 サイクル：週 2 回 2 週間投与後 1 週間休薬	♂, ♀	0, 0.075, 0.1 1.2 mg/kg/回	0.1 mg/kg/回	0.1 mg/kg/回群以上で末梢神経線維変性，腎尿細管変性/肥大，骨髄低細胞性及びリンパ節萎縮。
副作用	前治療歴のある多発性骨髄腫患者を対象とした海外第 III 相試験（26866138-MMY-3021）及び海外第 I 相試験（26866138-CAN-1004）の皮下投与群（SC 群）と静脈内投与群（IV 群）で発現率に 10%以上の差が認められた本剤との因果関係が否定できない有害事象（PT）は，無力症（9% vs 20%）及び下痢（20% vs 30%）であり，いずれも発現率は SC 群の方が低かった。また，いずれかの投与群で発現率が 10%以上に認められた本剤との因果関係が否定できない有害事象において，SOC 別の本剤との因果関係が否定できない有害事象は，神経系障害（53% vs 63%），血液およびリンパ系障害（47% vs 48%），全身障害および投与局所様態（34% vs 40%），胃腸障害（33% vs 41%）であった。 未治療のマントル細胞リンパ腫を対象とした国際共同第Ⅲ相試験における安全性評					

	価対象例において，240 例（日本人 7 例を含む）中 227 例（94.6%）に副作用（臨床検査値異常を含む）が認められた。主な副作用は［10%以上を記載］，好中球数減少［190 例 79.2%］，血小板数減少［163 例 67.9%］，白血球数減少［100 例 41.7%］，貧血［86 例 35.8%］，下痢［57 例 23.8%］，末梢性感覚ニューロパチー［52 例 21.7%］，リンパ球数減少［48 例 20.0%］，悪心［44 例 18.3%］，疲労［42 例 17.5%］，便秘［41 例 17.1%］，発熱性好中球減少症［36 例 15.0%］，発熱［33 例 13.8%］，食欲不振［31 例 12.9%］，無力症［29 例 12.1%］，神経痛［25 例 10.4%］であった。
会社	ヤンセンファーマ株式会社　製剤：輸入

【変更】

化学名・別名	
構造式	
効能・効果	多発性骨髄腫 マントル細胞リンパ腫 原発性マクログロブリン血症及びリンパ形質細胞リンパ腫 全身性 AL アミロイドーシス
用法・用量	1. 未治療の多発性骨髄腫 他の抗悪性腫瘍剤との併用において，通常，成人に1日1回，ボルテゾミブとして1.3 mg/m^2（体表面積）を1，4，8，11，22，25，29，32日目に静脈内投与又は皮下投与し，10日間休薬（33～42日目）する。この6週間を1サイクルとし，4サイクルまで投与を繰り返す。5サイクル以降は，1日1回，1，8，22，29日目に静脈内投与又は皮下投与し，13日間休薬（30～42日目）する。この6週間を1サイクルとし，9サイクルまで投与を繰り返す。本剤は最低72時間空けて投与すること。 2. 再発又は難治性の多発性骨髄腫 通常，成人に1日1回，ボルテゾミブとして1.3 mg/m^2（体表面積）を週2回，2週間（1，4，8，11日目）静脈内投与又は皮下投与した後，10日間休薬（12～21日目）する。この3週間を1サイクルとし，投与を繰り返す。本剤は最低72時間空けて投与すること。 8サイクルを超えて継続投与する場合には上記の用法・用量で投与を継続するか，又は維持療法として週1回，4週間（1，8，15，22日目）静脈内投与又は皮下投与した後，13日間休薬（23～35日目）する。この5週間を1サイクルとし，投与を繰り返す。 3. マントル細胞リンパ腫 他の抗悪性腫瘍剤との併用において，通常，成人に1日1回，ボルテゾミブとして1.3 mg/m^2（体表面積）を1，4，8，11日目に静脈内投与した後，10日間休薬（12～21日目）する。この3週間を1サイクルとし，6サイクルまで（6サイクル目に初めて奏効が認められた場合は8サイクルまで）投与を繰り返す。本剤は最低72時間空けて投与すること。なお，静脈内投与が困難な場合には，皮下投与することもできる。 5.　原発性マクログロブリン血症及びリンパ形質細胞リンパ腫 通常、成人に1日1回、ボルテゾミブとして1.3mg/m^2（体表面積）を1、4、8、11日目に静脈内投与又は皮下投与した後、10日間休薬（12～21日目）する。この3週間を1サイクルとし、投与を繰り返す。本剤は最低72時間空けて投与すること。 6.　全身性ALアミロイドーシス 他の薬剤との併用において、通常、成人に1日1回、ボルテゾミブとして1.3 mg/m^2（体表面積）を1，8，15，22日目に皮下投与する。28日間を1サイクルとし、6サイクルまで投与を繰り返す。注射部位反応が発現した場合には、静脈内投与することもできる。
劇薬等の指定	
市販名及び有効成分・分量	
毒性	
副作用	副作用発現率（臨床検査値異常を含む）156/ 193 例＝80.8% ［日本を含む国際共同第 III 相試験（54767414AMY3001 試験）］ 副作用の種類　例数 末梢性感覚ニューロパチー　52/193（26.9%） 便秘　37/193（19.2%） 下痢　34/193（17.6%） 血小板減少症　26/193（13.5%） リンパ球減少症　22/193（11.4%） 貧血　21/193（10.9%） 疲労　21/193（10.9%）
会社	