



**Australian Government**

**Department of Health**

Therapeutic Goods Administration

# Australian Public Assessment Report for bortezomib

Proprietary Product Name: Velcade

Sponsor: Janssen-Cilag Pty Ltd

**February 2016**

**TGA** Health Safety  
Regulation

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- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
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## Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	adverse event
ASA	Australian Specific Annex
ASCT	autologous stem cell transplant
BR	bendamustine-rituximab
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CR	complete response
CRu	complete response unconfirmed
DILI	drug induced liver injury
DOR	duration of response
EMA	European Medicines Agency
FDA	Food and Drug Administration (US)
HBV	hepatitis B virus
HDT	high dose therapy
HDT/SCT	high dose therapy/stem cell transplant
HR	hazard ratio
HyperCVAD	cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine
GCB	germinal center B cell like
IV	Intravenous(ly)
MCL	mantle cell lymphoma
MM	multiple myeloma
NHL	non Hodgkin Lymphoma
OS	overall survival
PFS	progression free survival

Abbreviation	Meaning
PD	pharmacodynamics
PI	Product Information
PK	pharmacokinetics
PR	partial response
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-FC	rituximab, fludarabine, and cyclophosphamide
RMP	Risk Management Plan
SC	Subcutaneous(ly)
SCT	stem cell transplant
TTP	time to progression
VcR-CAP	Velcade, rituximab, cyclophosphamide, doxorubicin, and prednisone
VDT	Velcade /dexamethasone/thalidomide WBC white blood cell

# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	18 November 2015
<i>Date of entry onto ARTG</i>	25 November 2015
<i>Active ingredient:</i>	Bortezomib
<i>Product name:</i>	Velcade
<i>Sponsor's name and address:</i>	Janssen-Cilag Pty Ltd 1-5 Khartoum Road Macquarie Park NSW 2113
<i>Dose form:</i>	Powder for injection
<i>Strengths:</i>	1 mg and 3.5 mg
<i>Approved therapeutic use:</i>	Velcade, in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL).
<i>Routes of administration:</i>	Intravenously (IV) or subcutaneously (SC)
<i>Dosage:</i>	The recommended dosage for bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP) for the treatment of patients with previously untreated Mantle Cell Lymphoma is 1.3 mg/m <sup>2</sup> body surface area twice weekly for 2 weeks on days 1, 4, 8, and 11 followed by a 10 day rest period on days 12-21. This 3 week cycle is considered a treatment cycle.
<i>ARTG number:</i>	238257

## Product background

This AusPAR describes the application by Janssen-Cilag Pty Ltd to extend the indication for Velcade (trade name; active ingredient, bortezomib). Bortezomib is currently registered for the treatment of multiple myeloma. The proposed indication is for combination treatment with bortezomib and rituximab, cyclophosphamide, doxorubicin and prednisone in adults with previously untreated mantle cell lymphoma (MCL).

The proposed dosing regimen for MCL is 1.3 mg/m<sup>2</sup> IV bortezomib twice weekly for two weeks (on days 1, 4, 8 and 11, ≥72 h between doses), followed by a 10 day rest period (days 12-21). This 3 week cycle is repeated for 6 cycles, with an optional additional 2 cycles. This dosing regimen is the same as that approved for multiple myeloma

indications. Details of the dosing regimen for the combination are provided in the Product Information (PI).

### Regulatory status

The international regulatory status for frontline MCL at the time of this submission is listed in Table 1.

**Table 1: International regulatory status.**

Country	Date submitted or intend to submit	Approval date	Approved indication
EU*	12 Jun 2014	30 Jan 2015	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
USA	14 Jul 2014	8 Oct 2014	Velcade is indicated for the treatment of patients with mantle cell lymphoma
Canada	31 Jul 2014	17 Mar 2015	Velcade (bortezomib) for Injection is indicated as follows: <ul style="list-style-type: none"> <li>•as part of combination therapy for the treatment of patients with previously untreated mantle cell lymphoma who are unsuitable for stem cell transplantation.</li> </ul>
Singapore	24 Nov 2014	28 Jul 2015	Velcade (bortezomib) for Injection 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
Switzerland	26 Sep 2014	N/A	N/A

\* The Rapporteur is Italy and the Co-Rapporteur is Finland

## Product information

The approved PI current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

## III. Nonclinical findings

The nonclinical dossier comprised 14 literature publications. Of these, six were considered of particular relevance as they were peer reviewed publications of the effects of bortezomib alone or in combination with rituximab or cyclophosphamide in mantle cell lymphoma cells (primary and cell lines). No nonclinical data were provided to support the combination of bortezomib with doxorubicin or prednisone, or for the full proposed combination. Therefore, the evaluation of efficacy of the proposed combination of bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone relies on the clinical data.

The sponsor's conclusion in the nonclinical overview is supported by the literature submitted:

*Preclinical studies of the mechanism of action of bortezomib supports its activity in MCL. Through reversible inhibition of the proteasome activity, bortezomib inhibits the NF- $\kappa$ B pathway, upregulates important cell cycle inhibitors such as p27 and p21, and activates proapoptotic pathways such as Noxa. These changes contribute to cycle arrest and induction of cell death resulting in MCL tumor cell growth inhibition. In nonclinical combination studies, bortezomib was additive or synergistic with other clinically active agents in MCL.*

Rituximab enhanced the activity of bortezomib in the inhibition of cell survival and nuclear NF- $\kappa$ B of MCL cell lines or primary MCL cells isolated from patients. The triple combination of bortezomib, rituximab and cyclophosphamide induced apoptosis more than single treatments in MCL cells. In a mouse xenograft model of MCL, the same triple combination was significantly more effective than single agents in the reduction of tumour size and prolongation of event free survival.

There are no nonclinical studies investigating the toxicological interactions of the proposed combination. However, the absence of nonclinical toxicity studies on new drug combinations is not uncommon for combination therapies in the treatment of cancer.

*There are no nonclinical objections to the extension of indications provided efficacy and safety have been adequately demonstrated by clinical data.*

## IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.



## Introduction

### Clinical rationale

MCL is an uncommon type of B cell non Hodgkin Lymphoma (NHL) characterised by the t(11;14) chromosomal translocation and overexpression of cyclin D1. It accounts for 2-10% of all B-NHL and occurs most often in older people (median age at diagnosis 65 years). Although the disease can follow a variable course, most patients are diagnosed with Stage III or IV disease and have both bone marrow and extranodal disease.

The treatment of MCL is generally unsatisfactory and it is generally regarded as incurable with conventional chemotherapy. MCL is responsive to a range of chemotherapy regimens but responses are generally short lived and the median survival is only 4-5 years with most deaths a direct result of disease. While R-CHOP is generally regarded as standard of care, in recent years other chemotherapy regimens, including the combination of bendamustine-rituximab (BR) and the Nordic protocol (which incorporates high dose cytarabine into the induction regimen before autologous stem cell transplant [ASCT]) have demonstrated improved complete remission (CR) rates and progression free survival (PFS).

Consequently, there is an emerging consensus that high dose chemotherapy with ASCT should be recommended for young, fit patients whose MCL has responded to induction chemotherapy.

As many patients with MCL will not be candidates for ASCT (either because of age or comorbidity) there is undoubted merit in seeking to improve outcomes through introduction of novel agents to established conventional chemotherapy.

VcR-CAP appears to improve outcomes in non ASCT eligible patients with MCL, including CR rates, CR duration, PFS, and treatment free interval.

### Guidance

The relevant European Medicines Agency (EMA) guideline,<sup>1</sup> which has been adopted by the TGA, applies to this application, and compliance with these guidelines is considered in the relevant sections of this report.

### Contents of the clinical dossier

The submission contained the following clinical information:

- 1 randomised, open label, multicentre, prospective Phase III study in patients with MCL who were ineligible or not considered for ASCT (LYM-3002)
- 1 uncontrolled single arm, 3 stage, multicentre, prospective Phase II study in patients with relapsed/refractory MCL (PINNACLE Study)
- 1 randomised, open label, multicentre, prospective Phase II study in subjects newly-diagnosed with non GCB subtype of Diffuse Large B Cell NHL (LYM-2034)
- Post marketing reports
- Literature references

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<sup>1</sup> European Medicines Agency, "Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4)", 13 December 2012.

**Paediatric data**

The submission did not include paediatric data. This is appropriate as MCL generally does not occur in children (median age at diagnosis 65 years) and the submission is seeking approval only for the use of Velcade (bortezomib) in adult patients with mantle cell lymphoma.

**Good clinical practice**

The clinical study reports for the submitted studies included assurances that the studies were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP).

**Pharmacokinetics****Studies providing pharmacokinetic data**

None of the studies included in support of the submission included pharmacokinetic data and all used established doses of Velcade currently approved for use in Australia and detailed in the PI.

**Evaluator's conclusions on pharmacokinetics**

In general, the pharmacokinetics of bortezomib appear to have been adequately investigated in previous studies in patients with multiple myeloma and, consequently, no additional PK or PD studies were conducted in support of this submission.

There is no reason to anticipate that the components of the VcR-CAP regimen would have any clinically relevant effects on the pharmacokinetics of bortezomib or vice versa.

While all 3 studies in this submission (LYM-3002, M34103-053, LYM-2034) utilized IV administration of bortezomib, Phase I PK data, clinical studies in patients with multiple myeloma and post marketing studies all provide support for SC administration of bortezomib in patients with MCL.

**Pharmacodynamics****Studies providing pharmacodynamic data**

None of the studies included in support of the submission included pharmacodynamic data and all used established doses of Velcade currently approved for use in Australia and detailed in the PI.

**Evaluator's conclusions on pharmacodynamics**

None of the submitted studies provided pharmacodynamic data and no additional biopharmaceutical, PK or PD studies were conducted in support of this submission. Consequently, no updates have been made to the Summary of Clinical Pharmacology Studies and Summary of Biopharmaceutical Studies and Associated Analytical Methods.

**Dosage selection for the pivotal studies**

The starting dose of bortezomib of 1.3mg/m<sup>2</sup> was selected for MCL because it has been shown to demonstrate efficacy and safety in large series of patients with multiple

myeloma – both as monotherapy and in combination with dexamethasone and with combination chemotherapy.

The starting doses of the chemotherapy agents that comprise the remainder of VcR-CAP (rituximab, cyclophosphamide, doxorubicin and prednisolone) were selected as they are equivalent to the standard doses of these agents in R-CHOP, which has established safety and efficacy in patients with MCL and other forms of NHL.

## **Efficacy**

### **Studies providing efficacy data**

The pivotal efficacy study assessing bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone in the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) was **Study LYM-3002**. The LYM-3002 study was a phase 3, randomised, open-label, multicentre, prospective study in patients with newly diagnosed stage II, II or IV MCL who were judged ineligible or not considered for bone marrow transplantation.

Meanwhile, **Study M34103-053** was a Phase II, single arm, 3 stage, international, multicentre, prospective study in subjects with relapsed or refractory MCL. Study recruitment was in 35 centres – principally in Europe, southeast Asia, the UK and USA. Primary objective was to determine if bortezomib monotherapy increases median time to progression (TTP) compared with historical controls in patients with MCL who have relapse or progression following 1-2 prior lines of antineoplastic therapy. Study objectives included response rate [CR/unconfirmed CR (CRu) + partial response (PR)], duration of response (DOR), TTP and overall survival (OS).

### **Evaluator's conclusions on efficacy**

The sponsor has provided efficacy data from a pivotal randomised Phase III, open label, multicentre, prospective study comparing VcR-CAP and R-CHOP in subjects with newly-diagnosed MCL (LYM-3002) and 1 Phase II single arm, open label, multicentre prospective study in subjects with relapsed or refractory MCL (M34103-053). The studies used standard end points to determination of efficacy in MCL.

For patients with newly diagnosed MCL judged to be transplant ineligible VcR-CAP resulted in a significant improvement in PFS relative to R-CHOP of 9.2-10.3 months. This benefit was shown for all patient groups including low, intermediate and high risk groups of patients according to the MIPIb prognostic score. VcR-CAP was also associated with improvements in TTP, time to next anti-lymphoma treatment, CR rates and CR duration. Data is not mature enough to determine whether VcR-CAP improves OS.

For patients with relapsed/refractory MCL, single agent bortezomib appears to be efficacious, with almost one third of patients (32%) responding to treatment and some patients (8%) obtaining a CR/CRu. In responding patients, median TTP was 12.4 months, median DOR was 9.2 months, median time-to-next-treatment was 14.3 months and median OS was 35.4 months. These results were all higher than in non responders and in historically reported data in similar populations.

Overall, the data are sufficient to establish the efficacy of bortezomib in MCL. Insufficient data is available in transplant eligible patients to determine the relative efficacy of bortezomib containing regimens compared with induction regimens that include high dose chemotherapy with stem cell rescue.

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## Safety

### Studies providing safety data

The following studies provided evaluable safety data: LYM-3002, LYM-2034 and M34103-053. Both individual study data and pooled safety data were included in the submission. Data from LYM-3002 and LYM-2034 are pooled by treatment group (VcR-CAP versus R-CHOP) while data from Study M34103-053 (Velcade monotherapy) is presented as study data.

482 subjects were included in the LYM-3002 safety analysis set, 161 patients with newly diagnosed DLBCL were included in the LYM-2034 safety analysis and 155 subjects were treated with bortezomib monotherapy in Study M34103-053.

The pooled safety analysis set included 321 patients treated with R-CHOP and 322 subjects treated with VcR-CAP.

### *Pivotal efficacy studies (LYM-3002 and M34103-053)*

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed at every visit throughout the study through history, physical examination and laboratory evaluations. AEs were graded according to WHO criteria and National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).
- AEs of particular interest, including peripheral neuropathy, which was assessed by history and physical examination, and AEs leading to dose reduction, dose delay/withholding, dose discontinuation and/or death on treatment.
- Physical examination, including measurement of vital signs, occurred at regular intervals throughout the trial.
- ECGs were performed at baseline and at regular intervals.
- Laboratory tests, including the following were performed at regular intervals:
  - Haematology: total white blood cell (WBC) count, haemoglobin, haematocrit, platelet count, absolute neutrophil count (ANC), and WBC differential.
  - Biochemistry: sodium, potassium, chloride, bicarbonate, urea, glucose, albumin, creatinine, total bilirubin, alanine aminotransferase (AST), aspartate aminotransferase (ALT), alkaline phosphatase, magnesium, phosphorus, calcium, amylase and lipase.
  - Coagulation parameters: prothrombin time and partial thromboplastin time

### *Pivotal studies that assessed safety as a primary outcome*

Primary support for the safety profile was provided by Study LYM-3002.

Studies LYM-2034 and M34103-053 (PINNACLE), provided secondary support.

### *Dose-response and non-pivotal efficacy studies*

There were no studies in the submission that were designed to assess dose-response. No other non-pivotal efficacy studies were included in the submission.

### *Other studies evaluable for safety only*

#### *Study LYM-2034*

A randomiSed, open label, multicentre, prospective, Phase II study of the efficacy and safety of VcR-CAP versus R-CHOP in subjects newly diagnosed with the non GCB subtype

of DLBCL in subjects with newly diagnosed non GCB subtype DLBCL randomised to either VcR-CAP (n = 82) or R-CHOP (n = 79).

#### *M34103-053 (PINNACLE)*

A single arm, 3 stage, multicenter, prospective, Phase II study designed to evaluate the efficacy and safety of Velcade in subjects with documented relapsed or refractory MCL.

*Comment: As this study provided only safety data and contributed to a pooled safety dataset – the safety data from this study will be discussed in relation to pivotal studies/pooled data.*

#### **Clinical pharmacology studies**

There were no clinical pharmacology studies included in the submission.

#### **Pooled safety analysis**

In the submission, the sponsor presented analysis of safety based on pooled data from 2 studies: LYM-3002 and LYM-2034. The pooled safety analysis set included 321 subjects treated with R-CHOP and 322 subjects treated with VcR-CAP, thus enabling comparison of the safety of these 2 regimens. For these studies the safety populations included all randomised subjects who received at least 1 dose of the study drug.

Safety findings Study M34103-053 (PINNACLE), a single arm, 3 stage, multicentre, prospective, Phase II study designed to evaluate the efficacy and safety of single agent Velcade (n = 155) in subjects with documented relapsed or refractory MCL was examined to help identify the contribution of Velcade to the safety profile of the VcR-CAP regimen in an MCL population.

#### **Patient exposure**

In the 3 submitted clinical studies, a total of 477 subjects received the study drug (bortezomib) alone (n = 155) or in combination with other chemotherapy drugs (n = 322).

Both for LYM-3002 and the pooled treatment groups most subjects (>80%) were able to complete treatment with either R-CHOP or VcR-CAP.

#### **Safety issues with the potential for major regulatory impact**

##### ***Liver toxicity***

The clinical studies submitted with did not suggest that the substitution of bortezomib for vincristine in the treatment of untreated MCL (VcR-CAP) would be likely to produce severe drug induced liver injury (DILI). This is consistent with existing data on bortezomib in patients with multiple myeloma, which suggests that hepatic AEs are uncommon or rare.

##### ***Haematological toxicity***

The substitution of bortezomib for vincristine contributes additional haematological toxicity to the combination of rituximab, cyclophosphamide, doxorubicin and prednisone used to treat patients with newly diagnosed, previously untreated MCL. Haematological AEs, including neutropenia, thrombocytopenia, anaemia and lymphopenia are all more common with VcR-CAP than R-CHOP. While these haematological toxicities may be associated with increased rates of infection, they are generally predictable, cyclical and self limiting and can be appropriately managed with supportive care, judicious transfusion, antimicrobial prophylaxis and G-CSF as needed. Consequently, despite the increased haematological toxicity, deaths are not increased with VcR-CAP relative to R-CHOP and there is a trend to increased OS with VcR-CAP in patients with untreated MCL.

***Serious skin reactions***

While local injection site reactions can occur with subcutaneous injection of bortezomib, these studies do not report any instances of serious skin toxicity such as Stevens Johnson syndrome or toxic epidermal necrolysis.

***Cardiovascular safety***

The clinical studies submitted suggest that bortezomib administered as part of VcR-CAP is not associated with a higher incidence of cardiovascular toxicity when compared with R-CHOP. Cardiovascular toxicity, including arrhythmia and cardiac arrest were uncommon in both groups.

***Unwanted immunological events***

Data from LYM-3002 and the pooled safety dataset suggests that serious immunological events due to bortezomib, including drug hypersensitivity, are uncommon.

**Post marketing data**

AE reported from post-marketing sources of patients with relapsed MCL treated with bortezomib – as monotherapy or in combination with other chemotherapy – is consistent with the established safety profile of bortezomib in the treatment of patients with multiple myeloma. There is no post marketing data on patients with previously untreated MCL.

**Evaluator's conclusions on safety**

The results of the LYM-3002 study and the pooled data for R-CHOP and VcR-CAP indicate that the majority of the AEs associated with VcR-CAP can be attributed to the rituximab, cyclophosphamide, doxorubicin, prednisolone backbone shared with R-CHOP.

The substitution of bortezomib for vincristine, however, does appear to contribute added haematological toxicity, with higher rates of thrombocytopenia and neutropenia. Greater haematological toxicity with VcR-CAP contributes to higher rates of Grade 3 or higher adverse events and serious adverse events for VcR-CAP relative to R-CHOP. For the most part, however, these toxicities are predictable, cyclical and easily manageable by tertiary haematology services with transfusion support, supportive care and appropriate dose modification and as such, did not result in significant differences in treatment emergent deaths and treatment discontinuations, which were infrequent and similar in both the VcR-CAP and R-CHOP groups. Nevertheless, VcR-CAP appears to require greater use of G-CSF to maintain treatment intensity and avoid infective complications of neutropenia, higher rates of platelet transfusion to prevent bleeding complications of thrombocytopenia and antiviral prophylaxis to reduce the incidence of herpes zoster reactivation/infection.

Perhaps surprisingly, given the experience with bortezomib in patients with multiple myeloma, the substitution of bortezomib for vincristine contributed less neurotoxicity than would have been anticipated, with rates of peripheral neuropathy similar between the 2 treatment groups. (This may have been because vincristine is also associated with peripheral neuropathy, particularly in older patients.) Importantly, complete recovery of peripheral neuropathy was documented in most cases in both the R-CHOP and VcR-CAP groups. Given the increasing administration of bortezomib subcutaneously rather than intravenously, rates of peripheral neuropathy can be expected to be lower in target populations than in the study populations.

## First round benefit-risk assessment

### First round assessment of benefits

The benefits of VcR-CAP relative to R-CHOP in transplant ineligible patients with newly diagnosed MCL are:

- Improved PFS that is clinically and statistically highly significant;
- Improved time to progression, time to next anti lymphoma therapy and duration of treatment free interval, and
- Improved overall response rate and complete response rate.

While there is a trend to a survival benefit with VcR-CAP relative to R-CHOP the data is insufficient to judge whether VcR-CAP provide a survival advantage in patients with newly diagnosed MCL.

### First round assessment of risks

The risks of substituting bortezomib for vincristine in the treatment of patients with newly diagnosed MCL judged unsuitable for transplantation are:

- Higher rates of peripheral neuropathy (Grade 2 or higher and Grade 3 or higher). Importantly, differences in peripheral neuropathy did not lead to greater rates of treatment discontinuation or higher rates of permanent neuropathy, with neuropathy completely resolving in the vast majority of patients.
- Higher rates of herpes zoster reactivation/infection: 1-2% for R-CHOP versus 7% for VcR-CAP (largely prevented by antiviral prophylaxis).
- Higher rates of all-grade and Grade 3 or higher thrombocytopenia, but not leading to higher rates of all-grade bleeding events, Grade 3 or higher bleeding events or higher rates of discontinuation of all study drugs. This appears to be because thrombocytopenia occurring with VcR-CAP is appropriately managed with platelet transfusion, that were more often administered in patients treated with VcR-CAP (20-23%) than in patients treated with R-CHOP (3%).
- Higher rates of all-grade and grade 3 or higher neutropenia – but not leading to higher rates of febrile neutropenia or discontinuation of study drugs – which were low and similar for R-CHOP and VcR-CAP (14-16% subjects treated with R-CHOP and 15-17% of patients treated with VcR-CAP developed febrile neutropenia). This is likely, in part, because patients treated with VcR-CAP were administered prophylactic or therapeutic G-CSF more frequently than patients treated with R-CHOP.

### First round assessment of benefit-risk balance

The benefit-risk balance of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP) for the treatment of patients with newly diagnosed patients with MCL who are not eligible for transplant is favourable when compared with R-CHOP.

There is insufficient data to judge the relative efficacy and safety of VcR-CAP in patients with newly diagnosed patients with MCL who are candidates for autologous transplantation and received initial treatment that includes high dose chemotherapy with stem cell rescue. There is also insufficient data to judge the relative efficacy and safety of VcR-CAP with newly diagnosed patients with MCL treated with bendamustine containing regimens.

### **First round recommendation regarding authorisation**

It is recommended that the application be approved, subject to provision of further information being provided as requested below.

### **Clinical questions**

#### **Efficacy**

- Please provide an update on the LYM-3002 study, specifically in relation to PFS, duration of remission and OS. Has the trend to increased OS with VcR-CAP been realised with longer follow-up?
- Please provide any data on comparison of VcR-CAP with induction regimens containing high dose therapy with Stem Cell Rescue, for example, Nordic Protocol and comparison of VcR-CAP with BR regimen, either in untreated MCL or in patients with relapse/refractory MCL.

#### **Safety**

- Please provide any update on post marketing surveillance data on thrombocytopenia, neutropenia and related morbidity – bleeding, febrile neutropenia and infection – in non trial populations of patients with MCL in markets where bortezomib has been approved for use in MCL.

### **Second round evaluation**

No second round evaluation

### **Second round benefit-risk assessment**

No second round benefit-risk assessment

## **V. Pharmacovigilance findings**

The TGA granted a waiver from the requirement for a Risk Management Plan (RMP) for this application.

### **Risk management plan**

The sponsor submitted an EU-RMP version 29.1 dated 10 October 2014 (data lock point 31 December 2013) and Australian Specific Annex (ASA) version 1.0 dated 22 October 2014) which was reviewed by the RMP evaluator.

### **Safety specification**

The sponsor provided a summary of ongoing safety concerns which are shown at Table 2.



**Table 2: Ongoing safety concerns.**

Important identified risks	<p>Peripheral motor neuropathy (including paralysis)</p> <p>Autonomic neuropathy</p> <p>Thrombocytopenia and thrombocytopenia with associated bleeding</p> <p>Neutropenia and neutropenia with associated infection</p> <p>Herpes zoster infection</p> <p>Heart failure</p> <p>Acute diffuse infiltrative pulmonary disease</p> <p>Acute hypersensitivity reaction</p> <p>Tumour lysis syndrome</p> <p>Posterior reversible encephalopathy syndrome</p> <p>Optic neuropathy and different degrees of visual impairment (up to blindness)</p> <p>Hepatotoxicity</p> <p>Pulmonary hypertension</p> <p>Pericardial disease</p>
Important potential risks	<p>Progressive multifocal leukoencephalopathy</p> <p>Ventricular rhythm abnormalities</p> <p>Guillain-Barre syndrome</p> <p>Other central nervous system disorders</p> <p>Medication/dispensing errors</p>
Important missing information	<p>Safety in patients with cardiac impairment or with NYHA Class III or IV impairment</p> <p>Safety in patients with ECOG &gt;2</p> <p>Second primary malignancies with VcTD induction therapy</p>

***RMP evaluator comment***

The evaluator has noted that the following safety concerns associated with the use of bortezomib are missing from the above list:

- Hypotension;
- Use in patients with severe renal impairment (CrCL <30mL/min);
- Use in paediatric patients <18 years of age;
- Drug interactions with strong CYP3A4 inhibitors/inducers.

However, as information and advice on these risks have been provided in the approved Australian PI, the sponsor's approach is acceptable.

**Pharmacovigilance plan**

The sponsor has proposed routine pharmacovigilance to monitor all the safety concerns including targeted follow-up questionnaires for the following:

- Important identified risks: 'optic neuropathy and different degrees of visual impairment (up to blindness)',
- Important potential risks: 'progressive multifocal leukoencephalopathy', 'other central nervous system disorders', 'medication/dispensing errors',
- Missing information: 'second primary malignancies with VcTD induction therapy'

Additional pharmacovigilance activities proposed/conducted by the sponsor include the following:

- Adjudication by a panel of external experts to monitor the important potential risk 'progressive multifocal leukoencephalopathy';
- A survey targeting healthcare professionals and other specialised personnel involved in the prescription, dispensing, preparation and/or administration of Velcade to monitor the important potential risk 'medication/dispensing errors'.

#### ***RMP evaluator comment***

The expected date for the results of the healthcare professional survey was the second or third quarter of 2014. The sponsor should provide an update on the survey results, in particular, any safety findings from the survey.

The sponsor's proposal to monitor the safety concerns using routine and additional pharmacovigilance measures is reasonable. Therefore, this is acceptable.

#### **Risk minimisation activities**

The sponsor states in the ASA:

*The educational program for Australia is detailed in Table 3 below and is similar to the one detailed in EU RMP v29.1 under 'Annex 10.1: Proposed Additional Risk Minimisation Measures: Rationale and Objectives of Bortezomib Educational Program in Europe'. The overall goal of the educational program in Australia is to provide appropriate and accurate tools to prevent medication dosing error with respect to IV and SC administration...*

*The educational program for Australia is detailed in Table 4 below and is similar to the one detailed in the EU RMP v29.1 'Annex 10.2: Transplant Induction Setting Additional Educational Programme: Rationale and Objectives'. The overall goal of this educational program in Australia is to provide appropriate and accurate tools to prevent medication dosing error with respect to administering the incorrect regimens in the Transplant Induction Setting.*

*Australia-specific materials are being utilised in Australia and are equivalent to those described as part of the EU Transplant regimens educational program.*

#### ***Potential for overdose***

The sponsor has advised in the proposed PI that '*in patients, over dosage more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes*'. The sponsor has also proposed educational program to mitigate the risk of medication/dispensing errors including potential for overdose.

#### ***Potential for transmission of infectious disease***

The sponsor states:

*As bortezomib is not a biologic agent manufactured under sterile conditions, transmission of infectious agents is not expected. Good Manufacturing Practices are followed by the market authorisation holder (MAH).*

#### **Potential for misuse for illegal purpose**

The sponsor states:

*Velcade is an antineoplastic agent and has no abuse potential. Therefore, the concern for potential illegal use is unlikely.*

#### **Potential for off-label use**

The sponsor recognises the use of Velcade in unapproved conditions. Consequently, the sponsor has proposed continuous monitoring and reporting in PSURs.

#### **Potential for paediatric off label use**

The sponsor states:

*The potential for off label paediatric use is low. MCL and multiple myeloma affects mostly the elderly population. The experience in children and adolescents is limited.*

#### **RMP evaluator comment**

On 16 July 2014, the sponsor issued a 'Direct Healthcare Professional Communication' in the EU following complaints from Germany and the USA about broken or cracked vials of Velcade. The sponsor should provide an update on the risk minimisation measures it has employed to mitigate the risk.

#### **Reconciliation of issues outlined in the RMP report**

The following section summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

#### **Recommendation #1 in RMP evaluation report**

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

#### **Sponsor response**

The company agrees to ensure that the information provided in response to the safety considerations that may be raised by the nonclinical and clinical evaluators includes a consideration of the relevance for the RMP.

#### **Evaluator's comment**

The sponsor's response is satisfactory.

#### **Recommendation #2 in RMP evaluation report**

The expected date for the results of the healthcare professional survey was the second or third quarter of 2014. The sponsor should provide an update on the survey results, in particular, any safety findings from the survey.

#### **Sponsor response**

Further to agreement with CHMP in the EU, the survey content was developed and planned to be implemented in Q1 2014 and results were to be presented in the

PBRER/PSUR No. 20 covering the period 26 October 2013 to 25 April 2014. Prior to dissemination of the survey, agreement was sought from respective regulatory agencies in the EU and Switzerland, where required by local regulations. As regulatory approvals for the survey content and dissemination were delayed, it was not possible to complete the data collection and analysis until the PBRER/PSUR No. 21 covering the period 26 April 2014 to 25 April 2015 which was submitted to the TGA on 22 June 2015. In addition, the survey was not conducted in Greece due to delays in the health authority approval process not allowing the execution of the survey prior to November 2014.

The survey results report (RRA-14542: Survey of the Effectiveness of the Velcade Medication Errors Educational Programme For the Minimization of the Important Potential Risk of Medication Errors with Respect to the Different Routes of Administration) with summary of the methods, results, conclusions and recommendations is attached.

The aim of the survey was to assess the level of spontaneous awareness of information provided by the MAH to HCPs as well as on the utility and effectiveness of tools and trainings on the correct preparation and administration of VELCADE. No AEs were collected or identified from the responses to the survey questions.

The core questions on the preparation of Velcade 3.5 mg vials for SC versus IV administration were answered correctly by  $\geq 90\%$  of HCPs. This result is considered by the MAH to be highly satisfactory. In addition,  $>90\%$  of HCPs indicated that the MAH provided sufficient documents/training on the administration of Velcade and  $>90\%$  of HCPs rated the documents/training provided by the MAH as either "Very helpful" or "Helpful".

Based on these results, the MAH considers having implemented an effective educational program, including tools and training to ensure the correct and safe treatment of patients with Velcade administered by the SC or IV route. Given the highly satisfactory results of the survey, a repeat survey is not considered necessary and no changes to the established educational program are considered required. The MAH will continue to inform HCPs on the correct use of Velcade and to monitor any risks via routine pharmacovigilance activities.

#### ***Evaluator's comment***

The sponsor's response is satisfactory. The evaluator has noted the 'Post-launch Evaluation Report' included as an attachment.

#### ***Recommendation #3 in RMP evaluation report***

On 16 July 2014, the sponsor issued a 'Direct Healthcare Professional Communication' in the EU following complaints from Germany and the USA about broken or cracked vials of Velcade. The sponsor should provide an update on the risk minimisation measures it has employed to mitigate the risk.

#### ***Sponsor response***

Two complaints were received from the market for broken Velcade vials which resulted in the issuance of DHCPL on 12 May 2014 in Australia.

Based on a detailed review of the processes at Nuovo Ompi (glass manufacturer), BSP, transportation companies and Janssen, no definitive root cause for the broken vials could be identified.

Extra visual inspections were performed on: empty retain glass samples, unlabeled BSP lots in inventory, Velcade retain samples. No additional broken vials were found.

Although no root cause was identified, several process improvements and/or preventative actions were identified to further reduce the stress on the vials.

- Soft plastic pushers have replaced the stainless steel pushers used for transferring the vials.
- The pallet configuration has been changed to decrease the number of tray layers per pallet.
- A polyethylene cardboard layer has been placed on the base of the pallet.
- An interim visual check was also implemented at the packaging sites (US & Belgium) to confirm that vials are not broken during shipment. Three batches were inspected upon arrival. No broken vials were detected.

Based on the visual re-inspection result and lack of a systemic issue identified with the manufacturing process, there is no impact to the BSP Velcade inventory and no other DHCPL was considered warranted.

***Evaluator's comment***

The sponsor's response is satisfactory.

***Recommendation #4 in RMP evaluation report***

As the educational programs have already been conducted, the sponsor should clarify whether the educational program is continuing or has been completed. It is noted that the focus of the educational program is on correct dosing including reconstitution, dosage calculation, and administration. However, the sponsor should still clarify whether it plans to make any update to the educational materials to include information on this extension of indication.

***Sponsor response***

The educational program in Australia was split in to two parts, one focusing on how to reconstitute and administer bortezomib vials for IV versus SC and the measures to avoid confusion, and one focusing on prevention of medication dosing error with respect to administering the incorrect regimens in the Transplant Induction Setting. Both parts of the educational program in Australia remain ongoing.

Education is provided both through the Janssen Medical information department, which provides on demand standard responses to questions asked from healthcare professionals (HCPs) and patients, and also via the distribution of educational materials by sales reps.

The educational program focusing on how to reconstitute and administer bortezomib vials for IV versus SC and the measures to avoid confusion is considered to be applicable across all indications for which SC is locally approved. The other educational program is only applicable within the MM Transplant Induction setting; therefore there are no plans in place to update the current educational materials to include information on this extension of indication. However, the transplant induction educational materials are currently being updated to include the warning statement that patients receiving Velcade in combination with Thalidomide should adhere to the pregnancy prevention program of Thalidomide. Once finalised, the updated materials will continue to be distributed via the methods outlined in the ASA.

***Evaluator's comment***

The sponsor's response is satisfactory.

***Recommendation #5 in RMP evaluation report***

Hepatitis B virus (HBV) reactivation: In 2013, the Japanese regulator Pharmaceuticals and Medical Devices Agency (PMDA) requested that HBV reactivation be added as a precaution to the Japanese prescribing information. Warnings against HBV reactivation and infection appear to have been included in the updated SmPC along with the extension of indication.

It is recommended that the Delegate considers the same warnings and advices on screening and monitoring of HBV be added to the Australian PI.

### ***Sponsor response***

As per the request in the RMP report, the MAH proposes to add the following to the Australian PI. The text has not been added in the PI as we await further comments in the Delegate's Overview.

Under precautions in the section Adverse Effects:

*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 local Product Information of rituximab for more information.*

Under summary of clinical trials in the section Adverse Effects:

*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).*

### ***Evaluator's comment***

The sponsor's response is satisfactory. The recommendation on PI content remains for Delegate consideration.

## **Summary of recommendations**

### ***Outstanding issues***

*Issues in relation to the RMP*

The sponsor's response is satisfactory. The PI amendment proposed by the sponsor regarding HBV reactivation remains for consideration by the Delegate.

### ***Comments on the safety specification of the RMP***

*Clinical evaluation report*

The Prescription Medicines Authorisation Branch (PMAB) of the TGA has provided the following comments in the clinical evaluation report:

*The Safety Specification in the draft RMP is satisfactory.*

*Nonclinical evaluation report*

The Scientific Evaluation Branch (SEB) of the TGA has provided no comments on the safety specification of the RMP.

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**Suggested wording for conditions of registration****RMP**

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

*Implement EU-RMP version 29.1 dated 10 October 2014 (data lock point 31 December 2013) and ASA version 1.0 dated 22 October 2014 and any future updates as a condition of registration.*

**VI. Overall conclusion and risk/benefit assessment**

The submission was summarised in the following Delegate's overview and recommendations:

**Quality**

Not applicable.

**Nonclinical**

Some literature based information was provided. There were no nonclinical study reports. The nonclinical evaluator had no objections to the extension of indications on nonclinical grounds. There were no changes proposed to the nonclinical section of the PI.

**Clinical**

An initial clinical evaluation was written (a "Round 1" report) and several questions were sent to the sponsor arising from this report. The sponsor's responses have been taken into account in this overview, so a "Round 2" report has not been commissioned.

**Overview of data**

The sponsor's cover letter describes the supporting Dossier as containing:

- LYM-3002, a Phase III, randomised study of VcR-CAP versus R-CHOP in subjects newly diagnosed with MCL and ineligible or not considered for ASCT.
- M34103-053 ("PINNACLE"), a non randomised, Phase II study of single agent Velcade in subjects with relapsed or refractory MCL. *The sponsor is not proposing use in this population.*
- LYM-2034, a randomised, Phase II study of VcR-CAP versus R-CHOP in newly diagnosed non germinal centre B like diffuse large B cell lymphoma (contributing to safety data). *The sponsor is not proposing use in this population.*

**Pharmacology**

No PK or PD data are available in the target population (patients with untreated MCL).

There is an assumption that PK and PD in patients with untreated MCL would resemble that in patients with multiple myeloma. Median age at diagnosis is ~65-70 yrs, close to that of multiple myeloma. Male to female ratio in MCL is 4:1; and most patients are diagnosed with Stage IV disease. Splenomegaly may be considerable. Hepatomegaly is



seen, and may be associated with altered liver function (in multiple myeloma, altered renal function is more frequent).

The clinical evaluator notes that studies in MCL used IV administration of bortezomib, but states that studies in multiple myeloma “provide support for SC administration of bortezomib in patients with MCL”.

### ***Efficacy***

#### ***LYM-3002***

LYM-3002 was a randomised comparison of VcR-CAP versus R-CHOP in adults with **newly diagnosed**, stage II-IV MCL who were **judged medically ineligible** (according to the treating physician, e.g. due to age or co-morbidities) or **not considered for ASCT** (for example, because of unavailability or lack of consent). The study was run from 2008 to 2013.

VcR-CAP refers to Velcade (bortezomib), rituximab, cyclophosphamide, doxorubicin and prednisone. R-CHOP refers to rituximab, vincristine, cyclophosphamide, doxorubicin and prednisone. Thus, bortezomib is being substituted for vincristine. Otherwise, doses of each agent are the same across arms.

487 subjects were enrolled across 28 countries. Inclusion and exclusion criteria are described. Given that the exclusion criteria ensured patients with serious co-morbidities were not enrolled, and that a key inclusion criterion was ineligibility for ASCT (for example, due to age or co-morbidity), the enrolled patient group can be considered representative of only a fraction of newly diagnosed MCL patients (crudely, patients had to be old or sick, but not too sick). A key point is that most patients were enrolled on the basis of medical ineligibility for BMT (414/487), but for 73/487, ‘other reasons’ were given for not proceeding with BMT (CER page 23). Age was the primary reason for transplant ineligibility (in 73% of all subjects), with inability to tolerate high dose chemotherapy the reason in 6%, and co-morbidity in 15%, but these reasons are likely to be overlapping.

There was an imbalance in ECOG performance score across arms (35% of the R-CHOP group had PS = 0; 46% of the VcR-CAP group had a score of 0). There was also a slight imbalance in the proportion of subjects with Asian race (28% versus 36% respectively).

Randomisation was stratified by IPI score and disease stage at diagnosis. 244 patients were randomised to R-CHOP, and 243 to VcR-CAP.

Patients received six 21 day cycles of R-CHOP or VcR-CAP, but could receive up to eight cycles if response was first seen at cycle 6. Bortezomib was given IV.

The primary efficacy endpoint was **PFS**, as measured in the ITT population. **Median PFS was 14.4 months in the R-CHOP group, but 24.7 months in the VcR-CAP group (HR favouring the bortezomib containing arm, 0.63 [95% CI 0.50-0.79] based on IRC results)**. The difference was even more pronounced based on investigator assessment. Analysis of PFS in subgroups showed a treatment effect favouring VcR-CAP in almost all cases, although the difference across arms narrowed somewhat for ‘higher risk’ patients.

The Clinical Study Report also shows that the VcR-CAP arm sustained its advantage over R-CHOP in the 73 subjects ‘not considered for transplant by investigator’ (excluded from this group were subjects 60+ years of age, or ineligible for transplant because of inability to tolerate high dose chemotherapy or because of co-morbidity), with a Hazard Ratio (HR) as per Independent Review Committee (IRC) of 0.42 (95% CI 0.21-0.84). This group essentially constitutes a ‘transplant fit’ group within the study. The sponsor’s medical monitor also assessed a total of 80 study subjects as ‘transplant eligible’ (n = 42 in the R-CHOP arm and n = 38 in the VcR-CAP arm) and in this group the hazard ratio was 0.59 (95% CI 0.31-1.13).



Other efficacy endpoints are described and clearly favour VcR-CAP, although OS data were immature. Mature OS data are expected at the end of Q3 2017. In the 'transplant eligible' group of 80 subjects, the overall complete response rate per IRC was 39% for R-CHOP and 66.7% for VcR-CAP.

The clinical evaluator observes that there are insufficient data in **transplant eligible patients** to determine relative efficacy of bortezomib containing regimens with induction regimens that include high dose chemotherapy with stem cell rescue. The sponsor reports in its Section 31 response that there are no data on comparison of VcR-CAP with induction regimens containing HDT then stem cell rescue or comparison of VcR-CAP with bendamustine and rituximab regimens.

#### *Study M34103-053*

This was a Phase II, single arm study in adults with **relapsed or refractory MCL**. It examined whether bortezomib monotherapy increased time to progression (TTP), compared to historical controls. The study was conducted from 2003 to 2006. The sponsor submitted an initial CSR (data cut off 1 December 2005) and an addendum (data cut off 1 August 2007).

Patients required relapse or progression following 1 or 2 prior lines of antineoplastic therapy, one of which must have included an anthracycline or mitoxantrone, and one of which must have included rituximab.

All patients (n = 155) received bortezomib, 1.3 mg/m<sup>2</sup> on days 1, 4, 8 and 11, every 21 days, **for up to 17 cycles**, or 4 cycles beyond initial complete response or unconfirmed complete response, or until discontinuation for progressive disease, unacceptable toxicity, or patient / clinician decision. Patients received a median of 4 cycles, but the range was 1-21.

81% of subjects were male and median age was 65 years. 91% had received all three of an alkylating agent, an anthracycline or mitoxantrone, and rituximab. 77% had Stage IV disease at screening.

Using the 2007 data cut off, median TTP was 6.7 months. 8% of subjects achieved complete response or complete response (unconfirmed) and a further 24% achieved partial response. Median OS was 713 days (23.4 months), with 12 month survival estimated as 68.6%.

The clinical evaluator considers that there are sufficient data to support efficacy of bortezomib in this setting. However, in terms of overall response rate, 32% is not especially compelling. Up-To-Date Topic 4735 Version 29.0 refers to a range of chemotherapies, with ORRs ranging up to 92%. Evidently, historical comparison is prone to many biases, for example, patient populations under study will vary.

The sponsor has not requested approval for bortezomib monotherapy in this relapsed/refractory setting.

#### **Safety**

In addition to safety data from LYM-3002 and M34103-053, the sponsor provided safety data from LYM-2034 (VcR-CAP versus R-CHOP in newly diagnosed non germinal centre B cell like diffuse large B cell lymphoma). The clinical evaluation report has a detailed tabulation of the exposure to VcR-CAP or bortezomib monotherapy across studies, by cycle.

Safety results from LYM-3002 (VcR-CAP versus R-CHOP in newly diagnosed MCL) are set out. The substitution of bortezomib for vincristine resulted in slightly higher frequencies of certain AE categories, for example treatment discontinuation due to AEs was 9% for VcR-CAP versus 7% for R-CHOP; and serious AEs were 38% versus 30% respectively. There was no increase in treatment related deaths in the VcR-CAP arm. Of most note,

thrombocytopenia was much more frequent with VcR-CAP (72% versus 19%), and Grade 3 or higher thrombocytopenia followed this pattern (57% versus 6%), as did the need for platelet transfusion (23% versus 3%). Severe bleeding events were seen rarely in either arm. Anaemia and neutropenia were also moderately more common in the VcR-CAP arm, with febrile neutropenia reported in 11% versus 8% respectively, pneumonia seen in 8% versus 3% respectively, herpes zoster in 7% versus 1%, and severe infection in 21% versus 14% respectively. Despite substitution of vincristine for bortezomib in the VcR-CAP arm, rates of peripheral neuropathy were similar across the arms (30%, VcR-CAP versus 29%, R-CHOP); indeed, Grade 3+ events were reported in 8% versus 4% respectively. There was some indication that peripheral neuropathy in the bortezomib containing arm resolved faster than in the vincristine-containing arm (median time to resolution, 91 versus 168 days).

Study LYM-2034 tested the same treatment arms in a slightly different population (one subtype of DLBCL). Again 6 cycles of treatment were proposed (similar to LYM-3002). Subjects were slightly younger in this study than in LYM-3002. In LYM-2034, again the bortezomib-containing arm experienced much more thrombocytopenia, although here neutropenia was seen to a similar degree across arms. In LYM-2034 there was a smaller difference in the frequency of serious AEs than in LYM-3002 (here, 38% for VcR-CAP versus 34% for R-CHOP). Considerably more subjects required dose reduction in the VcR-CAP arm (50%) than the R-CHOP arm (25%), and there was a fairly dramatic imbalance with regard to dose withholding (74% versus 8% respectively).

Study M34103-053 was a single arm study of bortezomib monotherapy (in relapsed or refractory MCL), and a fraction of patients received prolonged therapy. Peripheral neuropathy was a frequent concern (55% of subjects reported this AE). Most subjects in this study had earlier been treated with vinca alkaloids.

The clinical evaluator considers that, with regard to peripheral neuropathy, rates may be lower if bortezomib is given subcutaneously.

With regard to the elevated frequency of herpes zoster, the clinical evaluator notes the importance of antiviral prophylaxis; indeed, the LYM-3002 protocol was amended to incorporate prophylaxis (in subjects without prophylaxis, the frequency of herpes zoster was 11% for VcR-CAP versus 2% for R-CHOP; in subjects with prophylaxis, the frequencies were 4% vs 0% respectively).

With regard to HBV reactivation, the PI text is to be updated at the pre Advisory Committee on Prescription Medicines (ACPM) stage (Section 31 response to RMP Q5). The proposed text seems appropriate.

### **Risk management plan**

Despite previous approval of the use of bortezomib in multiple myeloma settings, this application provided the first opportunity to evaluate an RMP for bortezomib.

The RMP proposed by the sponsor was considered generally acceptable by the TGA.

A proposed condition of registration is:

*Implement EU-RMP version 29.1 dated 10 October 2014 (data lock point 31 December 2013) and ASA version 1.0 dated 22 October 2014 and any future updates as a condition of registration*

The RMP encompasses uses in multiple myeloma as well as MCL.

## Risk-benefit analysis

### Delegate's considerations

#### Indication

The sponsor has proposed use of bortezomib (as part of VcR-CAP) in adult patients with previously untreated MCL. The clinical evaluator considers that there are insufficient data to support use in **transplant eligible** previously untreated MCL patients. Specifically, from the clinical evaluation report:

*There is insufficient data to judge the relative efficacy and safety of VcR-CAP in... newly diagnosed patients with MCL who are candidates for autologous transplantation and received initial treatment that includes high-dose chemotherapy with stem cell rescue. There is also insufficient data to judge the relative efficacy and safety of VcR-CAP with newly diagnosed patients with MCL treated with bendamustine-containing regimens.*

The Delegate agrees that LYM-3002 and M34103-053 do not provide robust, direct support for use in transplant eligible previously untreated MCL patients.

The transplant eligible newly diagnosed MCL population is distinct from patients unsuitable for transplant, for example, in terms of age and co-morbidity. Younger, fitter patients may be offered different first line treatment options, for example:

- conventional chemoimmunotherapy (for example R-CHOP, R-CVP, bendamustine + rituximab) followed by high dose chemotherapy and ASCT, or
- intensive chemoimmunotherapy (for example R-Hyper-CVAD/cytarabine/MTX) alone

A small number of patients (~73) were treated with VcR-CAP or R-CHOP in LYM-3002 for reasons other than medical ineligibility. In this group, there was no evidence that the advantage conferred by VcR-CAP over R-CHOP was diminished.

One view (as set out by Freedman et al. in 'Up-to-date' topic 4719 v29.0)<sup>2</sup> is that candidates for ASCT may receive conventional chemoimmunotherapy induction, and if there is a response, proceed to high dose chemotherapy and ASCT. R-CHOP is one form of conventional induction, amongst seemingly many approaches.

It could be argued that LYM-3002 establishes VcR-CAP as a reasonable alternative to R-CHOP for the purpose of response induction. However, comparison of VcR-CAP and R-CHOP in LYM-3002 was in a different setting (that is, in subjects who for the most part would be ineligible for ASCT anyway). In a less closely related setting, DLBCL, in LYM-2034, VcR-CAP did not prove quite as effective as R-CHOP in inducing responses (efficacy outcomes in this study has not been evaluated within this application).

Tangentially, Velcade has been studied and approved as an induction therapy prior to ASCT in the context of multiple myeloma, so there is no suggestion it adversely affects ASCT per se. However, there are no data in the dossier about the use of VcR-CAP followed by high dose chemotherapy and ASCT.

Bendamustine is indicated in "previously untreated CD20-positive, stage III-IV Mantle Cell Lymphoma in combination with rituximab, in patients ineligible for autologous stem cell transplantation". The basis of this approval as suggested by the bendamustine PI was study NHL1-2003, comparing BR to R-CHOP in indolent NHL and MCL. 46-48 patients per arm had MCL. The median PFS for the B-R arm was 35.4 months, and for the R-CHOP arm, 22.1 months (HR 0.49, 95% CI 0.28-0.79).

<sup>2</sup> <http://www.uptodate.com/contents/initial-treatment-of-mantle-cell-lymphoma>

While comparison of VcR-CAP and BR would be useful in transplant ineligible patients (and even in transplant-eligible patients, as per Freedman et al. though this is an off label use of bendamustine) it may not be practical to compare VcR-CAP with all the main treatment strategies employed in newly diagnosed MCL, given there is no one preferred approach. The comparison with R-CHOP seems reasonable (for example, it was used in the bendamustine registration Study NHL1-2003).

The EMA has opted to approve use in the more restricted setting:

*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.*

Key argument in the EMA assessment report on this topic is included.

This approach is quite distinct from that taken by the US FDA, which has approved bortezomib broadly in MCL, apparently on the basis of the same key data.

Given that:

- MCL is a rare condition where there is no clear consensus about the best treatment approach;
- MCL will be managed in a specialist setting and the exact treatment approach is likely to be highly tailored to an individual's circumstances;
- R-CHOP and similar regimens can be used for induction prior to high dose chemotherapy and ASCT and there is evidence VcR-CAP is a good alternative to R-CHOP in a related setting (that is, transplant ineligible previously untreated MCL); and
- there is some limited evidence that VcR-CAP maintains an efficacy advantage over R-CHOP even in previously untreated patients who are transplant eligible

the Delegate thinks it is reasonable to provide flexibility for clinicians and patients by approving the broader indication proposed by the sponsor, that is, treatment of adult patients with previously untreated mantle cell lymphoma.

### ***Maintenance***

LYM-3002 supplies the main evidence in support of this application. In this study, the comparator was R-CHOP. There is some evidence that in R-CHOP responders, **maintenance rituximab** reduces the risk of progression or death.<sup>3</sup> It is not clear how maintenance therapy fits into the regimen envisaged by the sponsor. The sponsor is invited to comment on this issue, and to draw attention to any studies of VcR-CAP planned or in progress that will directly address this issue of maintenance.

### ***Administration***

LYM-3002 used IV bortezomib, but subcutaneous use of bortezomib is also possible. The Clinical Evaluator suggests that an advantage of SC use might be lower rates of peripheral neuropathy. The current PI notes that systemic exposure as reflected by AUClast was equivalent for IV and SC injection, in myeloma patients, but that Cmax was considerably lower with SC use than IV use (20 ng/mL versus 223 ng/mL). The proposed PI also implies that bortezomib within VcR-CAP maybe be given SC, in that the initial section of the 'Dosage and Administration' section, which is not specific to MM or MCL, states that Velcade may be given IV or SC. The MCL specific part of this section of the PI avoids specifying IV (or mentioning SC) use. This approach appears reasonable.

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<sup>3</sup> Kluin-Nelemans HC, et al. (2012) Treatment of older patients with mantle-cell lymphoma. *N Engl J Med.* 367: 520-531.

**Proposed action**

The Delegate proposes to ask advice of the ACPM, as per 'Summary information' above.

**Request for ACPM advice**

The sponsor proposes an indication in adults with previously untreated MCL.

The pivotal study LYM-3002 was in a narrower group, for the most part **patients unsuitable for ASCT**. Patients suitable for ASCT are a distinct group (that is, younger and fitter).

In patients unsuitable for ASCT, VcR-CAP appears to offer an advantage over an appropriate comparator, R-CHOP. Although VcR-CAP has a moderately worse safety profile than R-CHOP (due to much higher rates of thrombocytopenia and moderately higher rates of neutropenia, febrile neutropenia and severe infection), there is a pronounced benefit in terms of PFS with VcR-CAP.

The committee is requested to provide advice on the following specific issue:

- Is it acceptable to allow use of VcR-CAP in newly diagnosed MCL patients *suitable* for autologous stem cell transplantation?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

**Response from sponsor**

The sponsor agrees with the Delegate's pre ACPM preliminary assessment proposing to approve the application. The proposed indication remains as follows:

*Velcade in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma.*

The efficacy results for Study LYM-3002 show that relative to R-CHOP, the VcR-CAP regimen provides substantial clinical benefit to patients with newly diagnosed MCL. The primary and all additional analyses of the PFS endpoint demonstrated a clinically highly meaningful improvement favouring VcR-CAP therapy over R-CHOP therapy. By IRC (primary), the median was 14.4 months for R-CHOP versus 24.7 months for VcR-CAP (HR = 0.63; p<0.001). The contribution of Velcade to the safety profile of the VcR-CAP regimen was predictable and manageable. Rates of treatment discontinuation due to adverse events were low and similar (R-CHOP: 7%; VcR-CAP: 9%).

The front line indication in MCL was approved in the US on 8 October 2014, the EU on 30 January 2015, Canada on 17 March 2015 and Japan on 26 June 2015.

The sponsor notes that the clinical evaluator has commented that the data provided in relapsed and refractory MCL patients supports the efficacy of Velcade in this patient population. Therefore, an indication in relapsed and refractory MCL is discussed further in the 'Indication' section.

The sponsor wishes to comment on the following items.

**Indication**

*VcR-CAP in newly diagnosed MCL patients suitable for autologous stem cell transplantation*

The Delegate has asked the ACPM for advice as to whether it is acceptable to allow use of VcR-CAP in newly diagnosed MCL patients suitable for ASCT. The sponsor agrees with the Delegate's comments that such a broader indication would provide to clinicians more flexibility in their treatment of patients with MCL.

The company feels that there is sufficient data to support the approval of this broader indication in the use of VcR-CAP in newly diagnosed patients who are suitable for autologous stem cell transplantation. In transplant-eligible patients with newly diagnosed MCL, induction therapy aims at inducing high complete response rates while allowing successful mobilization of hematopoietic stem cells for reinfusion after high dose chemotherapy consolidation. Results from VcR-CAP in the LYM-3002 study (in **transplant eligible** MCL patients) demonstrated convincing efficacy data which supports the VcR-CAP regimen as a valid treatment option in transplant eligible MCL. VcR-CAP in study LYM-2034 (DLBCL), and VELCADE in combination with the other chemotherapy agents of VcR-CAP (doxorubicin, cyclophosphamide and steroids) in multiple myeloma, also indicates that the VcR-CAP regimen can be a valid treatment option in transplant eligible patients.

In LYM-3002, VcR-CAP induced a higher complete response rate (CR/CRu) by IRC of 67% than R-CHOP (46%) (OR = 4.05, p = 0.015) in the subgroup of patients (n = 70) who were eligible for bone marrow transplantation (younger than 60 years and no medical ineligibility reason) as reported by investigator. Also, in the subgroup of patients (n = 77) confirmed by sponsor medical monitor as eligible for bone marrow transplantation due to age or medical reasons, VcR-CAP induced a consistently high complete response rate (CR/CRu) by IRC of 67% than R-CHOP (39%) (OR = 3.69, p = 0.012). This high CR/CRu rate of VcR-CAP is in line with the complete response rates reported for other induction regimens such as R-DHAP (76%),<sup>4</sup> alternating R-CHOP/R-DHAP (54%),<sup>5</sup> and R-HyperCVAD (55%)<sup>6</sup> prior to stem cell transplantation in newly diagnosed MCL, and allows subsequent consolidation with high dose therapy and stem cell transplantation if accessible to or desired by the patient. In LYM-3002, the CR/CRu of VcR-CAP was very durable. In the subgroup of patients (n = 70) eligible for bone marrow transplantation as reported by the investigator, the median duration of CR/CRu in VcR-CAP was 49.1 months (22.7 months in R-CHOP) and the median PFS was 49.8 months by IRC and 42.6 months by investigator (16.6 months by IRC and 20.6 months by investigator in R-CHOP). Also, in the subgroup of patients (n = 77) confirmed by sponsor medical monitor as eligible for bone marrow transplantation, VcR-CAP induced durable complete responses: median duration of CR/CRu in VcR-CAP was 45.9 months (28.6 months in R-CHOP), while the median PFS was 32.6 months by IRC and 42.6 months by investigator (12.0 months by IRC and 20.6 months by investigator in R-CHOP). This duration of CR/CRu and this PFS after 6 to 8 cycles of VcR-CAP are even in the range of results obtained in the randomized study of consolidation with stem cell transplantation in newly diagnosed MCL (median PFS of 39 months).<sup>7</sup>

In LYM-2034 (the DLBCL patient population), patients treated with VcR-CAP could receive stem cell transplantation as subsequent therapy. Of the 84 patients in the VcR-CAP group, 9 (11%) received high dose therapy and autologous stem cell transplantation during subsequent therapy. Stem cell collection after the VcR-CAP regimen was successful (median CD34+ cell yield of  $6 \times 10^6$ /kg) in all 7 patients for whom details were provided.

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<sup>4</sup> Le Gouill S, et al. (2012) Clinical, Metabolic and Molecular Responses After 4 Courses of R-DHAP and After Autologous Stem Cell Transplantation for Untreated Mantle Cell Lymphoma Patients Included in the LyMa Trial, a Lysa Study. *Blood (ASH Annual Meeting Abstracts)* 120: Abstract 152.

<sup>5</sup> Hermine O, et al. (2012) Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) increases overall survival when compared to 6 courses of CHOP plus rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: final analysis of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net). *Blood (ASH Annual Meeting Abstracts)* 120: Abstract 151.

<sup>6</sup> Bernstein SH, et al. (2013) A phase II multicenter trial of hyperCVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma; SWOG 0213. *Ann Oncol*. 24: 1587-1593.

<sup>7</sup> Dreyling M, et al. (2005) Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. *Blood* 105: 2677-2684.

In 4 patients only granulocyte colony stimulating factors were used and in 3 patients chemotherapy was used as a mobilising regimen. In 6 of the 7 patients, 1 apheresis procedure was sufficient, and the remaining subject had 2 apheresis procedures performed. Therefore, in the LYM-2034 study, the safety of the VcR-CAP regimen was shown in those patients receiving stem cell transplantation as subsequent therapy.

There is also evidence in multiple myeloma that Velcade containing combination regimens are safe and efficacious induction therapy in transplant eligible patients:

- Velcade induction combination regimen (Velcade /dexamethasone/thalidomide [VDT]) prior to high dose therapy/stem cell transplant (HDT/SCT) has been approved in Australia, the EU and other countries.
- Velcade induction regimen in combination with steroid (VDT or Velcade/dexamethasone) prior to HDT/SCT has been approved in Australia, the EU and other countries. Also, the combination with doxorubicin and dexamethasone prior to HDT/SCT has been approved in Switzerland.
- Published literature has provided experience in the VELCADE Induction regimen (VDT/cyclophosphamide<sup>8</sup> or cyclophosphamide/VELCADE/dexamethasone<sup>9</sup>) prior to HDT/SCT.

Therefore, as the benefit of ASCT in CHOP responders is evidence based<sup>10</sup> but does not lead to long term disease control due to lower CR rates after induction therapy compared with more effective cytarabine containing induction regimens, VcR-CAP could be considered as an induction alternative with higher and more durable CR rates than seen in CHOP-based regimens.

Despite the smaller number of transplant eligible patients studied in the pivotal trial LYM-3002, Velcade treatment has still shown comparable clinical benefit observed for patients not suitable for transplant. A consistent treatment effect in favour of VcR-CAP was observed in patients who had not received a transplant for medical reasons or age ( $\geq 60$  years) as well as in patients who had not received a transplant for other reasons. Also, the VcR-CAP regimen has been demonstrated to be effective in both treatment naïve transplant and non transplant eligible patients in DLBCL and MM patient populations. The company fully supports the position of the delegate that the broader indication of the use of VcR-CAP in newly diagnosed patients who are suitable for autologous stem cell transplantation would provide more flexibility to clinicians in their treatment of patients with MCL.

#### *Relapsed or refractory MCL*

The Delegate has noted that the clinical evaluator considers there is sufficient data to support the efficacy of bortezomib in the setting of relapsed and refractory MCL. The Delegate also notes that the overall response rate of 32% is not especially compelling given there are some chemotherapies with ORRs ranging up to 92% and also notes that the historical comparison can be prone to biases, for example, patient populations under study will vary.

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<sup>8</sup> Ludwig H, et al. (2013) Randomized phase II study of bortezomib, thalidomide, and dexamethasone with or without cyclophosphamide as induction therapy in previously untreated multiple myeloma. *J Clin Oncol.* 31: 247-255.

<sup>9</sup> Reeder CB, et al. (2009) Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. *Leukemia* 23: 1337-1341; Reeder CB, et al. (2010) Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. *Blood* 115: 3416-3417.

<sup>10</sup> Dreyling M, et al. (2005) Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. *Blood* 105: 2677-2684.

Study M34103-053, a non randomised, Phase II study of single agent Velcade in subjects with relapsed or refractory MCL, was included in this application as additional supporting data. This study provided the basis for the approval of Velcade monotherapy in relapsed/refractory MCL in 54 countries, including the US, Canada, and Switzerland.

In the US, an indication in patients with MCL who have received at least 1 prior therapy was approved 9 December 2006. In Canada, the following indication was approved on 9 June 2008:

*VELCADE (bortezomib) for Injection is indicated for the treatment of patients with mantle cell lymphoma who have relapsed or were refractory to at least 1 prior therapy.*

The data from Study M34103-053 confirmed that Velcade is an effective therapy for patients with MCL who have received at least 1 prior therapy, and that Velcade provides clinical benefit to these patients in the form of durable responses, including complete responses, a prolonged time to initiation of alternate therapy in subjects who responded to therapy, and prolonged overall survival in patients who responded to therapy. Velcade was also able to induce responses in patients refractory to their last prior treatment.

While noting the Delegate's comments that a 32% ORR is not overly compelling on its own, the 1-year survival rate in Study M34103-053 was 69% overall and 91% in responders. Further the median survival was 35.4 months for all responders (CR + CRu + PR) and 36 months for complete responders (CR + CRu). At final analysis 62 of 155 subjects (40%) were alive. Whilst the sponsor acknowledges the limitations of the data set, along with the age of the study, we also note that many other Health Authorities did believe that use in relapsed/refractory patients did confer some clinical benefit.

Based on data submitted to the TGA on 22 July 2014 as part of the Orphan Drug Designation Application for Velcade in MCL, the prevalence of MCL in Australia is very low. Based on data directly from the Australian Cancer Database and extrapolation in line with the growth of population in Australia, it is estimated that the prevalence of MCL in Australia is approximately 818. The subpopulation of patients with relapsed or refractory MCL would be a much smaller subset again. Therefore, this additional indication would apply only to a small number of patients.

Should the ACPM and the Delegate consider that the use of Velcade in relapsed and refractory MCL is clinically appropriate in Australia, the sponsor would be willing to accept the following additional indication (Canadian approved wording):

*Velcade is indicated for the treatment of patients with mantle cell lymphoma who have relapsed or were refractory to at least 1 prior therapy.*

If recommended for approval, the sponsor will provide an updated draft PI accordingly, with information specific to relapsed and refractory MCL added to the Indications, Dosage and Administration, Adverse Effects and Clinical Trials sections, consistent with the text approved in the US.

#### *Maintenance*

The Delegate has noted there is some evidence that in R-CHOP responders, maintenance rituximab reduces the risk of progression or death.<sup>11</sup> The Delegate has also noted that it is not clear how maintenance therapy fits into the regimen envisaged by the sponsor and has invited the sponsor to comment on this issue and to draw attention to any studies of VcR-CAP planned or in progress that will directly address this issue of maintenance.

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<sup>11</sup> Kluin-Nelemans HC, et al. (2012) Treatment of older patients with mantle-cell lymphoma. *N Engl J Med.* 367: 520-31.



The sponsor is aware of the role of maintenance in treatment of patients with mantle cell lymphoma and high grade lymphomas. There have been a number of investigator led trials in this area which has demonstrated efficacy of maintenance therapy in patients with multiple myeloma (GEM2005MAS65 study).<sup>12</sup> However, the sponsor has not done any maintenance studies with the VcR-CAP regimen and currently is not proposing a maintenance regime for treatment of MCL at this time.

### **Conclusion**

The magnitude of improvement in efficacy outcomes with VcR-CAP compared with R-CHOP, coupled with the manageable safety profile for VcR-CAP, demonstrates that the benefits of VcR-CAP for subjects suffering from newly diagnosed MCL outweigh the risks. In addition, the data from Study M34103-053 confirmed that Velcade is also effective for patients with MCL who have received at least 1 prior therapy. Therefore, the sponsor proposes the following indications for Velcade use in MCL:

*Velcade in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma.*

*Velcade is indicated for the treatment of patients with mantle cell lymphoma who have relapsed or were refractory to at least 1 prior therapy.*

### **Advisory committee considerations**

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Velcade powder for injection containing 1 mg and 3.5 mg of bortezomib to have an overall positive benefit-risk profile for the indication;

*Velcade, in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL).*

In making this recommendation, the ACPM:

- Noted that MCL is a rare condition, with small numbers of patients who will be managed in a specialist setting.
- Was of the view that the broader indication proposed by the sponsor provided flexibility for clinicians and patients.

### **Proposed conditions of registration**

The ACPM agreed with the Delegate on the proposed conditions of registration.

### **Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments**

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- Include a stronger recommendation regarding the use of Herpes zoster virus prophylaxis considering the extent of Herpes zoster reactivation in the clinical trials.
- Consider the inclusion of more specific dosing instructions for patients with renal impairment as there is considerable experience with use of bortezomib in patients with multiple myeloma, many presenting with renal failure at diagnosis, and requiring dose adjustments when starting treatment with bortezomib.

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<sup>12</sup> Mateos M-V, et al. (2012) Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. *Blood* 120: 2581-2588.

- Highlight the data limitations and provide a suitable precautionary statement around use in patients eligible for ASCT.
- Remove the reference to mmol/L of haemoglobin and replace with g/L, the current Australian measurement unit.

#### *Specific advice*

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- Is it acceptable to allow use of VcR-CAP in newly diagnosed MCL patients suitable for autologous stem cell transplantation?

The ACPM noted that the clinical trials presented in the application included patients who received Velcade in combination with VcR-CAP who were medically ineligible for ASCT. However, it was noted that some were not considered for ASCT for other reasons. The ACPM advised that it should be made clear that some patients did not have ASCT for reasons other than medical ineligibility

The ACPM noted that although there were limited trial data and experience with use of bortezomib in patients with newly diagnosed MCL who were suitable for ASCT; the indication proposed by the sponsor would allow use in some patients who were suitable for transplant but declined for transplant for non-medical reasons.

If the sponsor's proposed wording for the indication was approved, the ACPM was of the view that that combination treatment with bortezomib would not be used instead of ASCT or intensive chemo-immunotherapy in younger patients as these treatments are considered the standard of care for these patients.

The ACPM considered that combination bortezomib might be used pre ASCT instead of R-CHOP in patients with MCL if the indication as proposed by the sponsor is accepted but as there are no data in this setting, use would probably be limited, if at all. However, the ACPM acknowledged there is some evidence that bortezomib if used in this way would be effective and that it would not adversely affect the outcome of ASCT per se. The ACPM advised that the PI should clearly indicate that there are limited data for use in pre-ASCT and no data in the MCL setting.

The ACPM noted that patients with MCL would be treated in large specialist centres and treatment would be tailored to individual patient's needs. The ACPM was of the view that use of VcR-CAP should be allowed in newly diagnosed MCL patients suitable for autologous stem cell transplantation and that the broader wording of the indication as proposed by the sponsor would allow more options for clinicians

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

#### **Outcome**

Based on a review of quality, safety and efficacy, TGA approve the registration of VELCADE containing bortezomib. The new approved indication is:

*Velcade, in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL).*

The full indications are now:

- *Velcade, in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated multiple myeloma who are not candidates for high dose chemotherapy.*
- *Velcade, as part of combination therapy, is indicated for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients under 65 years of age with previously untreated multiple myeloma.*
- *Velcade is also indicated for the treatment of multiple myeloma patients who have received at least one prior therapy, and who have progressive disease.*
- *Velcade, in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL).*

#### **Specific conditions of registration applying to these goods**

- For all injectable products, the PI must be included with the product as a package insert.
- The Velcade EU-RMP version 29.1 dated 10 October 2014 (data lock point 31 December 2013) and ASA version 1.0 dated 22 October 2014, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

### **Attachment 1. Product Information**

The PI approved for Velcade at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

### **Attachment 2. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

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