PUBLIC SUMMARY DOCUMENT
Product: Bortezomib, powder for injection, 1 mg (solvent required), Velcade®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: March 2011

1. Purpose of Application

The submission sought an extension to the current Authority Required listing for bortezomib to include the first-line treatment of multiple myeloma in patients newly diagnosed who have severe renal failure or in patients treated with thalidomide who have a resultant GFR drop to ≤ 30 (mL/ min).

2. Background

Following three previous rejections and a deferral, the PBAC recommended the listing of bortezomib on the PBS at its July 2007 meeting for the third line treatment of patients with refractory MM on the basis of acceptable cost-effectiveness when compared to a mixture of salvage treatments and where the extent of substitution from mini-allogeneic transplants is zero. The PBAC recommended no more than 11 cycles of treatment be authorised, and where a confirmed complete response was achieved, no more than two additional cycles administered beyond a confirmation. Listing was effective from 1 November 2007.

A copy of the PSD from the meeting is available from:
www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-bortezomib-july07

At the July 2009 meeting, the PBAC considered a submission requesting listing under the Intravenous Chemotherapy Supply Program (ICSP) arrangements for treatment, in combination with a corticosteroid and melphalan or cyclophosphamide, of previously untreated symptomatic MM or MM with related organ or tissue damage, in patients with a WHO performance status of 2 or less, and who were ineligible for high dose chemotherapy. The PBAC recommended the listing of bortezomib on the PBS through the ICSP for the first-line treatment of patients with MM in combination with melphalan or cyclophosphamide and corticosteroids on a cost minimisation basis compared with thalidomide.

A copy of the PSD from the meeting is available from:
www.health.gov.au/internet/main/publishing.nsf/Content/BD4FE2D9D27ED43BCA2576560082FD42/$File/Bortezomib%20VELCADE%20Janssen-Cilag%20PBAC%20PSD%206-1%202009-07%20FINAL%20merged.pdf

At the March 2010 meeting, the PBAC rejected a re-submission for cost-effectiveness of bortezomib, in combination with prednisolone and melphalan or cyclophosphamide, for the treatment of newly diagnosed multiple myeloma (MM) patients who are not eligible for high dose chemotherapy, on the basis that superiority had not been proven. The PBAC advised that the cost-minimisation recommendation from the July 2009 meeting therefore should be maintained. A*s of May 2011, the listing has not proceeded.*

A copy of the PSD from the meeting is available from:
www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-bortezomib-mar10

The PBAC recommended that consideration should also be given to identifying a sub-group of patients for first-line treatment with bortezomib such as patients with renal failure where there is an unmet clinical need.

Following the March 2010 PBAC meeting, the Department of Health and Ageing hosted a meeting between the PBAC, the Myeloma Scientific Advisory Group (MSAG) of the Myeloma Foundation of Australia and Janssen to discuss the treatment of patients with renal impairment, with a view to informing the preparation of a PBAC submission. The data presented and discussion at this meeting formed the basis of the submission.

Bortezomib was recommended, out of session following the August 2010 PBAC Special meeting for retreatment in patients who have experienced a good response to prior bortezomib treatment. Listing was effective from 1 March 2011.

3. Registration Status

Bortezomib (1 mg vial size) was TGA registered on 1 June 2009.
The approved indications for bortezomib are:

- Treatment, in combination with melphalan and prednisone, of patients with previously untreated multiple myeloma, who are not suitable for high dose chemotherapy.
- Treatment of multiple myeloma patients who have received at least one prior therapy, and who have progressive disease.

4. Listing Requested and PBAC's View

Authority required

Initial PBS subsidised treatment as monotherapy or in combination with a corticosteroid and melphalan or cyclophosphamide in a patient with symptomatic multiple myeloma and severe renal impairment (GFR ≤30, after adequate hydration):
1) who is newly diagnosed and is receiving bortezomib as frontline therapy; or
2) who commenced treatment on thalidomide with a resultant GFR drop to ≤ 30 (with adequate hydration). For these patients there is 1) no requirement to experience treatment failure after a trial of at least 4 weeks of thalidomide or 2) to have failed to achieve at least a minimal response after at least 8 weeks of thalidomide treatment.

Authority Required

Continuing first-line PBS-subsidised treatment of a patient with multiple myeloma who has received an initial authority prescription for bortezomib and who, at the time of application has demonstrated at least a partial response at the completion of cycle 4.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Multiple myeloma is a cancer of plasma cells. It is a progressive haematological disease, which is incurable. Common clinical manifestations include hypercalcaemia, anaemia, renal damage, increased susceptibility to bacterial infection and impaired production of normal immunoglobulin. Diffuse osteoporosis, usually in the pelvis, spine, ribs and skull is also characteristic of MM.

Bortezomib would provide an alternate to thalidomide as a first-line PBS treatment for multiple myeloma in patients with renal failure at diagnosis or for patients who develop renal failure whilst being treated with thalidomide.

6. Comparator

The submission nominated a thalidomide based regimen as the main comparator which was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented new data from the key clinical trial as follows:

- one retrospective review of newly diagnosed patients with MM and renal impairment who were treated with bortezomib or thalidomide/lenalidomide based regimens (Roussou et al 2010). Patients in the bortezomib arm received concomitant high dose dexamethasone; patients in the thalidomide/lenalidomide arm received high dose dexamethasone and/or cyclophosphamide or melphalan. Patients were enrolled based on CrCl <50ml/min. The subgroups of patients with severe renal impairment (CrCl <30mL/min) was 13 in the bortezomib arm and 25 in the thalidomide/lenalidomide arm.

The submission presented the following supportive data:

- a post-hoc sub-group analysis of patients with renal impairment from the VISTA trial, where patients with previously untreated MM were enrolled and treated with bortezomib, melphalan and prednisone (VcMP) or melphalan and prednisone (MP); and
- a post-hoc sub-group analysis of patients with renal impairment from the APEX trial where patients with relapsed MM (received one to three previous therapies) were enrolled and treated with bortezomib or high-dose dexamethasone.

The studies and trials (and associated reports) published at the time of submission are presented in the following table:

Trial ID / First author	Protocol title / Publication title	Publication citation
Roussou et al 2010	Comparative retrospective review of bortezomib vs thalidomide in newly diagnosed untreated patients with renal impairment	
Roussou M,et al	Reversibility of renal failure in newly diagnosed patients with multiple myeloma and the role of novel agents.	ASH Annual Meeting Abstracts 2009; 114 (22): Abstract 955.
Roussou M et al	Reversibility of renal failure in newly diagnosed patients with multiple myeloma and the role of novel agents.	Leuk Res 2010; 34(10): 1395-1397
VISTA	Retrospective analysis of renal cohort in RCT comparing bortezomib to MP. In front-line patients.	
Dimopoulos M et al	VMP (bortezomib, melphalan, and prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: cohort analysis of the phase III VISTA study.	Journal of Clinical Oncology 2009; 27 (36): 6086-6093.
Dimopoulos M et al	Bortezomib-melphalan-prednisone (VMP) in newly diagnosed multiple myeloma patients with impaired renal function: cohort analysis of the phase III	[abstract no. 1727] Blood 2008; 112 (11): 608.

	VISTA study [abstract no. 1727]	
Dimopoulos M, et al	Bortezomib-melphalan-prednisone (VMP) in newly diagnosed multiple myeloma patients with impaired renal function: cohort patients with impaired renal function: cohort analysis of the phase III VISTA study	ASH Annual Meeting Abstracts 2008; 112 (11): 172.
APEX	Retrospective analysis of renal cohort in RCT comparing bortezomib to dexamethasone in patients with relapsed MM.	
San-Miguel M et al	Efficacy and safety of bortezomib in patients with renal impairment: results from the APEX phase 3 study.	Leukemia 2008; 22 (4): 842-849.

8. Results of Trials

The key results for time to renal response are summarised below:

The median time to major renal response in the Roussou study was reported to be significantly shorter in the bortezomib arm than the thalidomide/lenalidomide arm; 0.69 months (0.07-3.0 months) versus 1.6 months (0.1-6.0 months) (p=0.007).

In the VISTA trial, bortezomib regimens appear to be superior to chemotherapy alone (MP) in reversing renal impairment (GFR ≤ 50ml/min to GFR >60ml/min) (RR 1.28 (0.92, 1.77)). Bortezomib regimens are also associated with a greater proportion of patients achieving a CrCl increase of greater than 20 ml/min (RR 1.37 (1.05, 1.79)). The PBAC noted that a test for interaction conducted during the evaluation comparing patients in the VISTA trial with GFR <30ml/min to patients with GFR 30-<50ml/min indicated that there was no statistically significant difference (RR=4.67, 95% CI: 0.63, 34.90) in terms of the reversal of renal impairment (defined as GFR >60ml/min), however there is a trend to increased benefit in patients with GFR <30ml/min. Results were reported in the submission that corresponded with the population proposed in the restriction GFR<30.

The PBAC considered that overall the Roussou et al (2010) study is weak evidence that bortezomib is preferable to thalidomide based treatment for MM in patients with severe renal impairment. However, the PBAC had the following key concerns with reliance on this exploratory study:

- it is a retrospective case series
- there are important baseline differences
- high risk of outcome reporting bias
- imprecise (small) estimates
- confounded by cyclophosphamide effects
- GFR responses are not patient relevant outcomes.

The results of the Roussou et al (2010) study for myeloma response illustrated that there is no statistically significant difference in the proportion of patients achieving at least a partial response of myeloma between the bortezomib regimen compared to the IMiD (thalidomide/lenalidomide) regimen.

For PBAC's view of the results, see Recommendation and Reasons.

The Roussou et al (2010) study found no differences regarding toxicity among patients with or without renal impairment in all treatment groups. No further information was reported.

There were no statistically significant different adverse events (AEs) between any of the treatment and comparator arms in the supportive trials (VISTA and APEX). Adverse events included neutropenia, thrombocytopenia and anaemia.

9. Clinical Claim

The submission described bortezomib based regimens as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over thalidomide/lenalidomide based regimens.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a new stepped economic evaluation.

The base case modelled economic evaluation is constructed as a simple Markov model with three mutually exclusive health states:

- GFR >30;
- GFR ≤30; and
- Dialysis.

The supplementary modelled economic evaluation is constructed as a simple Markov model with four mutually exclusive health states:

- GFR >30;
- GFR ≤30;
- Dialysis; and
- Death.

The model included cost for treatment (bortezomib or thalidomide, epoetin alfa, sevelamer hydrochloride), medical services (IV administration of bortezomib, full blood counts and specialist visits) and hospital costs (dialysis). Utilities are applied to patients with GFR >30ml/min, GFR ≤30ml/min and those on dialysis).

The base case incremental cost per extra QALY gained was estimated in the submission to be less than $15,000. The incremental cost per extra patient free from dialysis gained was estimated to be greater than $200,000.

Results of the sensitivity analyses indicated that the model was most sensitive to the transition probabilities from 'GFR < 30' to 'GFR > 30' and the mean dose of thalidomide. The model was also quite sensitive to the dose and treatment duration of of bortezomib.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated by the submission to be less than 10,000 in Year 5 for newly diagnosed patients with GFR ≤30ml/min and patients currently treated with thalidomide who drop to GFR ≤30ml/min.

The financial cost/year to the PBS (excluding co-payments) minus any savings in use of other drugs was estimated by the submission to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC acknowledged the clinical need for bortezomib in patients with severe renal failure and noted that the International Expert Opinion published in the Journal of Clinical Oncology, November 2010, supported use of bortezomib in combination with high dose dexamethasone or melphalan in patients with renal impairment of any grade.

The PBAC agreed that the appropriate comparator is thalidomide.

The key clinical trial presented in the submission was Roussou et al (2010), a retrospective review comparing bortezomib with thalidomide/lenalidomide regimens in newly diagnosed multiple myeloma (MM) patients with renal impairment. Supportive data were presented from a sub-group analysis of patients with renal impairment in the VISTA trial (Vc(bortezomib, melphalan, prednisolone)MP versus MP in patients with previously untreated MM who were non-transplant eligible (NTE)).

The PBAC considered that the results of the Roussou et al (2010) study illustrated that there is no statistically significant difference in the proportion of patients achieving at least a partial response of myeloma between the bortezomib regimen compared to the IMiD (thalidomide/lenalidomide) regimen. The PBAC noted that in Roussou study, the median time to major renal response was reported to be significantly shorter in the bortezomib arm than the thalidomide/lenalidomide arm; 0.69 months (0.07-3.0 months) versus 1.6 months (0.1-6.0 months) (p=0.007). However, the PBAC considered that the Roussou et al (2010) study is relatively weak evidence that bortezomib is preferable to thalidomide based treatment for MM in patients with severe renal impairment. The PBAC held key concerns with reliance on this exploratory study.

In the VISTA trial, bortezomib regimens appear to be superior to chemotherapy alone (MP) in reversing renal impairment (GFR ≤ 50ml/min to GFR >60ml/min) (RR 1.28 (0.92, 1.77)). Bortezomib regimens are also associated with a greater proportion of patients achieving a CrCl increase of greater than 20 ml/min (RR 1.37 (1.05, 1.79)).The PBAC noted that a test for interaction conducted during the evaluation comparing patients in the VISTA trial with GFR <30ml/min to patients with GFR 30-<50ml/min indicated that there was no statistically significant difference (RR=4.67, 95% CI: 0.63, 34.90) in terms of the reversal of renal impairment (defined as GFR >60ml/min), however there is a trend to increased benefit in patients with GFR <30ml/min. The PBAC considered that it is unclear whether bortezomib treatment regimens will lead to a reduction in dialysis. Notwithstanding these concerns, the PBAC noted the internal consistency of the study results and that a more rapid improvement in reversal of renal failure was seen with bortezomib.

The submission described bortezomib based regimens as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over thalidomide/lenalidomide based regimens. The PBAC acknowledged the likely improvement in speed of response from Roussou et al 2010, however, considered that stronger evidence of an improvement in patient-relevant outcomes, such as the need for dialysis, would form a better basis for a claim of superior efficacy. The PBAC noted that bortezomib and thalidomide were associated with different toxicities.

The submission presented a new stepped economic evaluation. The VISTA bortezomib dose and treatment duration and Facon (2007) thalidomide dose and duration was applied in the economic evaluation with the efficacy of the treatments based on those observed in the Roussou et al (2010) study. The PBAC noted that the results of the sensitivity analyses indicate that the model is most sensitive to the transition probabilities from 'GFR ≤30' to 'GFR >30', and the mean dose of thalidomide and that the model is quite sensitive to the dose and treatment duration of bortezomib. The PBAC also noted that the incremental cost per patient free of dialysis was estimated to be greater than $200,000 in the trial-based economic evaluation.

The PBAC considered that the number of patients who would be eligible under the requested restriction represented more than 15% of all newly diagnosed MM patients and was therefore an overestimate. However, the PBAC considered that if a more severe subgroup could be identified the ICER for the patient relevant endpoint would decrease substantially. The PBAC considered that as patients who require dialysis or who are at substantial risk of requiring dialysis have improved renal outcomes with bortezomib, this patient population might represent a suitable subgroup.

The PBAC therefore deferred the submission to enable discussion with clinicians and the sponsor regarding eligibility criteria for first-line use in a patient with acute renal failure whose GFR is falling and where a renal physician would consider the patient at risk of requiring dialysis, so that those with the greatest clinical need will have access to PBS-subsidised bortezomib.

The PBAC acknowledged and noted the consumer comments on this item.

Recommendation:
Defer

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Janssen are committed to working with the PBAC to determine the relevant group of patients with renal impairment suitable for first line use of bortezomib.