PUBLIC SUMMARY DOCUMENT
Product: BORTEZOMIB, powder for injection, 1 mg, Velcade®
Sponsor: Janssen-Cilag Pty Ltd.
Date of PBAC Consideration: March 2010

1. Purpose of Application

The resubmission requested an Authority required listing for 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.

2. Background

This was the second submission for bortezomib for first line treatment for patients not eligible for stem cell transplant.

At the July 2009, 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, using the thalidomide costs accepted by the PBAC in March 2009 for first-line treatment of multiple myeloma. This was not the basis of the listing for bortezomib requested by the sponsor in the July 2009 submission.

For further details see the Public Summary Document from the July 2009 PBAC meeting at www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Bortezomib-jul09.

3. Registration Status

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

The submission proposed two restriction listings (Option A or Option B), and a change to the current relapsed/refractory bortezomib listing for use after thalidomide (Relapsed/refractory listing change).

OPTION A:

Authority Required

Initial PBS-subsidised treatment of a patient with newly diagnosed symptomatic multiple myeloma in combination with a corticosteroid and melphalan or cyclophosphamide who is ineligible for high dose chemotherapy.

The authority application must be made in writing and must include:
(1) a completed authority prescription form; and
(2) a completed Multiple Myeloma Authority Application - Supporting Information Form, which includes details of diagnosis, ineligibility for high dose chemotherapy and patient body surface area (BSA);
(3) a signed patient acknowledgment.

Authority required
Continuing first-line PBS-subsidised treatment of a patient with newly diagnosed symptomatic multiple myeloma, in combination with a corticosteroid and melphalan or cyclophosphamide, who has received an initial authority prescription of bortezomib and who, at the time of application, has demonstrated:
(i) no progressive disease; and
(ii) has not yet achieved a best confirmed response to bortezomib.

Continuing PBS-subsidised supply will not be approved if there is a gap of more than 9 months between the initial application and this application.

Further applications for continuing PBS-subsidised bortezomib will not be approved after this application.

OPTION B:

Authority Required
Initial PBS-subsidised treatment of a patient with newly diagnosed symptomatic multiple myeloma in combination with a corticosteroid and melphalan or cyclophosphamide who is ineligible for high dose chemotherapy.

The authority application must be made in writing and must include:
(1) a completed authority prescription form; and
(2) a completed Multiple Myeloma Authority Application - Supporting Information Form, which includes details of diagnosis, record ineligibility for high dose chemotherapy, patient body surface area (BSA); and nomination of which disease activity parameters will be used to assess response. To enable confirmation by Medicare Australia of response, current diagnostic reports of at least one of the following are required:
(a) the level of serum monoclonal protein; or
(b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or
(c) the serum level of free kappa and lambda light chains; or
(d) bone marrow aspirate or trephine; or
(e) if present, the size and location of lytic bone lesions (not including compression fractures); or
(f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or
(g) if present, the level of hypercalcaemia, corrected for albumin concentration.
As these parameters will be used to determine response, results for either (a) or (b) or (c) should be provided for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma either (c) or (d) or if relevant (e), (f) or (g) should be provided. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-

secretory or nonsecretory nature of the multiple myeloma (either previous or current serum M protein less than 10g per L and urinary Bence-Jones protein undetectable or less than 200mg per 24 hours) must be provided; and
(3) a signed patient acknowledgment.

Authority required
Continuing PBS-subsidised treatment, in combination with a corticosteroid and melphalan or cyclophosphamide, of previously untreated multiple myeloma in a patient who has previously received 4 six-week treatment cycles of bortezomib and who, at the time of application, has demonstrated at least a partial response to bortezomib.

If serum M protein and urine Bence-Jones protein levels are measurable, partial response (PR) compared with baseline (prior to treatment with bortezomib) is defined as:
(a) at least a 50% reduction in the level of serum M protein (monoclonal protein); or
(b) at least a 90% reduction in 24-hour urinary light chain M protein excretion or to less than 200 mg per 24 hours.
If serum M protein and urine Bence-Jones protein levels are unmeasurable as in non-secretory/oligo-secretory multiple myeloma, partial response compared with baseline is defined as:
(c) at least a 50% reduction in the difference between involved and uninvolved serum free light chain (FLC) levels.
If serum M protein and urine Bence-Jones protein and serum FLC are unmeasurable/unavailable, partial response compared with baseline is defined as:
(d) at least a 50% reduction in bone marrow plasma cells; or
(e) no increase in size or number of lytic bone lesions (development of compression fracture does not exclude response); or
(f) at least a 50% reduction in the size of soft tissue plasmacytoma(by clinical or applicable radiographic examination, i.e. MRI or CT-Scan);or
(g) normalisation of corrected serum calcium to less than or equal to 2.65 mmol per L.
For the purpose of assessing eligibility for continuing PBS-subsidised bortezomib treatment beyond 4 six-week cycles, the patient must have achieved at least a partial response at the completion of cycle 4. The results of the response assessment must be included in a written application to Medicare Australia for further treatment. Where a response assessment is not submitted to Medicare Australia prior to cycle 5, patients will be deemed to have failed to respond to treatment with bortezomib. Continuing PBS-subsidised supply will not be approved if there is a gap of more than 9 months between the initial application and subsequent applications. The same disease activity parameters nominated in the initial authority for assessment of response are to be used to demonstrate at least a partial response to treatment.
The authority application must be made in writing and must include:
(1) a completed authority prescription form; and
(2) a completed Multiple Myeloma Authority Application - Supporting Information Form; and
(3) diagnostic reports demonstrating the patient has achieved at least a partial response..
Diagnostic reports must be no more than 1 month old at the time of application.
No more than 2 six-week cycles of treatment beyond the cycle at which a confirmed complete response was first achieved will be authorised. Confirmation requires 2 determinations a minimum of 6 weeks apart.

RELAPSED/REFRACTORY LISTING CHANGE:

The submission requested the addition of the following note to the listing for relapsed/refractory MM.

Note:
For patients who have not been previously treated with a course of bortezomib.

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 first line PBS treatment for multiple myeloma.

6. Comparator

Thalidomide (in combination with melphalan and prednisone). This is as previously agreed by the PBAC.

7. Clinical Trials

No new trials were identified. The same trials that were presented in the previous submission (VISTA, Facon 2007, Hulin 2009, Palumbo 2008, Gulbrandsen 2008, Wijermans 2008) were presented in the resubmission. The citation details for these studies may be found in the Public Summary Document from the July 2009 PBAC meeting. Updated data (as a result of longer follow-up) from the bortezomib VISTA and three of the thalidomide (Hulin 2009, Palumbo 2008, Wijermans 2008) trials were used.

The previous submission presented an indirect comparison of bortezomib versus thalidomide (including all five thalidomide trials in a meta-analysis) to support a claim of superiority, however the PBAC considered that the clinical trial data presented did not demonstrate superior efficacy of bortezomib over thalidomide in the first-line setting. The current submission selected two of the thalidomide trials (Gulbrandsen 2008/07, Wijermans 2008) in a base case indirect comparison to support a claim of superiority of bortezomib versus thalidomide and presented a comparison with all five trials as a supplementary analysis.

8. Results of Trials

Although the updated follow-up data had resulted in some numerical differences in the odds ratio (OR), relative risk (RR) and risk difference (RD) values reported, it had not affected the conclusions of each of the trials i.e.,

- VISTA demonstrates that (Velcade (bortezomib), melphalan, prednisone) VcMP is superior to melphalan and prednisone (MP) for OS at 1, 2 and 3 years;
- Hulin (2009) demonstrates no differences between melphalan, prednisone and thalidomide (MPT) and MP at 1 or 2 years, but MPT is superior to MP at 3 years;
- Palumbo (2008) demonstrates no differences between MPT and MP at 1, 2 or 3 years; and
- Wijermans (2008) demonstrates no differences between MPT and MP at 1, 2 or 3 years.

The results for the Facon (2007) and Gulbrandsen (2008) remain unchanged from the previous submission i.e.

- Facon (2007) demonstrates superiority of MPT versus MP at 1, 2 and 3 years. At 1 year, a significant difference is demonstrated with RR and RD, but not OR; and
- Gulbrandsen (2008) demonstrates no differences between MPT and MP at 1, 2 or 3 years.

The resubmission presented an indirect comparison of the VISTA trial with the results of a meta-analysis of two thalidomide trials (Gulbrandsen 2008 and Wijermans 2008) as its base case and an indirect comparison of the VISTA trial with the results of a meta-analysis of all five thalidomide trials as a supplementary analysis. An indirect comparison of the VISTA trial and the Facon (2007) thalidomide trial was conducted during the evaluation.

The indirect comparison of VISTA versus two thalidomide trials (Gulbrandsen 2008 and Wijermans 2008, the resubmission's base case) demonstrated a statistically significant difference between therapies, in favour of bortezomib, at 1 and 3 years (in year 3 by OR only, but not by RR or RD) in terms of overall survival. However, the PBAC noted that the selection of these two trials is likely to favour bortezomib. Neither the VISTA versus all five thalidomide trials (the resubmission's supplementary analysis) indirect comparison nor the VISTA versus Facon (2007) (analysis conducted during the evaluation) demonstrated statistically significant differences in OS between bortezomib and thalidomide at 1, 2 or 3 years (by OR, RR and RD). The PBAC noted that at 3 decimal places the OR for overall survival for VcMP at 1 year for the VISTA versus all five thalidomide trials (the resubmission's supplementary analysis) indirect comparison was significantly superior to MPT.

The indirect comparisons presented in the re-submission use odds ratio, relative risk, and risk difference to indirectly estimate the relative efficacy of bortezomib and thalidomide in terms of overall survival. However, the conclusion that bortezomib was superior was not consistent at years 1, 2 and 3. The PBAC considered that hazard ratios would be a more appropriate way of analysing time to event data, such as overall survival.

The PBAC noted the results which presented the results of overall survival (OS) hazard ratios (HR) reported in VISTA and the 5 direct MPT versus MP trials, as well as indirect comparisons using all 5 thalidomide trials, the 2 trials proposed by the submission (Gulbrandsen 2008/07 and Wijermans 2008) and Facon 2007 alone.

When hazard ratios were used, the results showed no statistically significant difference between bortezomib and thalidomide for any of the indirect analyses. Against Facon 2007 alone, the point estimate suggested thalidomide may be better (HR=1.09); against all 5 thalidomide trials, the point estimate suggests bortezomib may be better HR=0.78 (0.55, 1.10); and against the 2 thalidomide trials selected by the submission, the point estimate favoured bortezomib HR=0.67 (0.43, 1.02) and approached statistical significance. Overall, none of the analyses using hazard ratios showed a statistically significant result that could conclusively form the basis of a claim of superiority.

The PBAC had previously noted that the adverse events profiles of bortezomib and thalidomide were different. As the safety data provided in the resubmission varied only slightly from that considered previously, the PBAC concluded that there was insufficient

evidence to support the claim that bortezomib had a superior safety profile to thalidomide in this setting.

9. Clinical Claim

The submission claimed bortezomib was superior in terms of comparative effectiveness on the basis of overall survival at 1 and 3 years in the base case (Gulbrandsen 2008 and Wijermans 2008 trials) and superior in terms of comparative safety over thalidomide. The PBAC considered that, based on the totality of the evidence presented in the submission, the description regarding the comparative effectiveness of bortezomib and thalidomide was not reasonable.

10. Economic Analysis

An updated modelled economic evaluation was presented, as the resubmission provided a modelled economic evaluation of VcMP versus MPT

The modelled economic evaluation to 10 years using either two trials (Gulbrandsen 2008 and Wijermans 2008) or five trials (Facon 2007, Hulin 2009, Palumbo 2008, Gulbrandsen 2008 and Wijermans 2008) showed a discounted cost per life year gained and a discounted cost per quality adjusted life-year (QALY) in the range of $15,000 to $45,000.

The modelled economic evaluation assumed that bortezomib will only be used once in a patient's lifetime as that is currently the circumstances of use determined by the PBAC in 2007. All patients receiving bortezomib as first treatment continued to thalidomide second-line and lenalidomide third-line, whereas 20% of patients receiving thalidomide as first treatment can be re-treated with thalidomide.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 10,000 in Year 5, with the financial cost per year to the PBS being less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC noted that the comparator was thalidomide (in combination with melphalan and prednisone) which was as previously agreed. No new clinical trials were identified and the re-submission presented the same trials as in the previous submission (VISTA, Facon 2007, Hulin 2009, Palumbo 2008, Gulbrandsen 2008, Wijermans 2008). The PBAC noted that updated data (as a result of longer follow-up) from the bortezomib VISTA and three of the thalidomide (Hulin 2009, Palumbo 2008, Wijermans 2008) trials were used.

The re-submission selected two of the thalidomide trials (Gulbrandsen 2008/07, Wijermans 2008) in a base case indirect comparison to support a claim of superiority of bortezomib versus thalidomide and presented a comparison with all five trials as a supplementary analysis.

The indirect comparison demonstrated a statistically significant difference between therapies, in favour of bortezomib, at 1 and 3 years (in year 3 by OR only, but not by RR or RD) in terms of overall survival. However, the PBAC noted that the selection of these two trials is likely to favour bortezomib. Also, the PBAC considered the meta-analysis of these selected trials indicated that MPT is no better than MP in terms of overall survival at 1, 2 or 3 years. However, that this contradicts the therapeutic advantage of the addition

of thalidomide to an MP regimen previously accepted by the PBAC, as well as the totality of clinical trials experience with thalidomide.

In the VISTA versus all five thalidomide trials meta-analysis (the resubmission's supplementary analysis), the PBAC considered that there were no differences in OS between bortezomib and thalidomide at 2 or 3 years (by OR, RR and RD). The PBAC noted that at 3 decimal places the OR for overall survival for VcMP at 1 year was significantly superior to MPT. The PBAC considered that the supplementary indirect comparison presented in the submission of VISTA versus a meta-analysis of all five thalidomide trials was not fully appropriate for a number of reasons, including:

1. Differences in the baseline patient (age) and disease characteristics (different ISS categories) across the trials.
2. Differences in the thalidomide dose (ranging from 100 mg/day to 400 mg/day).
3. Differences in the number of cycles of MPT (6 to 12 cycles).
4. Differences in the use of thalidomide as maintenance therapy (after first-line treatment cessation).
5. Differences in the second-line treatment regimens employed in the trials which may confound the results reported for overall survival as the effectiveness and safety of the second-line regimens are likely to differ.
6. Differences in the primary outcomes of trials.

The PBAC noted an indirect comparison of the VISTA trial and the Facon 2007 thalidomide trial was conducted again during the evaluation using the updated VISTA trial data. The Facon (2007) trial utilised a treatment regimen relevant to the Australian context, enrolled patients with a comparable median age to those enrolled in VISTA and was powered to detect a difference in OS. In addition, the Facon (2007) trial was used as the basis of the economic evaluation presented for the listing of thalidomide in the first-line setting. The PBAC considered that the indirect comparison of the VISTA trial (for bortezomib) and Facon 2007 (for MPT), using MP as the common reference, provides consistency with previous submissions. It is acknowledged that, like each of the two other analyses considered, this comparison has caveats which create uncertainty. The PBAC agreed that the results indicated that there was no statistically significant difference in OS between bortezomib and thalidomide at 1, 2 or 3 years (by OR, RR and RD).

The PBAC noted that the indirect comparisons presented in the re-submission use odds ratio, relative risk, and risk difference to indirectly estimate the relative efficacy of bortezomib and thalidomide in terms of overall survival. However, as noted above, the conclusion that bortezomib is superior is not consistent at years 1, 2 and 3. The PBAC agreed that hazard ratios would be a more robust and appropriate way of analysing time to event data, such as overall survival, for use in the indirect comparison.

The PBAC noted the results which presented the results of overall survival (OS) hazard ratios (HR) reported in VISTA and the 5 direct MPT versus MP trials, as well as indirect comparisons using all 5 thalidomide trials, the 2 trials proposed by the submission (Gulbrandsen 2008/07 and Wijermans 2008) and Facon 2007 alone.

The PBAC noted that when hazard ratios are used, the results show no statistically significant difference between bortezomib and thalidomide for any of the indirect

analyses. Against Facon 2007 alone, the point estimate suggests thalidomide may be better (HR=1.09); against all 5 thalidomide trials, the point estimate suggests bortezomib may be better HR=0.78 (0.55, 1.10); and against the 2 thalidomide trials selected by the submission, the point estimate favours bortezomib HR=0.67 (0.43, 1.02) and approaches statistical significance. The PBAC concluded that none of the analyses using hazard ratios shows a statistically significant result that could conclusively form the basis of a claim of superiority. Therefore, bortezomib has neither superior nor inferior effectiveness to thalidomide in this setting.

The PBAC has previously noted that the adverse events profiles of bortezomib and thalidomide were different. As the safety data provided in the resubmission varied only slightly from that considered previously, the PBAC concluded that there is insufficient evidence to support the claim that bortezomib has a superior safety profile to thalidomide in this setting.

The PBAC noted that the modelled economic evaluation assumed that bortezomib will only be used once in a patient's lifetime. The PBAC noted that the base case ICER in the re-submission was in the range of $15,000 to $45,000/QALY.

The PBAC considered bortezomib use once per lifetime was reasonable in 2007 when initially approved, but with evolving practice and better management of toxicities this is now unreasonable from a clinical perspective. The PBAC considered that it was clinically appropriate that patients who have previously responded to bortezomib could receive re-treatment. Urgent 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.

The PBAC therefore, rejected the submission for cost-effectiveness on the basis that superiority had not been proven. The cost-minimisation recommendation from the July 2009 meeting should be maintained.

The PBAC noted that the submission meets criteria for independent review.

Recommendation:
Reject

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-Cilag has engaged in further constructive discussions with the PBAC and clinicians to address issues raised by the Committee, with a view to ensuring access to bortezomib through the PBS for groups of newly diagnosed patients and for patients who will benefit from subsequent retreatment with bortezomib.