PUBLIC SUMMARY DOCUMENT

Product: Bortezomib, powder for I.V. injection, 3.5 mg,Velcade®

Sponsor: Janssen-Cilag Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The resubmission requested an Authority Required PBS listing for initial and continuing treatment of multiple myeloma patients who have failed specified other therapy, have undergone or are ineligible for a primary stem cell transplant and who meet certain criteria.

2. Background

At the March 2006 meeting, the PBAC rejected a submission for an Authority Required listing for patients with multiple myeloma who meet certain criteria because of uncertain clinical benefit over the mix of comparators and uncertain, but unacceptable cost effectiveness.

3. Registration Status

Bortezomib was registered by the TGA on 8 February 2006 for the 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 requested an initial authority required listing on the PBS for '*…treatment of multiple myeloma in patients who have progressive disease with a WHO performance status of 2 or less, who have received at least one priory therapy and who have already undergone or are ineligible for a primary stem cell transplant…'*, and who are either '*unsuitable for thalidomide'* or '*have treatment failure*' to thalidomide according to certain criteria.

The submission requested that continuing PBS subsidised treatment for up to 6 cycles be dependent on certain criteria measuring the extent of disease progression (ie not experiencing [free of] disease progression). Continuing PBS subsidised treatment beyond 6 cycles is to be dependent on specified continuation criteria (ie achievement of at least a partial treatment response).

See Recommendation and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

Multiple myeloma (MM) is currently incurable. In Australia, more than 1,400 new cases are diagnosed annually. After initial treatments fail, effective treatment options are limited and resistance to conventional chemotherapy develops.

Bortezomib will be used in patients who have a good performance status following failure of the standard first and second line agents.

Current third-line therapies include IV chemotherapy and high dose therapy/autologous stem cell transplant and mini - allogeneic transplant.

6. Comparator

The submission nominated a mixture of salvage treatments, including autologous and allogeneic stem cell transplant and a number of standard chemotherapy regimens.

The PBAC accepted this as appropriate.

7. Clinical Trials

No changes were made to the trial data presented in the previous submission.

8. Results of Trials

There were no changes to the key results presented in the previous submission.

See Recommendations and Reasons.

9. Clinical Claim

The submission claimed that:
(i) bortezomib is more effective than high dose dexamethasone (HDD) and has an equivalent but a different toxicity profile. The PBAC considered that the claim of an 'equivalent' toxicity profile is questionable given the higher incidence of Grade 3 or 4 adverse events in the bortezomib arm. The incidences of Grade 4 adverse events, serious adverse events and in serious adverse events leading to death were not significantly different between bortezomib and HDD groups.
(ii) bortezomib is also more effective than the main comparator, a mixture of salvage treatments including autologous and allogeneic stem cell transplant and standard chemotherapies, and has similar or less toxicity. The PBAC noted that the Phase III evidence supporting this claim was limited to HDD. Eleven single-arm comparator studies were included to confirm the applicability of HDD as representative of the comparator mix of salvage treatments to support the claim.

10. Economic Analysis

An updated preliminary economic evaluation was presented.

An updated modelled economic evaluation was presented.

The base case modelled incremental discounted cost/extra QALY was estimated to be in the range $45,000 – 75,000. The base case modelled incremental discounted cost/extra LYG was estimated to be in the range $15,000- $45,000.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated to be < 10,000 in Year 4.

The financial cost/year to the PBS (excluding co-payments) minus any savings in use of other drugs was estimated to be up to < $10 million in Year 4.

12. Recommendation and Reasons

The PBAC acknowledged the intention of the requested restriction to target use to a cost-effective population, reflected by the use of a continuation rule. However, despite the clinical need for treatments in this group of patients, the PBAC considered the positioning of this

drug in the treatment algorithm for multiple myeloma is not yet established. Thus, there were concerns about the practicality of such a complex restriction and the appropriateness of the qualifying and continuation criteria.

As previously, the PBAC agreed that the comparator used in the APEX trial, HDD, would not be the only therapy likely to be replaced by bortezomib and that the use of a mixture of salvage treatments as an overall comparator was appropriate. However, there was again uncertainty about whether bortezomib would substitute for mini-allogeneic stem cell transplant and in what proportion of patients, in terms of cost offsets. The PBAC considered that candidates for these transplants would likely have different characteristics than patients who would receive bortezomib. Such patients would always remain transplant candidates and use of bortezomib would simply delay the transplant in some patients. The PBAC noted that mini-allogeneic transplants are the most costly option within stem cell transplantation.

The PBAC noted there were no changes to the key trial data. However, the incremental benefits of bortezomib treatment in the model were assumed to be larger than in the previous submission, because of the use of the continuation rule and responders experiencing greater survival than non-responders. As with the previous submission, there were some uncertainties about the economic model.

The PBAC agreed that it was clinically plausible for the base-case to be re-specified so that the treatment benefit for responders to continue for three years and for the time horizon of the model to go over six years. The PBAC considered the calculated cost-effectiveness ratios ($45,000 - $75.000), adjusted for the decrement in utility, to be unacceptably high.

Therefore, the PBAC rejected the submission because of unacceptable cost effectiveness, which was also uncertain because of cost offsets claimed for stem cell transplantation and relied on the implementation of the continuation rule in the restriction. There was also uncertainty about the implementation and suitability of the requested restriction in an environment where the place of bortezomib in the treatment of multiple myeloma, in the PBAC's view, has yet to be determined.

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 and the PBAC are in agreement that there is a clinical need for access to treatments such as bortezomib for Australian multiple myeloma patients who have failed standard 1st and 2nd line treatments. Janssen-Cilag is committed to ongoing interaction with the PBAC and clinicians to address the remaining areas of uncertainty, with a view to ensuring access to bortezomib through the PBS.