Public Summary Document

Product:	Bortezomib, powder for I.V. injection, 3.5 mg, Velcade®
Sponsor:	Janssen-Cilag
Date of PBAC Consideration:	March 2006

1. Purpose of Application

The submission requested an authority required listing on the Pharmaceutical Benefits Scheme (PBS) for initial and continuing treatment of multiple myeloma patients who have failed specified other therapy and meet certain criteria.

2. Background

This drug had not previously been considered by the Pharmaceutical Benefits Advisory Committee (PBAC).

3. Registration Status

Bortezomib was approved for marketing by the Therapeutic Goods Administration (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 authority required listing on the PBS for initial treatment of multiple myeloma patients with a WHO performance status of 0 - 2 who cannot take thalidomide or who are failing treatment with thalidomide according to certain criteria. Continuing PBS subsidised treatment would be dependent on the patient meeting certain other criteria.

The PBAC had a number of concerns with the requested listing including whether the restriction was likely to achieve its intended effect. These concerns were not a principle reason for rejection.

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 may be used in patients following failure of the standard first and second line agents.

6. Comparator

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

The PBAC agreed that the use of a mixture of salvage treatments as an overall comparator was appropriate.

7. Clinical Trials

The submission presented the APEX trial, a phase III, randomised controlled trial, as the key clinical study. This study compared bortezomib with high dose oral dexamethasone (HDD) in

multiple myeloma patients who required second, third or fourth-line therapy because of progressive disease, or relapse from complete response to previous therapy.

The PBAC had concerns that the APEX trial population was not representative of Australian multiple myeloma patients.

The submission also presented two supportive, non-randomised, open label studies of bortezomib in combination with oral dexamethasone (SUMMIT and Kropff et al). Eleven single-arm comparator studies were included to confirm the applicability of HDD as representative of the comparator mix of salvage treatments.

The key and supportive studies have been published as follows:

Trial/First author	Protocol/Publication title	Publication citation
Key trial		
APEX/ Richardson et al	Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma.	New England Journal of Medicine 2005; 352(24):2487-2498.
Supportive trials		
SUMMIT/Richardson et al Jagganath et al	A phase 2 study of bortezomib in relapsed, refractory myeloma.	New England Journal of Medicine 2003; 348(26):2609-17 Cancer 2005; 103(6):1195-200.
Kropff et al	Bortezomib in combination with dexamethasone for relapsed multiple myeloma.	Leukemia Res 2005; 29(5):587-90.

8. Results of Trials

The results of the key APEX trial are summarised in the table below:

	Bortezomib (N=333)	HDD (N=336)	Hazard ratio (95% CI) p-value [a]
Time to progression (ITT) Median, months	6.3	3.5	**0.55,** p<0.0001
Patients with one prior line, N Median, months **Patients with >1 prior lines, N** Median, months	132 7.1 200 4.9	119 5.6 217 2.9	**0.56** p=0.0021 **0.55,** p<0.0001
Overall survival (ITT)			
Survival probability at one year (%)	80	66	**0.57** p=0.0013 [a]

Data for analysis censored on or before 14 December 2003; date of progression determined by computer algorithm

[a] p-value from log-rank test adjusted by actual randomization stratification factors

There was a statistically significant difference in time to progression, number of deaths and survival favouring bortezomib. This difference was seen irrespective of the number of prior lines of treatment.

As reported in the APEX trial (bortezomib vs HDD):

- The overall incidences of adverse events (AEs) were similar in both groups with 100% and 98% of patients in the bortezomib and HDD groups, respectively, experiencing ≥1 treatment-emergent adverse event
- The overall pattern of adverse events differed between treatments. The most common adverse events in the bortezomib group were diarrhoea and nausea (57%), fatigue and

constipation (42% each), peripheral neuropathy (36%), vomiting, pyrexia, and thrombocytopenia (35% each), and anaemia (26%). The most commonly reported adverse events occurring with HDD were fatigue (32%), insomnia (27%), anaemia (22%), diarrhoea (21%), dyspnoea (17%) and pyrexia (16%).

- The incidence of Grade 3 events and adverse events leading to discontinuation was higher in the bortezomib group. 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;

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

9. Clinical Claim

The submission claimed that bortezomib was more effective than the main comparator, a mixture of treatments including autologous and allogeneic transplant and standard chemotherapy, and had similar or less toxicity.

For PBAC's view of this claim, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-effectiveness analysis as the preliminary economic evaluation.

A modelled economic evaluation was presented to extrapolate the survival from the APEX trial to 10 years for patients treated with bortezomib versus HDD as a surrogate for the main comparator using a cost-effectiveness and cost-utility approach. The base case modelled incremental cost per extra discounted life-year gained was in the range $45,000 - $75,000 while the base case modelled incremental cost per extra discounted quality adjusted life year (QALY) gained was in the range $75, 000 - $105,000.

For PBAC's view of these analyses, see Recommendations and Reasons

11. Estimated PBS Usage and Financial Implications

The submission estimated the net cost to the PBS to be just in excess of $10 million in year 4 of listing. The estimates presented in the submission were considered reasonable.

12. Recommendation and Reasons

A number of uncertainties arose over the interpretation of the APEX trial results. The PBAC acknowledged that bortezomib has significant advantages in the short term over the comparator HDD in terms of delaying time to progression (2.2 months) and increasing the proportion of individuals alive at one year. The difference between survival at one year was 14% in favour of bortezomib, however the 95% confidence intervals were wide. It was also noted that a large proportion of patients crossed over from the HDD arm to bortezomib which confounded interpretation of the results.

The PBAC considered there were doubts about the acceptability of HDD as being representative for the main comparator (a mix of treatments). In addition, the evidence for the mix of comparator treatments from the single-arm studies was considered weak.

The PBAC noted that there was a mismatch between the sources of the outcome information and the cost information used in the economic evaluations. The Committee further did not accept the validity of some of the claimed cost offsets.

There were a number of uncertainties over the modelled economic evaluation including the estimated long term mortality and the utilities associated with this mortality.

The PBAC thus rejected the submission because of uncertain clinical benefit over the mix of comparators and an uncertain, but high cost effectiveness ratio.

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

Due to the strong clinical need for an additional treatment in multiple myeloma, Janssen-Cilag has engaged in discussions with the PBAC and clinicians to clarify and address issues raised by the Committee with a view to ensuring access to bortezomib through the PBS.