PUBLIC SUMMARY DOCUMENT
Product: Bortezomib, powder for injection 1 mg (solvent required), Velcade®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: March 2012

1. Purpose of Application

The submission requested an extension to the current Authority Required listing to include induction therapy in a patient with newly diagnosed symptomatic multiple myeloma (MM) who is eligible for high dose chemotherapy, as part of combination therapy.

From 1 December 2011, bortezomib has been included in the Revised Arrangements for the Efficient Funding of Chemotherapy and listed under Section 100.

2. Background

Bortezomib has not previously been considered by the PBAC for this indication.

Bortezomib is currently PBS listed as a Section 100 (Efficient Funding of Chemotherapy) Public Hospital and Private Hospital/Private Clinic Authority Required benefit for the following indications:

- treatment, as monotherapy or in combination with a corticosteroid and/or cyclophosphamide, of a patient with a histological diagnosis of multiple myeloma who has progressive disease after at least 1 prior therapy and who has undergone or is ineligible for a primary stem cell transplant;
- treatment, as monotherapy or in combination with a corticosteroid and/or cyclophosphamide, of a patient with multiple myeloma who has progressive disease and who has been previously treated with PBS-subsidised bortezomib;

PBS listing of bortezomib for treatment of patients with newly diagnosed symptomatic multiple myeloma who are ineligible for high dose chemotherapy, in combination with a corticosteroid and melphalan or cyclophosphamide is expected to proceed later in 2012.

3. Registration Status

Bortezomib 1 mg powder for injection was TGA registered on 1 June 2009 for the indication: as part of combination therapy, 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.

Bortezomib is also TGA registered for the following indications:

- 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.
- 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

Note

PBS subsidised bortezomib will not be approved in combination with thalidomide or lenalidomide. No applications for increased maximum quantities and/or repeats will be authorised.

Authority Required
Initial PBS subsidised treatment, as part of combination therapy for induction therapy in a newly diagnosed patient with symptomatic multiple myeloma who is eligible for high dose chemotherapy.

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 usually characteristic of MM.

The submission proposed that the place in therapy of bortezomib, in combination therapy, is as an alternative to thalidomide and older induction chemotherapy regimens, such as VAD, prior to autologous stem cell transplant in patients with MM.

6. Comparator

The submission nominated thalidomide as the main comparator. The PBAC agreed that this was the appropriate comparator.

7. Clinical Trials

The basis of the submission was four randomised trials:

- Two trials comparing bortezomib-based induction regimens with vincristine-doxorubicin-dexamethasone (VAD) (HOVON-65/GMMG-HD4 and IFM 2005-01); and
- Two trials comparing thalidomide-based induction regimens with VAD (HOVON-50/GMMG-HD3 and Macro 2006.

Details of the trials published at the time of the submission are in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Bortezomib trials		
HOVON-65 / GMMG-HD4		
Sonneveld P, et al.	HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib, doxorubicin, dexamethasone (PAD) vs VAD followed by high-dose melphalan (HDM) and maintenance with bortezomib or thalidomide in patients with newly diagnosed multiple myeloma (MM).	*Blood ASH Annual Meeting Abstracts* 2010; 116 (21): 40
Sonneveld P, et al.	Bortezomib-based induction/maintenance therapy improved PFS vs standard induction/maintenance in patients with newly diagnosed myeloma [conference summary].	*Clinical Care Options Oncology* 2010.
Sonneveld P, et al. 2009	First analysis of HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib, adriamycine, dexamethasone (PAD) vs VAD as induction treatment prior to high dose melphalan (HDM) in patients with newly diagnosed multiple myeloma (MM) [Abstract no.	*Hematologica 94: 191.*

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Sonneveld P, et al.	First analysis of HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib, adriamycine, dexamethasone (PAD) vs VAD as induction treatment prior to high dose melphalan (HDM) in patients with newly diagnosed multiple myeloma (MM). [abstract no. 653]	*Blood* 2008; 112: 243-244.
Broyl A, et al.	Mechanisms of peripheral neuropathy associated with bortezomib and vincristine in patients with newly diagnosed multiple myeloma: a prospective analysis of data from the HOVON-65/GMMG-HD4 trial.	*Lancet Oncol* 2010; 11 (11): 1057-1065.
Scheid C, et al.	Influence of renal function on outcome of VAD or bortezomib, doxorubicin, dexamethasone (PAD) induction treatment followed by high-dose melphalan (HDM): a subgroup analysis from the HOVON-65/GMMG-HD4 randomized phase III trial for newly diagnosed multiple myeloma. [abstract]	*Blood* 2010; 116 (21).
IFM 2005-01 Harousseau J, et al.	Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial.	*Journal of Clinical Oncology:* 2010; 28: 4621-4629.
Harousseau J, et al.	Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantation (ASCT) in previously untreated multiple myeloma (MM): Updated data from IFM 2005/01 trial. [abstract no. 8505]	*Journal of Clinical Oncology: ASCO annual meeting proceedings* 2008; 26: 455.
Harousseau J, et al.	VELCADE/Dexamethasone (Vel/D) versus VAD as induction treatment prior to autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (MM): Updated results of the IFM 2005/01 trial. [abstract]	*Blood* 2007; 110.
Harousseau J, et al.	VELCADE/Dexamethasone (Vel/Dex) versus VAD as induction treatment prior to autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (MM): An interim analysis of the IFM 2005-01 randomized multicentre phase III trial. [abstract]	*Blood* 2006; 108: 21.
Moreau P, et al.	Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial.	*Blood* 2011; 117(11): 3041-3044.
Moreau P, et al.	Stem cell collection in patients with de novo multiple myeloma treated with the combination of bortezomib and dexamethasone before autologous stem cell transplantation according to IFM 2005-01 trial.	*Leukemia* 2010; 24(6): 1233-5.
Thalidomide trials		
HONOV-50/GMMG-HD3 Lokhorst H, et al.	A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-	*Blood* 2010; 115: 1113-1120.

	dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma.	
Lokhorst H. 2003	Phase III randomized study of doxorubicin, dexamethasone, and high-dose melphalan with or without thalidomide in patients with multiple myeloma.	National Institutes of Health, ClinicalTrials.Gov
Lokhorst H, et al.	Final analysis of HOVON-50 randomized phase III study on the effect of thalidomide combined with adriamycine, dexamethasone (AD) and high dose melphalan (HDM) in patients with multiple myeloma (MM) [abstract no. 157]	*Blood* 2008; 112(11): 64.
Lokhorst H, et al.	Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma.	*Haematologica* 2008; 93: 124-127.
Goldschmidt H, et al.	Joint HOVON-50/GMMG-HD3 randomized trial on the effect of thalidomide as part of a high-dose therapy regimen and as maintenance treatment for newly diagnosed myeloma patients.	*Annals of Hematology* 2003; 82: 654-659.
Van Marion A, et al.	Hypofibrinolysis during induction treatment of multiple myeloma may increase the risk of venous thrombosis.	*Thrombosis and haemostasis* 2005; 94: 1341-1343.
Breitkreutz I, et al.	Thalidomide in newly diagnosed multiple myeloma: influence of thalidomide treatment on peripheral blood stem cell collection yield.	*Leukemia* 2007; 21: 1294-1299.
Macro 2006 Macro M, et al.	Dexamethasone+thalidomide (Dex/Thal) compared to VAD as a pre-transplant treatment in newly diagnosed multiple myeloma (MM): A randomized trial. [abstract]	*Blood* 2006; 108: 22.

The submission presented two indirect comparisons (both using VAD (vincristine, doxorubicin, dexamethasone) as a common comparator):

- bortezomib-dexamethasone (VcD) versus thalidomide-dexamethasone (TD)
- bortezomib-doxorubicin-dexamethasone (VcAD) versus thalidomide-doxorubicin-dexamethasone (TAD).

8. Results of Trials

The 3-year results for progression free survival (PFS) across the trials were similar for patients receiving bortezomib (48%-50%) and thalidomide (47%). The 3-year overall survival (OS) results were also similar for patients receiving bortezomib (78%-81%) and thalidomide (73%). However, the PBAC noted that the comparisons for PFS and OS were confounded by differences in post-induction treatments between the trials.

The table below summarises the results of indirect comparisons of response rates to bortezomib and thalidomide via the common comparator VAD.

Summary of results of the indirect comparisons of response rates of bortezomib based regimens (VcD and VcAD) versus thalidomide based regimens (TD and TAD), via VAD as common comparator *(indirect ORs >1 favour bortezomib)*

	VcD vs TD via VAD as common comparator				VcAD vs TAD via VAD as common comparator			
	IFM 2005-01		Macro 2006		HOVON-65/ GMMG-HD4		HOVON-50/ GMMG-HD3	
	VcD N=240	VAD N=242	VAD N=104	TD N=100	VcAD N=371	VAD N=373	VAD N=268	TAD N=268
Achieving at least VGPR post induction								
n/N (%)	84/240[c] (35.0%)	33/242[c] (13.6%)	13/104[d] (12.6%)	35/100[d] (34.7%)	156/371 (42%)	56/373 (15%)	49/268 (18%)	98/268 (37%)
Trial OR (95% CI)[a]	**3.41 (2.12, 5.54)**		**3.77 (1.76, 8.35)**		**4.11 (2.86, 5.94)**		**2.58 (1.70, 3.92)**	
Indirect OR (95% CI)[b]	0.91 (0.36, 2.26)				1.59 (0.91, 2.78)			
Trial RR (95% CI)[a]	**2.57 (1.79, 3.68)**		**2.80 (2.14, 3.67)**		**2.80 (2.14, 3.67)**		**2.00 (1.48, 2.69)**	
Indirect RR (95% CI)[b]	0.92 (0.59, 1.44)				1.40 (0.94, 2.09)			
Trial RD (95% CI)a	**21.4% (13.9%, 28.8%)**		**22.5% (11.2%, 33.8%)**		**27.0% (20.8%, 33.2%)**		**18.3% (10.9%, 25.7%)**	
Indirect RD (95% CI)[b]	-1.1% (-14.6%, 12.4%)				8.7% (-1.0%, 18.4%)			
Achieving at least VGPR overall (on protocol post-transplant ± consolidation)								
n/N (%)	151/240[c] (62.9%)	102/242[c] (42.1%)	43/104 (41.7%)	44/100 (44.4%)	282/371 (76.0%)	205/373 (55.0%)	144/268 (53.7%)	176/267 (65.7%)
Trial OR (95% CI)[a]	**2.33 (1.59, 3.41)**		1.11 (0.62, 2.02)		**2.60 (1.88, 3.60)**		**1.65 (1.15, 2.37)**	
Indirect OR (95% CI)[b]	**2.10 (1.04, 4.24)**				1.58 (0.97, 2.56)			
Trial RR (95% CI)[a]	**1.49 (1.25, 1.78)**		**1.06 (0.77, 1.46)**		**1.38 (1.24, 1.54)**		**1.22 (1.06, 1.41)**	
Indirect RR (95% CI)[b]	1.41 (0.98, 2.03)				1.13 (0.95, 1.35)			
Trial RD (95% CI)[a]	**20.8% (12.0%, 29.5%)**		2.7% (-10.9%, 16.2%)		**21.1% (14.4%, 27.7%)**		**11.9% (3.7%, 20.2%)**	
Indirect RD (95% CI)[b]	**18.1% (2.0%, 34.2%)**				9.2% (-1.4%, 19.8%)			
Achieving at least PR post induction								
n/N (%)	175/240[c] (72.9%)	137/242[c] (56.6%)	NR	NR	289/371 (77.9%)	205/373 (55.0%)	153/268 (57.1%)	189/268 (70.5%)
Trial OR (95% CI)a	**2.06 (1.38, 3.08)**		NR		**2.89 (2.07, 4.03)**		**1.80 (1.24, 2.61)**	
Indirect OR (95% CI)[b]	NE				1.61 (0.97, 2.65)			
Trial RR (95% CI)a	1**.29 (1.11, 1.47)**		NR		**1.42 (1.27, 1.58)**		**1.24 (1.09, 1.41)**	
Indirect RR (95% CI)[b]	NE				1.15 (0.97, 1.36)			
Trial RD (95% CI)a	**16.3% (7.9%, 24.7%)**		NR		**22.9% (16.4%, 29.5%)**		**13.4% (5.4%, 21.5%)**	
Indirect RD (95% CI)[b]	NE				9.5% (-0.9%, 19.9%)			
Achieving CR or nCR post induction [e]								
n/N (%)	33/240[c] (14.8%)	14/242[c] (6.4%)	NR	NR	41/371 (11%)	19/373 (5%)	NR	NR
Trial OR (95% CI)[a]	**2.60 (1.35, 4.99)**		NR		**2.31 (1.32, 4.07)**		NR	
Indirect OR (95% CI)[b]	NE				NE			
Trial RR (95% CI)[a]	**2.38 (1.31, 4.33)**		NR		**2.17 (1.28, 3.67)**		NR	
Indirect RR (95% CI)[b]	NE				NE			
Trial RD (95% CI)a	**8% (3%, 13%)**		NR		**6% (2%, 10%)**		NR	
Indirect RD (95% CI)[b]	NE				NE			

Abbreviations: NR=not reported, NE=not estimated; CI = confidence interval; OR = odds ratio; RD = risk difference; RR = relative risk; TAD = thalidomide, doxorubicin, dexamethasone; TD = thalidomide, dexamethasone; VAD = vincristine, doxorubicin, dexamethasone; VcAD = bortezomib, doxorubicin, dexamethasone; VcD = bortezomib, dexamethasone; vs = versus.
CR=complete response, nCR=near complete response,

[a] Compared to common reference (VAD).

[b] indirect comparison (bortezomib based therapy over thalidomide based therapy) using CADTH ITC.

[c] calculated as ITT for consistency with the other 3 trials
[d] Note the Macro study reported 24.7% (TD) versus 7.3% (VAD) with VGPR prior to PBSC collection and 34.7% (TD) versus 12.6% (VAD) prior to HDM (Macro et al., 2006). The latter VGPR rate is used in this submission for post induction response in accordance with the public summary document for thalidomide (March 2009).
[e] Results estimated or extracted during the evaluation.
Bold typography indicates stat sig differences,

The indirect comparison of bortezomib- and thalidomide-based regimens (via VAD as a common comparator) did not find any statistically significant differences in Very Good Partial Response (VGPR) (post induction) rates for either the VcD versus TD or VcAD versus TAD comparisons.

For PBAC's view, see Recommendations and Reasons

The PBAC noted that in general, the adverse events reported were consistent with those known to be associated with bortezomib and thalidomide. Indirect comparisons of AEs between bortezomib and thalidomide could not be performed due to a lack of comparable adverse event data reported in the trials.

9. Clinical Claim

The submission described bortezomib as non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety compared to thalidomide.

For PBAC's view, see Recommendations and Reasons

10. Economic Analysis

The submission presented a cost minimisation analysis.

The equi-effective doses (based on dosages recommended in the product information documents) were estimated in the submission as:
- bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11 of the cycle for four 21-day cycles and
- thalidomide 200 mg daily over 28 days per cycle for four cycles.

The PBAC considered that the equi-effective doses should be based on the clinical trial data which provided the evidence of non-inferiority.

It was noted that the thalidomide dose used in the trials (3 months) was not consistent with the doses recommended in the product information (4 months). Hence, basing the cost of thalidomide on the assumption of four thalidomide cycles in the cost minimisation analysis was an over-estimate.

For PBAC's view, see Recommendations and Reasons

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated per year was estimated in the submission to be less than 10,000 in year 5, with estimated net savings to the PBS.

12. Recommendation and Reasons

The PBAC recommended listing of bortezomib, powder for injection 1 mg, on the PBS (Efficient Funding of Chemotherapy) as an Authority Required listing (Public and Private

Hospitals) for the treatment in combination with chemotherapy, of a patient with newly diagnosed symptomatic multiple myeloma who is eligible for high dose chemotherapy and a primary stem cell transplant on a cost-minimisation basis compared with thalidomide. The PBAC considered that the equi-effective doses should be based on the clinical trial data which provided the evidence of non-inferiority. The equi-effective doses were considered to be bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11 for four 21-day cycles (Trial IFM 2005-01) and thalidomide 200 mg daily for three months (Macro 2006).

The PBAC agreed that the appropriate comparator is thalidomide. The PBAC noted that, based on the regimens used in the trials, the submission presented two indirect comparisons (both using VAD (vincristine, doxorubicin, dexamethasone) as a common reference) of bortezomib versus thalidomide, one in combination with dexamethasone alone and the other in combination with doxorubicin and dexamethasone. The PBAC noted that the indirect comparison did not show any statistically significant differences in very good partial response (VGPR) rates for either the VcD (bortezomib, dexamethasone) versus TD (thalidomide, dexamethasone) or VcAD (bortezomib, doxorubicin, dexamethasone) versus TAD (thalidomide, doxorubicin, dexamethasone) comparisons, indirect OR (95%CI): 0.91 (0.36, 2.26) and 1.59 (0.91, 2.78), respectively). However, the PBAC noted that VGPR has been previously accepted as a measure of effectiveness of induction chemotherapy in the setting of stem cell transplants (SCTs) when the submission for thalidomide for newly diagnosed multiple myeloma patients was considered in 2009. From the previous thalidomide submission, the PBAC noted that a post-hoc analysis of eight year survival data conducted as part of the Barlogie trial (Barlogie et al (2008)) demonstrated a possible improvement in overall survival. The overall eight year survival estimates were 56% for the thalidomide group compared with 45% in the control group (p=0.09).

The PBAC noted that the current bortezomib submission did not provide supportive data regarding long term benefit. However, based on the indirect comparison of VGPR and the fact that PBAC has regarded bortezomib as equivalent to thalidomide for other multiple myeloma indications, the PBAC considered that bortezomib is likely to be non-inferior to thalidomide. The PBAC acknowledged it is very difficult to isolate the impact of one drug in an induction regimen given that multiple myeloma is treated with multiple other drugs over a relatively long period.

Lastly, the PBAC considered that there should be one Medicare application form for treatment with bortezomib which would indicate the PBS restriction for which the patient is eligible i.e. transplant eligible, transplant ineligible, transplant ineligible- severe renal failure patients, treatment in the relapsed/refractory setting and retreatment. This would enable data to be collected on the extent of use across the various restrictions.

Recommendation:
BORTEZOMIB, powder for injection 1 mg (solvent required)

Restriction: Note
PBS subsidised bortezomib will not be approved in combination with thalidomide or lenalidomide. A maximum of 4 cycles of treatment with bortezomib will be authorised.

Section 100 Revised Arrangements for the Efficient Funding of Chemotherapy
Authority Required (Public and Private Hospital)

First line treatment of multiple myeloma in a patient who is eligible for a stem cell transplant.

Treatment, in combination with chemotherapy, of a patient with newly diagnosed symptomatic multiple myeloma who is eligible for high dose chemotherapy and a primary stem cell transplant.

Note
Any queries concerning the arrangements to prescribe bortezomib may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Prescribing information (including Authority Application forms) is available on the Medicare Australia website at www.medicareaustralia.gov.au.

Applications for authority to prescribe bortezomib should be forwarded to:

Medicare Australia
Prior Written Approval of Specialised Drugs
Reply Paid 9826
GPO Box 9826
HOBART TAS 7001

Note
Special Pricing Arrangements apply.

Max quantity: 3 mg
Repeats: 15

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

The sponsor has no comments.