

15 December 2010

Proposal to fund bortezomib for patients with multiple myeloma

PHARMAC is seeking feedback on a proposal to fund bortezomib (Velcade) for patients with multiple myeloma through a provisional agreement with Janssen-Cilag Pty Limited.

PHARMAC also clarifies for which indications bortezomib has now been considered by PHARMAC. In accordance with criterion iv of the Cancer Exceptional Circumstances scheme, these indications will generally not be approved for funding under that scheme.

Further details of this proposal, including how to provide feedback and background information, can be found below and on the following pages. All changes would be implemented 1 March 2011 unless otherwise stated.

Feedback sought

PHARMAC welcomes feedback on this proposal. To provide feedback, please submit it in writing by **5 pm Wednesday, 12 January 2011** to:

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Therapeutic Group Manager	Fax: 04 460 4995
PHARMAC	Post PO Box 10 254, Wellington 6143

All feedback received before the closing date will be considered by PHARMAC's Board (or Chief Executive acting under delegated authority) prior to making a decision on this proposal.

Details of the proposal

Funding of bortezomib

- Bortezomib (Velcade) would be listed in Section B and in Part II of Section H of the Pharmaceutical Schedule at the following prices and subsidies (ex-manufacturer, excl. GST):

Presentation	Pack size	Price and subsidy
Inj 1.0 mg	1 vial	\$540.70
Inj 3.5 mg	1 vial	\$1,892.50
Inj 1 mg for ECP	1 mg	\$594.77

- Bortezomib would be listed in the Pharmaceutical Schedule as a Pharmaceutical Cancer Treatment (PCT), meaning that only DHB hospitals can claim for its use.
- The 3.5 mg vial and 1.0 mg for ECP presentations would be listed from 1 March 2011, whereas the 1.0 mg vial would be listed from 1 June 2011.

- Please note the proposed price and subsidy for the 1 mg for ECP presentation assumes 10% wastage based on the expected average dose, dosing schedule and number of patients treated. This price and subsidy may be amended by PHARMAC following review of actual data.
- Bortezomib (Velcade) would be listed in Section B of the Pharmaceutical Schedule subject to Special Authority criteria as follows:

SAXXX Special Authority for Subsidy
 Bortezomib – PCT only – Specialist
 Special Authority for Subsidy

Initial application – multiple myeloma - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 8 months for applications meeting the following criteria:

All of the following:

1. The patient has histological diagnosis of multiple myeloma; and
2. The patient has progressive disease as defined by IMGW 2006 criteria; and
3. The patient has received no more than one prior chemotherapy; and
4. The patient has not had prior publicly funded treatment with bortezomib; and
5. Maximum of 4 treatment cycles.

Renewal – multiple myeloma - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 8 months for applications meeting the following criteria:

Both:

1. The patient's disease obtained at least a partial response from treatment with bortezomib at the completion of cycle 4; and
2. Maximum of 4 further treatment cycles.

Note: Responding patients should receive no more than 2 additional cycles of treatment beyond the cycle at which confirmed complete response was first achieved.

Initial application - t(4;14) multiple myeloma - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 8 months for applications meeting the following criteria:

All of the following:

1. The patient has newly diagnosed multiple myeloma with t (4;14) cytogenetics; and
2. Haematopoietic stem cell transplantation is planned; and
3. The patient is multiple myeloma treatment naive; and
4. Bortezomib to be administered in combination with dexamethasone, followed by high-dose melphalan, prior to stem cell transplantation*; and
5. Maximum of 4 treatment cycles.

Note: Indications marked with * are Unapproved Indications

- DHB clinicians would be able to apply directly to PHARMAC for Special Authority approvals for existing patients (i.e. those being treated with bortezomib on 28 February 2011); clinicians would need to demonstrate that the patient would have met the proposed Special Authority criteria for initial applications prior to starting treatment with bortezomib and, if the patient had been on bortezomib for longer than 4 cycles at 28 February 2011, that the patient would also meet the proposed Special Authority renewal criteria.
- A confidential expenditure cap would apply to all subsidies for Velcade, with the exception of Exceptional Circumstances claims.

DHB Hospital resource implications

- It is anticipated that this proposal would result in approximately 200 MM patients accessing funded bortezomib annually.
- Each patient would have an average of 26 doses of bortezomib, with each dose being administered by bolus injection in a DHB hospital outpatient department.
- As well as the service required to administer bortezomib (see bortezomib background and dosing below for more details) and monitor disease response, there would also be increased resource implications for DHB hospitals for blood monitoring. In patients with relapsed MM receiving bortezomib, it is recommended they receive a full blood count test on days 1 and 11 of each treatment cycle as bortezomib is associated with thrombocytopenia.
- PHARMAC seeks specific feedback from DHBs on the resource implications of this proposal to fund bortezomib.

Consideration of Cancer Exceptional Circumstances applications for bortezomib

- The funding of bortezomib has now been considered by PHARMAC for:
 - Multiple Myeloma; and
 - AL Amyloidosis.
- Because funding for these diseases has been considered by PHARMAC, the funding of bortezomib for patients with these diseases will not generally meet the current Cancer Exceptional Circumstances criterion iv. As a result, unless the individual is distinct from others with these diseases such applications will generally be declined.

Background

Multiple myeloma (MM) is a cancer of plasma cells, a type of white blood cell normally responsible for the production of antibodies. Collections of abnormal cells accumulate in bones, where they cause bone lesions, and in the bone marrow where they interfere with the production of normal blood cells.

The annual incidence of MM in New Zealand has increased by approximately 150%–200% over the last 40 years (Cancer in New Zealand: Trends and Projects (2002)¹); some of this increase maybe due to better diagnostic methods and classification systems. Forecasts indicate approximately 300 new cases of MM in 2009, increasing to approximately 320 in 2014.

Multiple Myeloma predominantly affects older individuals, with a median age at diagnosis of 65–68 years. The risk of MM is approximately 40% higher in males than females, and Maori have a substantially higher risk of being diagnosed with, and dying from, MM than non-Maori.

Initial treatment of patients with MM is dependent on the age of the patient and eligibility for peripheral blood stem cell or bone marrow transplant. In New Zealand, currently, newly diagnosed patients with MM aged under 65 years and otherwise healthy patients with MM

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[http://www.moh.govt.nz/moh.nsf/82f4780aa066f8d7cc2570bb006b5d4d/8e1d731682cab3d9cc256c7e00764a23/\\$FILE/25-myeloma.pdf](http://www.moh.govt.nz/moh.nsf/82f4780aa066f8d7cc2570bb006b5d4d/8e1d731682cab3d9cc256c7e00764a23/$FILE/25-myeloma.pdf)

aged over 65 years would typically receive induction chemotherapy (e.g. vincristine, adriamycin and dexamethasone) followed by a stem cell transplant. Transplant-ineligible patients generally receive prednisone and melphalan. Following relapse patients would receive thalidomide (second line) usually in conjunction with steroids (often dexamethasone) and sometimes with oral chemotherapy (e.g. cyclophosphamide). Patients who subsequently relapse may receive a range of third line salvage regimens. Third-line options include any potential second-line option (or combination thereof) or high-dose dexamethasone.

Multiple Myeloma treatment algorithms are rapidly developing and PHARMAC has recently considered multiple funding applications for new treatments for MM (bortezomib and lenalidomide) and widening of access to existing treatment (thalidomide). This proposal, to fund bortezomib, does not preclude the future funding of lenalidomide, or widening of access to thalidomide, for MM patients.

There is a high unmet medical need for effective and curative MM treatments. Current treatments including bortezomib, are not curative, therefore, treatment goals are aimed at delaying disease progression, and extending and/or improving quality of life.

Bortezomib background and dosing

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. Bortezomib is indicated in New Zealand for:

- the treatment of patients who have received at least one prior therapy and who have progressive disease (relapsed/refractory MM); and
- the treatment of patients with previously untreated MM in combination with melphalan and prednisone in patients who are not suitable for high dose chemotherapy.

The funding of bortezomib is expected to result in a delay to disease progression in patients with MM compared with the most commonly used currently funded treatments.

Bortezomib is administered in hospital as a 3 to 5 second bolus intravenous (IV) injection. The recommended dose of bortezomib in relapsed/refractory MM patients is 1.3mg/m² twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). This 3-week period is considered a treatment cycle. It is estimated that in this setting on average patients would receive 6.5 cycles of treatment (26 doses).

In patients with previously untreated multiple myeloma who are not suitable for high dose chemotherapy, bortezomib is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles. In cycles 1 to 4, bortezomib is administered twice weekly and in cycles 5 to 9, bortezomib is administered weekly resulting in a total of 52 doses.

Bortezomib is not indicated for the first line treatment of patients with MM in combination with dexamethasone, followed by high-dose melphalan prior to stem cell transplantation. As such, the proposal for such funding of t4:14 MM patients is an off-label indication and therefore clinicians would need to comply with Section 25 of the Medicines Act to prescribe it in this setting. Section 25 prescribing is not an unusual situation for cancer treatments; it requires that clinicians obtain informed consent from their patients for 'off-indication' use. In this setting, bortezomib would be administered at a dose of 1.3mg/m² twice weekly for two weeks (days 1, 4, 8, and 11) in combination with dexamethasone for 4 cycles, followed by high-dose melphalan prior to stem cell transplantation (a total of 16 doses).

PTAC consideration

The funding of bortezomib has been considered by the Pharmacology and Therapeutics Advisory Committee (PTAC) and its Cancer Treatments Subcommittee (CaTSoP) on multiple occasions for various indications (including first, second and third-line treatment in various patient groups with multiple myeloma). In summary, PTAC has recommended that bortezomib be listed as a second-line agent for patients with relapsed/refractory MM with low priority and as a first-line treatment in MM in patients unable to be treated with high dose chemotherapy and transplant with medium priority.

A summary of the applications reviewed and recommendations made are provided below (full copies of PTAC and CaTSoP minutes are available at www.pharmac.govt.nz/PTAC/PTACminutes and www.pharmac.govt.nz/PTAC/PTACSCMinutes):

May 2006 – PTAC considered an application from the supplier for bortezomib in patients with MM who have received at least two prior therapies (3rd line therapy). PTAC recommended that a PHARMAC cost-utility analysis be performed and the application be referred to the Cancer Treatments Subcommittee (CaTSoP) for further advice regarding targeting criteria and the acceptability of the side effect profile of bortezomib as third-line treatment for patients with multiple myeloma.

October 2006 – CaTSoP considered an application from the supplier for bortezomib in patients with MM who have received at least two prior therapies (3rd line therapy). CaTSoP recommended that, given its side effect profile and uncertainty surrounding long-term benefit, bortezomib should not be listed on the Pharmaceutical Schedule. CaTSoP considered that there may be a place for bortezomib in combination with HDD or other drugs in earlier treatment of multiple myeloma; however, more data in this area are needed.

November 2008 – PTAC considered an application from the supplier for bortezomib for the second-line treatment of patients with multiple myeloma. PTAC requested that it reconsider this application following review by the Cancer Treatments Subcommittee and a PHARMAC cost-utility analysis.

February 2009 - CaTSoP considered an application from the supplier for bortezomib for the second-line treatment of patients with MM and recommended it be funded with a medium-to-high priority. CaTSoP recommended that initial applications be valid for three months, with the requirement for a partial response to be demonstrated after four cycles for further approval to be granted.

August 2009 – PTAC considered a cost utility analysis prepared by PHARMAC regarding the funding of bortezomib for the treatment of patients with relapsed/refractory multiple myeloma. PTAC also considered information from clinicians regarding the use of bortezomib in MM patients with renal impairment. PTAC recommended that bortezomib be listed as a second-line agent for patients with relapsed/refractory MM with a low priority. PTAC recommended that initial applications be valid for three months, with the requirement for a partial response to be demonstrated after four cycles for further approval to be granted. The Committee gave this recommendation a low priority. PTAC also considered that although renal impairment was relatively common in MM patients and although there was some evidence of benefit of bortezomib for these patients, the evidence was weak comprising small non randomised studies (largely case series).

November 2009 – CaTSoP reviewed a paper prepared by PHARMAC staff regarding applications for funding of cancer treatments which had been considered under the Cancer Exceptional Circumstances Scheme (CaEC). CaTSoP specifically reviewed a number of treatments that PHARMAC staff had identified as being the subject of a number of Cancer EC applications including bortezomib for amyloidosis and bortezomib for IgA/IgG/t(4:14 translocation) MM / Plasma Cell Leukaemia.

CaTSoP noted that bortezomib is currently being funded under the CaEC scheme for a small population of patients with amyloidosis or various genotype-specified plasma cell disorders. CaTSoP considered that specifying patient groups, and even individuals, at a molecular level (ie by genotype) is likely to be seen more in future funding applications as more therapies are being targeted in this way. CaTSoP considered that dealing with such applications under the Cancer EC scheme was problematic since all people are, in some way, unique; however, this does not mean that all cases are exceptional.

CaTSoP considered that it was appropriate for PHARMAC to consider funding applications for bortezomib in patients with amyloidosis or various genotype-specified plasma cell disorders and amyloidosis and recommended that PHARMAC staff request funding applications from the Haematology Society.

November 2009 – CaTSoP considered the cost utility analysis prepared by PHARMAC regarding the funding of bortezomib for the treatment of patients with relapsed/refractory multiple myeloma. CaTSoP noted that the CUA compared bortezomib plus dexamethasone with thalidomide plus dexamethasone. CaTSoP noted that since there have been no clinical trials directly comparing bortezomib with thalidomide, the CUA necessarily included a number of assumptions regarding the relative efficacy of the two treatments. CaTSoP considered that the PHARMAC CUA model was legitimate. CaTSoP considered that given that MM is incurable, most patients would require second-line treatment; therefore, it would be expected that uptake would be rapid such that by year 4, up to 250 patients would access second line treatment and that, if funded, bortezomib would likely replace thalidomide as the preferred second-line treatment.

February 2010 – PTAC considered an application from the supplier for the funding of bortezomib, in combination with melphalan and prednisone, as first-line treatment for patients with MM who are unable to be treated with high dose chemotherapy. PTAC recommended that bortezomib be funded for these patients with a low priority. PTAC further recommended that the application be reviewed by CaTSoP for advice regarding appropriate Special Authority criteria, including initial number of treatment cycles, and cost-utility analysis inputs.

April 2010 – CaTSoP considered an application from the supplier for the funding of bortezomib, in combination with melphalan and prednisone, as first-line treatment for patients with MM who are unable to be treated with high dose chemotherapy. CaTSoP noted that the application was for the same population that it had recently recommended for funding with thalidomide i.e. stem cell transplant ineligible patients and that it gave this thalidomide recommendation a high priority. CaTSoP considered that effective, curative, treatment of MM was an area of high unmet need. Members noted that with current treatments, including bortezomib, MM was not curable and, therefore, treatment goals were principally to extend and/or improve quality of life. CaTSoP recommended that bortezomib should be listed in the Pharmaceutical Schedule subject to Special Authority criteria for patients with newly diagnosed MM not eligible for high dose chemotherapy and transplant, CaTSoP gave this recommendation a medium priority. This recommendation was accepted by PTAC at its August 2010 meeting.

November 2010 – PTAC considered an application from [a clinician] for the funding of bortezomib on for the treatment of patients with systemic AL amyloidosis. PTAC recommended that the application be deferred until Phase III trial data is available.

November 2010 – CaTSoP considered applications from [clinicians] for the funding of bortezomib for the treatment of patients with systemic AL amyloidosis and patients with t(4:14) multiple myeloma. CaTSoP also considered a paper from PHARMAC staff regarding Cancer Exceptional Circumstances applications for bortezomib in patients with MM for use as a bridge to stem cell transplantation. Minutes are not yet available from this meeting.