pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Bortezomib (Velcade) **Funding Request:** For the treatment of patients with multiple myeloma pre-autologous stem cell transplantation in combination therapy and post-autologous stem cell transplantation as monotherapy	
Submitted By: Cancer Care Ontario Hematology Disease Site Group	**Manufactured By:** Janssen Inc.
NOC Date: N/A	**Submission Date:** October 29, 2012
Initial Recommendation: March 7, 2013	**Final Recommendation:** March 25, 2013

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) recommends funding bortezomib (Velcade) as a component of induction therapy pre-autologous stem cell transplantation (ASCT) for newly diagnosed patients with multiple myeloma who are eligible for ASCT. The Committee made this recommendation because it considered that there is a net clinical benefit of bortezomib in this setting and it could be cost-effective compared with current standard of care. pERC does not recommend funding bortezomib (Velcade) post-ASCT as a consolidation or maintenance therapy for patients with multiple myeloma. The Committee made this recommendation because, based on the current evidence, it was unclear that there is a net clinical benefit of bortezomib and because it is not cost-effective compared with standard of care in the post-ASCT setting.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified

SUMMARY OF pERC DELIBERATIONS

pERC discussed that, for patients with multiple myeloma who are eligible for autologous stem cell transplantation (ASCT), a number of regimens may be used for induction therapy pre-ASCT including high dose dexamethasone, vincristine/doxorubicin/ dexamethasone (VAD) and thalidomide/dexamethasone (TD). pERC noted that, of these, high dose dexamethasone is most commonly used in current practice. pERC also discussed treatments available for patients post-ASCT including lenalidomide, thalidomide or observation only. It was noted that, of these, observation has been considered the standard of care after ASCT in Canada. None of the currently available treatments are curative and there is a need for additional therapies that improve survival and quality of life.

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

The pCODR systematic review included seven randomized controlled trials investigating the use of bortezomib either pre-ASCT or post-ASCT, in patients with multiple myeloma who were candidates for ASCT. Of these, three studies provided relevant and useful information: the GIMEMA study (Cavo, 2010), the HOVON-65/GMMG-HD4 study (Sonneveld, 2012) and the IFM 2005-01 (Harousseau, 2010) study. All three studies included an induction phase pre-ASCT. pERC noted that there was a statistically significant and clinically meaningful improvement in progression-free survival in the bortezomib group compared with the control group in the GIMEMA study and the HOVON-65/GMMG-HD4 study. In addition, pERC discussed that this clinical effect was observed across different bortezomib-containing regimens and agreed with the pCODR Clinical Guidance Panel that the effect of bortezomib appears to be generalizable across different front-line therapies. Therefore, pERC considered that there was an overall net clinical benefit to the use of bortezomib as a component of induction therapy pre-ASCT.

pERC noted that while one of the studies provided information on the use of bortezomib pre-ASCT (IFM 2005-01) and two of the studies provided information on the use of bortezomib in both the pre-ASCT and post-ASCT setting (GIMEMA and HOVON-65/GMMG-HD4), none of the studies was able to isolate the incremental effects of using bortezomib post-ASCT. Therefore, because of the design of these studies, pERC could not reach a clear conclusion about the incremental benefit of using bortezomib post-ASCT as either consolidation or maintenance therapy.

pERC discussed the toxicity profile of bortezomib based on adverse event data from the three trials. It was noted that peripheral neuropathy was greater in the groups receiving bortezomib compared with the control groups. However, pERC noted that this toxicity appeared manageable, which was also consistent with patient advocacy group input on the toxicity of bortezomib.

pERC deliberated upon patient advocacy group input provided on bortezomib. It was noted that the large number of patients who had direct experience with bortezomib was very useful in determining if bortezomib aligned with patient values. Although improvements in quality of life were important to patients, there were no data from the clinical trials on quality of life. Patient input also indicated that peripheral neuropathy associated with treatments was a concern but that the majority were willing to tolerate this and other side effects if there was an improvement in efficacy over currently available treatments. Therefore, pERC considered that bortezomib aligned with patient values.

pERC deliberated upon the cost-effectiveness of bortezomib in both the pre-ASCT setting and the post-ASCT setting. It was noted that the economic analyses were limited by the lack of patient-level clinical trial data, which decreased pERC's confidence in the estimates. However, in this case, no major flaws were identified in the models and obtaining patient-level data for these analyses was likely not feasible. Therefore, pERC agreed with the pCODR Economic Guidance Panel's assessment and used the estimates from these models to inform their deliberations on cost-effectiveness. In the pre-ASCT setting, bortezomib was compared with VAD. pERC noted that there was some variability with respect to the comparator that would be used in Canadian clinical practice but that bortezomib could be cost-effective, depending on the comparator and assuming that issues related to drug wastage were appropriately addressed.

pERC noted that the pCODR Economic Guidance Panel's estimates of the use of bortezomib in both pre-ASCT and post-ASCT settings when compared with standard induction therapy and observation-only maintenance therapy was not cost-effective and that these estimates were heavily influenced by drug wastage, due to the dosing schedule when bortezomib is used as a maintenance therapy.

pERC considered the feasibility of implementing a recommendation for bortezomib and noted that there is a small proportion of patients with multiple myeloma eligible for ASCT and that the treatment protocol is for a short and well-defined period of time, which would facilitate implementation. However, pERC noted that potential drug wastage associated with the use of bortezomib vials could have a large budget impact, depending on the patient volumes being seen at individual treatment centers.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient advocacy group (Myeloma Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- one patient advocacy group (Myeloma Canada)
- the submitter (Cancer Care Ontario Hematology Disease Site Group)
- the manufacturer (Janssen Inc.)

The pERC initial recommendation was to recommend funding bortezomib (Velcade) as a component of induction therapy pre-autologous stem cell transplantation (ASCT) for newly diagnosed patients with multiple myeloma who are eligible for ASCT. pERC did not recommend funding bortezomib (Velcade) post-ASCT as a consolidation or maintenance therapy for patients with multiple because it was unclear that there was a net clinical benefit and bortezomib was not cost-effective compared with standard of care in the post-ASCT setting.

Feedback on the pERC Initial Recommendation indicated that the patient advocacy group and pCODR's Provincial Advisory Group agreed with the initial recommendation while the submitter and manufacturer agreed in part. The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the efficacy and safety of bortezomib (Velcade) as monotherapy or combination therapy prior to autologous stem cell transplantation (ASCT) (induction), immediately post-ASCT (consolidation or maintenance) or both pre-ASCT (induction) and post-ASCT (consolidation or maintenance) on patient outcomes compared to appropriate comparators, in patients with newly diagnosed multiple myeloma who are candidates for ASCT.

Studies included:

The pCODR systematic review identified seven randomized controlled trials investigating the use of bortezomib either pre- or post-ASCT, in patients with multiple myeloma who were candidates for ASCT. Four of the seven included studies provided only a limited amount of useful information related to the questions of interest in the review and so were not the focus of the review. Three studies were the basis

of the systematic review presented, GIMEMA (Cavo, 2010), HOVON-65/GMMG-HD4 (Sonneveld, 2012) and IFM 2005-01 (Harousseau, 2010).

- GIMEMA was an open-label randomized controlled trial that compared the efficacy and safety of thalidomide/dexamethasone (TD) in the induction phase and the consolidation phase (n=238) to bortezomib/thalidomide/dexamethasone (BTD) in the induction phase and the consolidation phase (n=236).
- HOVON-65/GMMG-HD4 was an open-label, randomized phase III trial that compared the efficacy and safety of bortezomib, doxorubicin, and dexamethasone (BAD) followed by ASCT followed by bortezomib maintenance (n=413) to vincristine, doxorubicin, dexamethasone (VAD) followed by ASCT followed by thalidomide maintenance (n=414).
- IFM 2005-01 was an open-label randomized phase III trial that compared the efficacy and safety of one of four induction treatment arms: bortezomib/dexamethasone (BD) vs. BD plus dexamethasone, cyclophosphamide, etoposide, cisplatinum (DCEP) vs. vincristine, doxorubicin, dexamethasone (VAD) vs. VAD plus DCEP.

All three of these studies included an induction phase pre-ASCT. However, pERC noted that while one of the studies provided information on the use of bortezomib pre-ASCT (IFM 2005-01) and two of the studies provided information on the use of bortezomib in both the pre-ASCT and post-ASCT setting (GIMEMA and HOVON-65/GMMG-HD4), none of the studies was able to isolate the incremental effect of using bortezomib post-ASCT.

Patient populations: newly diagnosed patients eligible for ASCT

The three studies that were the focus of the systematic review all included newly diagnosed patients with multiple myeloma who were eligible for ASCT.

Key efficacy results: meaningful improvement in progression-free survival pre-ASCT

Key outcomes deliberated on by pERC included overall survival, progression-free survival and response rate. The primary outcome in the HOVON-65/GMMG-HD4 study was progression-free survival and in the other two studies was response rate.

pERC noted that the primary outcome of response rate was achieved in the GIMEMA and IFM 2005-01 studies. However, pERC deliberations emphasized the more relevant outcomes of overall survival and progression-free survival. pERC noted that none of the studies were designed to detect a difference in overall survival. A statistically significant difference in overall survival was reported in the HOVON-65/GMMG-HD4 study based on an adjusted multi-variate analysis (HR=0.77, 95% CI 0.60 to 1.00, P=0.049). However, considering the complete body of evidence for bortezomib, pERC agreed with the pCODR Clinical Guidance Panel that this did not demonstrate a clear-cut overall survival advantage associated with bortezomib.

pERC noted that a statistically and clinically significant improvement in progression-free survival was observed with the addition of bortezomib in the GIMEMA study (PFS estimates of 68% vs. 56% at three years; HR=0.63, 95% confidence interval 0.45-0.88, P=0.0061) and the HOVON-65/GMMG-HD4 study (median 35 vs. 28 months; HR=0.75, 95% CI 0.62-0.90, P=0.002). The IFM 2005-01 showed a trend towards improved progression-free survival of similar magnitude relative to the other trials. pERC considered that overall these results demonstrated a statistically significant and clinically meaningful improvement in progression-free survival in the bortezomib group compared with the control group. In addition, pERC discussed that this effect was observed across different bortezomib-containing regimens and agreed with the pCODR Clinical Guidance Panel that the effect of bortezomib appears to be generalizable across different front-line therapies. Therefore, pERC considered that there was an overall net clinical benefit to the use of bortezomib as a component of induction therapy pre-ASCT.

Quality of life: choice in therapy, reduced toxicity with improved efficacy and convenience

None of the three studies that were the focus of the systematic review provided data on quality of life. pERC noted that based on patient advocacy group input, this was an outcome important to patients and that quality of life data from the trials would have been important to their deliberations. Patients are seeking a therapy that will help to improve their quality of life and enable them to partake in normal daily activities. However, pERC was unable to determine the impact of bortezomib on quality of life. pERC noted that trial investigators should collect and report high quality data for quality of life outcomes routinely in clinical trials.

Safety: increased peripheral neuropathy but toxicity profile manageable
Based on the three studies that were the focus of the systematic review, adverse events that were more frequently reported in the bortezomib group compared with the control group included neutropenia, anemia, thrombocytopenia and peripheral neuropathy. pERC discussed the toxicity profile of bortezomib however, pERC noted that toxicities appeared manageable. This was also consistent with patient advocacy group input on the toxicity of bortezomib, which indicated that patients were willing to tolerate the side effects if there was improved efficacy.

Limitations: studies not designed to assess incremental effect of bortezomib post-ASCT
pERC discussed that the evidence available in the pCODR systematic review was limited in its ability to determine the utility of providing bortezomib post-ASCT as consolidation or maintenance therapy to improve outcomes. pERC noted that while one of the studies provided information on the use of bortezomib pre-ASCT (IFM 2005-01) and two of the studies provided information on the use of bortezomib in both the pre-ASCT and post-ASCT setting (GIMEMA and HOVON-65/GMMG-HD4), none of the studies was able to isolate the incremental effect of using bortezomib post-ASCT. Therefore, because of the design of these studies, pERC could not reach a clear conclusion about the incremental benefit of using bortezomib post-ASCT as either consolidation or maintenance therapy.

Need: treatments that improve survival, remission duration and quality of life
Multiple myeloma is a cancer of the bone marrow with an incidence of approximately 2400 new cases per year in Canada and is incurable in the majority of cases. ASCT is frequently performed as part of front line myeloma therapy for eligible candidates, however, it is not curative and improving patient survival, remission duration and quality of life are important goals. Therefore, pERC considered that the clinically meaningful improvement in progression-free survival that is observed with bortezomib pre-ASCT would contribute to addressing the needs of patients seeking new treatments.

PATIENT-BASED VALUES

Values of patients with multiple myeloma: improving quality of life
From a patient perspective, quality of life while living with multiple myeloma is an important consideration. Pain, fatigue, infections, kidney problems and mobility were all aspects of myeloma that patients identified as impacting their quality of life. pERC discussed this patient input and noted that none of the three studies that were the focus of the systematic review provided data on quality of life. Therefore, pERC had difficulty in determining the impact of bortezomib on quality of life. pERC noted that trial investigators should routinely collect and report high quality data on quality of life outcomes in clinical trials.

Patient values on treatment: choice of treatments and willing to tolerate side effects
pERC deliberated upon patient advocacy group input provided on bortezomib. pERC noted that having patient input, which was based on objective assessments through a structured survey and which provided detailed descriptions of actual patient experiences with bortezomib, was useful in determining whether there was alignment with patient values. Patients indicated that drug therapies for multiple myeloma with less toxic side effect profiles that offer an improvement in efficacy and convenience over currently available therapies are important aspects when consideration is given to treatment. Patient input also indicated that peripheral neuropathy associated with treatments was a concern but that patients were willing to tolerate the side effects if there was an improvement in efficacy over currently available treatments. It was also noted that patients are seeking a choice of treatments and flexibility to manage their multiple myeloma. Therefore, pERC determined that bortezomib aligned with patient values.

ECONOMIC EVALUATION

Economic model submitted: cost effectiveness pre-ASCT and post-ASCT
The pCODR Economic Guidance Panel assessed a cost utility analysis in the pre-ASCT setting comparing bortezomib to vincristine, doxorubicin and dexamethasone (VAD).

The pCODR Economic Guidance Panel also assessed a cost utility analysis in both the pre-ASCT and post-ASCT setting. This analysis compared standard induction therapy and thalidomide maintenance therapy

with bortezomib combination induction therapy and bortezomib maintenance therapy. Re-analyses conducted by the pCODR Economic Guidance Panel explored the use of observation-only in the maintenance setting, which is closer to the Canadian clinical context.

Basis of the economic model: clinical and economic inputs

Costs included drug treatment costs, chemotherapy administration costs, post-progression costs and costs associated with adverse events. The submitter did not assume any costs due to drug wastage.

Key clinical effects included progression-free survival and overall survival data from the IFM-2005-01 study for the analysis of bortezomib in the pre-ASCT induction setting, based on four cycles of induction therapy. Clinical data from the HOVON-65/GMMG study was used for the analysis of bortezomib in both the pre-ASCT and post-ASCT setting based on three cycles of induction therapy and two years of maintenance treatment.

Drug costs: costs will increase if wastage occurs

Bortezomib costs $1,869.89 per 3.5 mg vial. When used as induction therapy, at the recommended dose of 1.3mg/m^2 on days 1, 4, 8 and 11 of three-week cycles in combination with dexamethasone and assuming a body surface area of 1.75 m^2, the cost of bortezomib per 28-day course is $7,292.57. Bortezomib was administered for three cycles in the GIMEMA and HOVON-65/GMMG-HD4 studies and four cycles in the IFM 2005-01 study.

When used as a maintenance therapy at the recommended dose of 1.3mg/m^2 every two weeks and assuming body surface area of 1.75 m^2, the cost of bortezomib per 28-day course is $2633.43. Bortezomib was administered as a maintenance therapy for two years in the HOVON-65/GMMG-HD4 study.

pERC discussed that based on the dosing schedule of bortezomib, the available vial size and the recommended stability of bortezomib, there could be considerable drug wastage associated with the use of bortezomib, which would have negative consequences for its cost-effectiveness and budget impact. pERC further noted that when bortezomib is used as a maintenance therapy, the dosing schedule would be even less frequent and greater drug wastage would likely occur.

Cost-effectiveness estimates: vary based on treatment regimens and wastage

pERC deliberated upon the cost-effectiveness of bortezomib in the pre-ASCT setting and the post-ASCT setting. It was noted that the economic analyses were limited by the lack of patient-level clinical trial data, which decreased pERC's confidence in the estimates. However, in this case, no major flaws were identified in the models and obtaining patient-level data for these analyses was likely not feasible. Therefore, pERC agreed with the pCODR Economic Guidance Panel's assessment and used the estimates from these models to inform their deliberations on cost-effectiveness.

In the pre-ASCT setting, bortezomib was compared with VAD. pERC noted that there was some variability with respect to the comparator that would be used in Canadian clinical practice but that bortezomib could be cost-effective, depending on the comparator and assuming that issues related to drug wastage were appropriately addressed. pERC accepted the pCODR Economic Guidance Panel's assessment that the best estimate of the incremental cost-effectiveness ratio when compared with VAD was approximately $101,761 per QALY without wastage and $150,856 per QALY if wastage occurs.

pERC discussed that the pCODR Economic Guidance Panel's estimates of the use of bortezomib in both pre-ASCT and post-ASCT settings when compared with standard induction therapy and observation-only maintenance therapy was not cost-effective. The pCODR Economic Guidance Panel's assessment that the best estimate of the incremental cost-effectiveness ratio when compared with standard induction therapy and observation-only maintenance therapy ranged from $130,874 per QALY and $271,642 per QALY. pERC further noted that when bortezomib is used as a maintenance therapy, these estimates are heavily influenced by drug wastage since bortezomib is only administered once every two weeks.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: drug wastage and increased chemotherapy chair time

pERC discussed the feasibility of implementing a funding recommendation for bortezomib and discussed potential barriers to implementation. pERC noted that there is a small proportion of patients with multiple myeloma who are eligible for ASCT and that the treatment protocol is for a short and well-defined period of time (i.e. three or four three-week treatment cycles), which would facilitate implementation. However, pERC noted that potential drug wastage associated with the use of bortezomib vials could have a large budget impact. pERC also discussed input from the pCODR Provincial Advisory Group (PAG) noting that in many jurisdictions extended stability of bortezomib is not recommended but that because bortezomib is also used for other indications, there may be limited wastage of the drug. These issues are jurisdictional and treatment site specific.

DRUG AND CONDITION INFORMATION

Drug Information	• Proteosome inhibitor • 3.5mg per vial • For induction pre-ASCT, 1.3 mg/m^2 intravenously or subcutaneously days 1, 4, 8, and 11 of 3-week cycles when used with dexamethasone or 1.5 mg/m^2 weekly when used with cyclophosphamide and dexamethasone. • For maintenance post-ASCT, 1.3 mg/m^2 intravenously or subcutaneously every two weeks
Cancer Treated	• Patients with multiple myeloma who are candidates for autologous stem cell transplantation (ASCT).
Burden of Illness	• Multiple myeloma is a cancer of the bone marrow with an incidence of approximately 2400 new cases per year in Canada. • Myeloma increases in incidence with age (median age 70 years), and is present in slight excess in males relative to females. • Myeloma is incurable in the vast majority of cases, with 1400 deaths from the disease expected in Canada in 2012.
Current Standard Treatment	• For eligible patients, high dose melphalan and autologous stem cell transplant as part of the initial treatment • As induction therapy, high dose dexamethasone in combination with other therapies, e.g. vincristine/doxorubicin/ dexamethasone (VAD) and thalidomide/dexamethasone • Standard of care for maintenance therapy is observation only. Thalidomide and lenalidomide may also be considered.
Limitations of Current Therapy	• Allogeneic stem cell transplantation can achieve long term disease control in some patients but is associated with a high treatment related morbidity and mortality and, therefore, is infrequently used in current practice. • Multiple myeloma often relapses repeatedly following courses of effective therapy, and eventually patients succumb to progressive disease and its complications. Resistance to treatment and the cumulative adverse effects of both disease and treatment have adverse effects on patient quality of life.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist;
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Lister, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Jo Nanson and Dr. Bill Evans who were not present for the meeting

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review bortezomib (Velcade) for multiple myeloma, through their declarations, two members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, but none of these members were excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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