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
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Bendamustine hydrochloride (Treanda) **Submitter's Funding Request:** For the treatment of patients with chronic lymphocytic leukemia (first line and relapsed/refractory) for whom fludarabine based therapy is not appropriate	
Submitted By: Lundbeck Canada Inc.	**Manufactured By:** Lundbeck Canada Inc.
NOC Date: August 24, 2012	**Submission Date:** April 24, 2012
Initial Recommendation: October 4, 2012	**Final Recommendation:** November 29, 2012

pERC RECOMMENDATION	In the relapsed/refractory setting, the pCODR Expert Review Committee (pERC) does not recommend funding bendamustine (Treanda) for the treatment of patients with chronic lymphocytic leukemia. pERC made this recommendation because the Committee was not confident of the net clinical benefit of bendamustine for relapsed/refractory disease. This was due to the limited information available from a small unpublished randomized controlled trial, which pERC considered to be inadequate to assess whether a benefit relative to alternative treatments exists. In the first-line setting, pERC acknowledged that based on the current evidence available, bendamustine appears to have a net clinical benefit and align with patient values. However, pERC lacked confidence in the information on cost-effectiveness, and a full deliberation on bendamustine in the first-line setting could not be completed in accordance with the pERC Deliberative Framework.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Deferral of Recommendation in First-Line Setting Until Appropriate Economic Evaluation Provided** pERC deferred making a recommendation on funding bendamustine in the first-line setting for patients with Binet Stage B and Stage C chronic lymphocytic leukemia. pERC noted the economic model submitted for the first-line setting had fundamental flaws and lacked face validity, despite a request from pCODR to address these issues during the review. pERC requested that an economic evaluation of bendamustine with appropriate modeling of survival benefit be provided so that it can determine cost-effectiveness, a key component of the pERC Deliberative Framework. An adequate economic model is requested from the Submitter within six months of the date on which the pERC Initial Recommendation was posted.

© 2012 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

SUMMARY OF pERC DELIBERATIONS

pERC discussed that in the relapsed/refractory setting of chronic lymphoctyic leukemia (CLL), there are no established treatments and options are limited for patients who are not candidates for a bone marrow transplant. One randomized controlled trial in patients with relapsed or refractory B-cell CLL (Medgenberg 2009) and five single arm studies were included in the pCODR systematic review. The Medgenberg 2009 study compared bendamustine with fludarabine in patients with Binet Stage B or C (Rai Stage II to IV) but is only available in abstract-form with few details and has not been published as a full peer-reviewed journal article. As a result, limited information was available to pERC for its deliberations on bendamustine in relapsed/refractory CLL.

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

pERC primarily deliberated upon the results of the Medgenberg 2009 study. It was noted that this was a relatively small study (N=96) and that there was insufficient information available to assess the quality of this randomized controlled trial. Although Medgenberg 2009 reported results on progression-free survival and response rate, pERC considered that the level of detail provided on the clinical trial design and results was not adequate to assess the effectiveness of bendamustine relative to treatments already being used in this patient population. pERC also considered that the five small non-randomized studies evaluating bendamustine in the relapsed/refractory setting provided inadequate evidence of a clinical benefit. The safety of bendamustine in patients with relapsed/refractory CLL was discussed but minimal safety data were reported from the Medgenberg 2009 study, and pERC did not consider the reported results sufficient for assessing the safety of bendamustine in these patients. pERC discussed that there is a need for new treatments in patients with relapsed or refractory CLL, given that CLL is a common leukemia and has a long natural history and that the burden of illness may be substantial in a prevalent population with limited treatment options. However, because of the limited information available from the Medgenberg 2009 study, pERC could not be certain that there is a net clinical benefit relative to other available treatments.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the manufacturer and a patient advocacy group suggesting that single-arm studies evaluating bendamustine in the relapse/refractory setting should have been deliberated upon in more depth. pERC considered these studies but, similar to the pCODR Clinical Guidance Panel, did not consider that they were sufficient to support decision-making regarding net clinical benefit in this context. pERC also discussed that when assessing the net clinical benefit, it is important to have comparative information to assess effectiveness relative to other treatments, and this information was not available in the single-arm studies evaluating bendamustine.

pERC considered patient values and noted that there is little data available to determine if bendamustine aligns with the patient values of inducing remission, decreasing fatigue, and improving quality of life. However, patient advocacy group input indicated a need for treatments in all stages of CLL and a desire for a choice of treatment options. pERC considered that bendamustine would align with these latter patient values.

pERC discussed the cost-effectiveness of bendamustine in the relapsed/refractory setting. pERC considered the pCODR Economic Guidance Panel's (EGP) assessment that the economic model submitted by the manufacturer for the relapsed/refractory setting had fundamental flaws and lacked face validity. This decreased the EGP's confidence in the cost-effectiveness estimates produced by the manufacturer's model and prevented the EGP from providing a best estimate of the cost-effectiveness of bendamustine in the relapsed/refractory setting. pERC accepted the EGP's assessment that it was not possible to determine the cost-effectiveness of bendamustine in the relapsed/refractory setting based on the submitted model. Regardless of cost-effectiveness, however, pERC considered that in the absence of a net clinical benefit for bendamustine in this setting, it could not recommend funding bendamustine.

© 2012 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

pERC considered the feasibility of implementing a recommendation for bendamustine in the relapsed/refractory setting. It was noted that drug wastage could be an important issue that may limit feasibility given the short stability of reconstituted bendamustine and increased drug costs that would result from wastage, particularly if 25 mg vials of bendamustine are not available. Upon reconsideration of the pERC Initial Recommendation, the Committee noted feedback from PAG indicating that the short stability of bendamustine will be a key issue influencing drug wastage and that provinces would need to manage this.

pERC also noted that in the relapsed/refractory setting there may be a large prevalent population who would require treatment, which could also have a substantial budget impact.

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 (CLL Patient Advocacy Group (CLL PAG))
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group (CLL Patient Advocacy Group (CLL PAG))
- pCODR's Provincial Advisory Group
- the Submitter (Lundbeck Canada Inc.)

The pERC Initial Recommendation was to defer making a recommendation on bendamustine (Treanda) in patients with chronic lymphocytic leukemia in the first line setting until an appropriate economic model was made available by the manufacturer. In the relapse/refractory setting, the pERC initial recommendation was to not fund bendamustine (Treanda) in patients with chronic lymphocytic leukemia because the committee was not confident of the net clinical benefit of bendamustine.

Feedback on the pERC Initial Recommendation indicated that the manufacturer and patient advocacy group agreed in part with the initial recommendation and pCODR's Provincial Advisory Group agreed with the initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope
The pCODR review evaluated the effect of bendamustine hydrochloride, either as a single agent or in combination with other chemotherapeutic agents on patient outcomes compared to appropriate comparators in the treatment of patients with chronic lymphocytic leukemia (CLL).

Studies included: one abstract of an RCT in relapsed or refractory patients
In the relapsed/refractory setting, the pCODR systematic review included one randomized study, which was only available as an abstract and not as a full journal publication.

The Medgenberg 2009 study was a randomized controlled trial comparing bendamustine to fludarabine in patients with Rai stage II-IV or Binet stage B or C relapsed or refractory B-cell CLL. A total of 96 patients were randomized to receive either bendamustine (100 mg/m2/d on days 1 and 2 every 4 weeks) or fludarabine (25 mg/m2/d on days 1 to 5 every 4 weeks). Patients in both arms continued until best response or a maximum of eight cycles. Patients were aged ≥18 years and had an ECOG performance status between 0 and 3. No information was available on the required sample size, randomization

© 2012 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

methods, masking of allocation, primary or secondary outcomes, or the statistical methods used in the analysis. The limited details provided on the design of the Medgenberg 2009 study prevented pERC from assessing the quality of the study and limited their confidence in the results.

Five small single-arm studies conducted in the relapsed/refractory setting were also included in the pCODR systematic review but pERC considered that they provided inadequate evidence to support a clinical benefit and were not deliberated upon further by the Committee. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the manufacturer and a patient advocacy group suggesting that the single-arm studies should be deliberated upon in more depth. pERC discussed these studies but did not consider that this evidence was sufficient to support decision-making in this context. The Committee noted that the studies did not include a control group, were of varying sizes and that limited information on response rate outcomes was provided. pERC also noted that when assessing the net clinical benefit, it is important to have comparative data to assess the effect of bendamustine relative to other treatments and this information was not available in the single-arm studies.

Key efficacy results: limited data to suggest a benefit compared with alternatives
The key efficacy outcomes deliberated upon by pERC in the Medgenberg 2009 study were progression-free survival and overall response rate. There was no statistically significant difference in progression-free survival for the bendamustine group compared with the fludarabine group (HR=0.87, 95% CI 0.59 to 1.28, P=0.27). The overall response rates were higher in the bendamustine group than the fludarabine group but statistical significance was not reported (78% versus 65%, respectively). pERC considered that these results did not suggest that bendamustine has a benefit compared with available treatment alternatives, and the limited information available from the study decreased pERC's confidence in the results.

Quality of life: valued by patients but no data reported
pERC noted that, from a patient perspective, treatment options that will extend life and bring about complete remission of the disease, while also allowing patients to enjoy a good quality of life are important. However, quality of life data were not reported in the abstract and it is unclear if quality of life data were collected in the Medgenberg 2009 study.

Safety: Minimal data reported and no benefit suggested compared with fludarabine
In the Medgenberg 2009 study, the proportion of patients reporting grade 3 or grade 4 infections was similar in the bendamustine and fludarabine groups (13% vs 15%, respectively). However, no additional adverse event data were reported. Therefore, pERC considered that there was inadequate information available to assess the safety of bendamustine and that the available data did not suggest that bendamustine offered a safety or tolerability benefit over fludarabine.

Need: Treatment options with improved tolerability and effectiveness
pERC noted that in relapsed/refractory CLL, there are no established treatments. A number of agents may be used such as fludarabine or chlorambucil but responses are generally infrequent and of shorter duration in this population than in untreated patients. Because CLL primarily affects older individuals (median age 72 years at diagnosis), patients may not be transplant candidates or able to tolerate toxic chemotherapy regimens and so have limited options. Therefore, pERC considered that there is a need for better tolerated agents that demonstrate a clinical benefit relative to treatments currently used in clinical practice.

PATIENT-BASED VALUES

Experiences of patients with CLL: significant fatigue and lower quality of life
Patient advocacy group input indicated that current treatments for CLL may extend life, but are not curative and that new treatment options are required for all stages of disease, including the relapsed/refractory setting. Patients with CLL often experience fatigue, which significantly impacts on social activities, ability to work and subsequent quality of life. It was also noted that the approach of watchful waiting, rather than treating, can cause anxiety and depression for patients. pERC considered these values of patients with CLL but noted that the limited clinical data available from the Medgenberg 2009 study did not allow the Committee to assess how bendamustine affects quality of life or fatigue. Upon reconsideration of the pERC Initial Recommendation, the Committee considered feedback from a

© 2012 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

patient advocacy group noting that patient input had indicated that patients reported a positive effect of bendamustine upon fatigue. pERC acknowledged the importance of patients' experiences in informing its deliberations on quality of life. Additionally, pERC considered that these observations enrich but do not replace valuable quality of life data from well-designed clinical trials.

Patient values on treatment: having a choice of treatments important to patients
Patient advocacy group input indicated that patients want treatment options that will extend their life and induce complete remission while maintaining quality of life. Patients indicated they would be willing to tolerate the side effects of a new therapy, if they are temporary and if there is a sustained improvement in quality of life. Patient input also noted that having additional treatment options which enable the patient to have a choice in their therapy, is important to them. pERC discussed the limited clinical information available on bendamustine and considered that it would align with patient values by providing another treatment option for patients with relapsed or refractory CLL.

ECONOMIC EVALUATION

Economic model submitted: cost utility in untreated and relapsed/refractory patients
The pCODR Economic Guidance Panel assessed an economic evaluation of the cost-utility of bendamustine compared to best supportive care in relapsed CLL.

Basis of the economic model: clinical and economic inputs
Costs included drug treatment acquisition costs, cost of routine follow-up for patients receiving active treatment and costs of routine health care resources involved in best supportive care.

Key clinical effects included progression-free survival and overall survival estimates. However, the Submitter did not have access to individual patient level data from the clinical study for these outcomes to allow for appropriate extrapolation of clinical trial results and validation of the economic model. pERC noted that this limited the pCODR Economic Guidance Panel in their ability to validate the results of the economic model.

Drug costs: wastage due to use of 100 mg vial could increase drug costs
At the list price, bendamustine costs $1,250 per 100 mg vial. For relapsed/refractory patients, when bendamustine is used alone at a dose of 100 mg/m^2 of body surface area (BSA) for 2 days within each 28 day cycle and assuming a mean BSA of 1.9m^2, the average cost per 28 day course is $4,750 assuming no vial wastage and $5,000 assuming no sharing of vials to prepare doses for multiple patients.

pERC noted that bendamustine is currently available in two vial sizes, 25 mg and 100 mg vials. pERC discussed estimates of the cost of bendamustine and considered that if 25 mg vials were not available, drug wastage would increase, leading to substantially greater bendamustine drug costs.

Cost-effectiveness estimates: fundamental flaws, unable to estimate cost effectiveness
pERC deliberated upon the cost-effectiveness of bendamustine and discussed the Economic Guidance Panel's (EGP) critique of the manufacturer's submitted economic evaluation in the relapsed/refractory setting. pERC noted that there were fundamental flaws in the manufacturer's submitted model that could not be corrected by the EGP. In addition, a number of flaws were identified that led the EGP to question the face validity of the economic model, and could not be validated by the EGP in the absence of the individual patient level data from the clinical study. This reduced the EGP's confidence in the cost-effectiveness estimates produced by the model and prevented the EGP from providing a best estimate of the incremental cost-effectiveness ratio for bendamustine in the relapsed/refractory setting.

pERC noted that other economic analyses of bendamustine have been referenced in the public domain. As pCODR did not have full access to these economic models and analyses, the EGP could only provide an evaluation of the economic model that was submitted to pCODR.

© 2012 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: prevalent cases and drug wastage could increase costs

Although the Health Canada approved indication for bendamustine in CLL is in the first-line setting, pCODR's Provincial Advisory Group (PAG) indicated that the use of bendamustine in relapsed/refractory CLL should be considered given the potential for indication creep in this setting. pERC noted this when making a recommendation for this setting. pERC also noted that no key barriers to implementation were identified by PAG.

pERC also discussed that for relapsed/refractory CLL, there may be a large prevalent population requiring treatment, which could have a substantial budget impact.

In addition, pERC noted that it would be important that 25 mg vials of bendamustine be available, otherwise substantial drug wastage could occur with bendamustine, which could also increase budget impact. pERC noted feedback from the manufacturer indicating that the 25 mg vial is available. However, PAG feedback on the initial recommendation indicated that the short stability of bendamustine may result in wastage, regardless of the vial size available. pERC considered that provinces will need to manage issues associated with bendamustine wastage due to its short stability.

© 2012 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

DRUG AND CONDITION INFORMATION

Drug Information	• Alkylating agent • 25 mg/vial and 100 mg/vial as a lyophilized powder, reviewed by pCODR • Studies used dosage of 100 mg/m2 as a single agent or 70 mg/m2 when used in combination with rituximab in relapsed/refractory CLL, administered IV
Cancer Treated	• Treatment of patients with CLL
Burden of Illness	• Most common leukemia in western countries • Primarily affects older population and has a long natural history
Current Standard Treatment	• In the relapsed/refractory setting there are no clearly established treatments.
Limitations of Current Therapy	• Limited effectiveness or tolerability of available treatment options, especially in an older and less fit population

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:

- Dr. Chaim Bell who was not present at this meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

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

- Dr. Chaim Bell who was not present at this meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

© 2012 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW

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 of bendamustine (Treanda) for CLL, through their declarations, seven members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was 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.

The pERC Final Recommendation may also be informed by feedback on the pERC Initial Recommendation from pCODR's Provincial Advisory Group, patient advocacy groups that provided input at the beginning of the review and the Submitter and/or the manufacturer of the drug under review if they were not the Submitter. Feedback on the pERC Initial Recommendation that was considered is posted on the pCODR website.

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.

Disclaimer
pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).

© 2012 pCODR | PAN-CANADIAN ONCOLOGY DRUG REVIEW