pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL 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.

Providing Feedback on this Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this 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 Issued:
October 4, 2012

pERC RECOMMENDATION

In the relapsed/refractory setting, the pCODR Expert Review Committee (pERC) does not recommend funding bendamustine (Treanda) in 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 This was due to the limited information available from a small unpublished randomized controlled trial, which pERC considered to be nadequate to assess whether a benefit relative to alternative treatments exists.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.

NEXT STEPS

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, which is a key component of the pERC Deliberative Framework. An adequate economic model is requested from the Submitter within six months.

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 was 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 their 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 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.

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.

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 if 25 mg vials of bendamustine are not available, given the short stability of reconstituted bendamustine and increased drug costs that would result from wastage. 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 two patient advocacy groups (the Leukemia & Lymphoma Society of Canada and the CLL Patient Advocacy Group) and input from pCODR's Provincial Advisory Group.

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 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.

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 that 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 benefit over fludarabine.

Need: Treatment options with improved tolerability and effectiveness

pERC noted that in the relapsed/refractory setting 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

patients (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 in the Medgenberg 2009 study did not allow the Committee to assess how bendamustine affects outcomes of fatigue or quality of life.

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, at the recommended dose of 70 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 $3,325 assuming no vial wastage and $3,750 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 drug costs associated with bendamustine.

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 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 a critique of the economic model that was submitted to pCODR.

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 in this setting. pERC also noted that no key barriers to the 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.

DRUG AND CONDITION INFORMATION

Drug Information	• Alkylating agent • 25 mg/vial and 100 mg/vial as a lyophilized powder, reviewed by pCODR • Recommended dosage of 70 mg/m^2 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

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.

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*.

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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