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: Bendamustine hydrochloride (Treanda) **Funding Request:** For the treatment of patients with chronic lymphocytic leukemia (first line) 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: January 31, 2013	**Final Recommendation:** February 19, 2013

RECOMMENDATION	In the first-line setting, the pCODR Expert Review Committee (pERC) recommends funding bendamustine (Treanda) for the treatment of patients with chronic lymphocytic leukemia (CLL) conditional on the cost-effectiveness being improved to an acceptable level. Bendamustine should be funded as a first line therapy in patients with Binet Stage B or C and WHO performance status ≤ 2 at the recommended dose. pERC considered that this recommendation is only applicable to patients who may not be medically fit to tolerate fludarabine-based regimens and who could be treated with other options such as chlorambucil. The recommended dose of bendamustine in first-line CLL is 100 mg/m2 of body surface area (BSA) for 2 on days 1 and 2 within each 28 day cycle. pERC made this recommendation because the Committee was confident of the net clinical benefit of bendamustine in this setting. However, due to considerable uncertainty with the submitted economic model, the Committee could not consider bendamustine cost-effective at the submitted price compared with chlorambucil.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given pERC was satisfied there is a net clinical benefit of bendamustine in the first-line setting, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of bendamustine to an acceptable level in this setting.

SUMMARY OF pERC DELIBERATIONS

pERC discussed that in the first line setting of chronic lymphocytic leukemia (CLL), medically-fit patients are often treated with fludarabine-based regimens such as FCR (fludarabine, cyclophosphamide, rituximab). pERC noted that patients who are not candidates for fludarabine are frequently treated with chlorambucil but there is a need for other more effective treatment options in this population. CLL is a common leukemia with a long natural history, therefore, the burden of illness may be substantial.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

One randomized controlled trial in patients with previously untreated CLL was included in the pCODR systematic review (Study 02CLLIII, Knauf 2009). pERC deliberated upon the results of Study 02CLLIII, which compared bendamustine with chlorambucil. Based on the clinically and statistically significant improvement in progression-free survival and in overall tumour response rates observed in Study 02CLLIII, pERC considered that there was a net clinical benefit associated with bendamustine in this setting and patient population. pERC noted that more patients in the bendamustine group than the chlorambucil group reported adverse events of neutropenia, leukopenia, vomiting, fever, infection and rash. pERC considered this adverse event profile to be tolerable in this setting. Since patients who were young and fit were not included in Study 02CLLIII and because of the design of the study, pERC noted that it could not determine the efficacy of bendamustine versus fludarabine-based treatment regimens or the net clinical benefit of bendamustine in patients who would be candidates for fludarabine.

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 determined that bendamustine is consistent with these latter patient values.

pERC discussed the cost-effectiveness of bendamustine in the first line setting of CLL. pERC considered the pCODR Economic Guidance Panel's (EGP) assessment that, following a deferral of deliberations, some improvements had been made to the economic model submitted by the manufacturer. However, fundamental flaws remained, and the impact could not be verified without access to patient-level clinical trial data. This decreased the EGP's confidence in the cost-effectiveness estimates produced by the manufacturer's model. pERC discussed various estimates of cost-effectiveness for bendamustine in first-line CLL and considered that the most reliable were those provided by the EGP. pERC noted that due to the uncertainty in the submitted economic model, the EGP was only able to provide a point estimate and could not confidently provide a range of incremental cost-effectiveness ratios. pERC discussed that this point estimate was already a high value and could potentially be even higher given the uncertainty in the range of estimates. Therefore, pERC concluded that bendamustine is not cost-effective because of the uncertainty in the information available to them.

pERC considered the feasibility of implementing a recommendation for bendamustine in the first line setting. It was noted that drug wastage could be an important issue that may limit feasibility if 25 mg vials of bendamustine were not available, given the short stability of reconstituted bendamustine and increased drug costs that would result from wastage.

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)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- the Submitter (Lundbeck Canada Inc.)

Feedback on the pERC Initial Recommendation indicated that the manufacturer agreed in part with the initial recommendation while the pCODR provincial advisory group (PAG) agreed fully with the initial recommendation. Feedback was not received from any patient advocacy group(s) on the initial recommendation. 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 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 CLL.

Studies included: one published randomized controlled trial in first-line setting

The pCODR systematic review included one open-label randomized controlled trial, Study 02CLLIII (Knauf 2009), which evaluated the superiority of bendamustine compared to chlorambucil in previously untreated patients. Patients were randomized to receive either 100 mg/m^2 bendamustine intravenously on day 1 and 2, every 4 weeks or to receive chlorambucil 0.8 mg/kg orally on days 1 and 15, every 4 weeks.

Patient populations: untreated patients not candidates for fludarabine

Patients included in Study 02CLLIII (N=319) were those with Binet Stage B or Binet Stage C and had a WHO performance status ≤ 2. pERC noted that the mean age of patients included in the study was 63 years and that older patients were not likely candidates for fludarabine-based treatment regimens. Therefore, pERC considered that the recommendation was only applicable to patients who may not be medically fit to tolerate fludarabine-based regimens and who would be treated with other options such as chlorambucil. pERC also noted that other patients unlikely to tolerate fludarabine-based regimens, such as those with renal dysfunction, were excluded from Study 02CLLIII.

Key efficacy results: improved progression-free survival and response rate

The key efficacy outcomes deliberated upon by pERC were progression-free survival and overall response rate, which were the co-primary outcomes of Study 02CLLIII, and overall survival.

Median progression-free survival, as assessed by an independent review committee, was statistically significantly improved for bendamustine compared to chlorambucil (21.6 months versus 8.3 months; HR=0.214, 95% confidence interval not reported, P<0.0001). A statistically significant improvement in overall response rate was also demonstrated for bendamustine compared to chlorambucil (68% versus 31%, respectively; P<0.0001). pERC discussed these results and noted that the magnitude of benefit observed for bendamustine was clinically significant and would offer patients a more effective treatment option than chlorambucil.

pERC discussed overall survival and noted that at the time of study publication there were insufficient data to comment on overall survival but that an updated analysis (Knauf 2012) reported no statistically significant difference after a follow-up of 54 months. pERC noted that these results may be confounded by patient cross-overs.

Quality of life: valued by patients but limited 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, only limited details on quality of life data were reported in Study 02CLLIII. Therefore, pERC could not make any definite conclusions regarding bendamustine's impact on quality of life.

Safety: tolerable side effect profile

In Study 02CLLIII, a higher proportion of patients in the bendamustine arm than in the chlorambucil arm experienced neutropenia, leukopenia, vomiting, fever, infection or rash. Similar proportions of patients reported grade 3 and grade 4 adverse events in each treatment group. pERC discussed these adverse events and considered that the side effect profile was tolerable.

Need: Treatment options with improved tolerability and effectiveness

pERC discussed that in the treatment of first-line CLL, the combination of fludarabine, cyclophosphamide and rituximab (FCR) is the standard of care for young, otherwise healthy patients but that due to significant toxicity, this regimen is often unsuitable for older or less medically-fit individuals. Those patients who are not candidates for fludarabine-based regimens often receive treatments such as chlorambucil. However, the efficacy of chlorambucil is limited and other effective but tolerable treatment options are needed.

Because CLL primarily affects older patients (median age 72 years at diagnosis), patients may not be candidates for transplants or be able to tolerate toxic chemotherapy regimens and, therefore, have limited treatment options. Therefore, pERC considered that there is a need for more effective and 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. 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 detail on quality of life from Study 02CLLII did not allow the Committee to adequately 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 efficacy and harms data available on bendamustine from Study 02CLLIII and considered that it would align with patient values by providing another effective treatment option for patients who cannot tolerate fludarabine-based treatment regimens and would receive treatments like chlorambucil instead.

ECONOMIC EVALUATION

Economic model submitted: cost utility in untreated patients

The pCODR Economic Guidance Panel assessed an economic evaluation of the cost-utility of bendamustine compared to chlorambucil in first line therapy of CLL.

Following a deferral of pERC deliberations, the original economic model submitted to pCODR was revised in order address fundamental flaws and allow pERC to determine the cost-effectiveness of bendamustine.

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, costs of health care resources involved in best supportive care, costs associated with disease progression and with the management of serious adverse events.

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. At the recommended dose, when used to treat first-line CLL, of 100 mg/m^2 of body surface area (BSA) on days 1 and 2 within each 28 day cycle and assuming a mean BSA of 1.9 m^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. It was noted that the recommended dose of bendmustine differs depending on the indication for which it is being used.

Chlorambucil costs $1.35 per 2 mg tablet. At the recommended dose of 0.8 mg/kg for two days within each 28 days cycle and assuming a body weight of 70 kg, the average cost per 28 day course is $75.87.

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 first-line setting. pERC noted that, despite improvements made by the manufacturer, fundamental flaws remained in the manufacturer's submitted model that could not be corrected by the EGP. This reduced the EGP's confidence in the cost-effectiveness estimates produced by the model, which could not be validated in the absence of the individual patient level data from the clinical study.

pERC discussed various estimates of cost-effectiveness for bendamustine in first-line CLL, including the EGP's, the manufacturer's and other cost-effectiveness estimates in the public domain. As pCODR did not have full access to these other economic models and analyses reported partially in the public domain, the EGP could only provide a critique of the economic model that was submitted to pCODR. pERC considered that the most reliable estimates were those provided by the EGP. pERC noted that due to the uncertainty in the submitted economic model, the EGP was only able to provide a point estimate and could not confidently provide a range of incremental cost-effectiveness ratios. pERC discussed that the EGP's point estimate of $98,321 per quality adjusted life year is already a high value and that there is also uncertainty in determining the range of estimates. pERC discussed a number of biases identified by the EGP that could increase the cost-effectiveness estimates such as the exclusion of patients who experienced toxicities in the clinical study from the survival analysis. Due to the limitations of the submitted model, however, and the lack of individual patient-level clinical trial data, the EGP could not explore these biases and their impact on cost-effectiveness any further. Based on these considerations, pERC considered that an estimate based on more complete evidence would very likely be higher than $98,321 per quality adjusted life year. Therefore, because of the uncertainty in the information available to them, pERC concluded that bendamustine is not cost-effective at the submitted price.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: drug wastage could increase costs
Wastage was identified as a possible barrier to implementation of a funding recommendation. 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 the 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 100 mg/m^2 per day on days 1 to 2 every 4 weeks, for up to 6 cycles, when used to treat first-line CLL administered IV
Cancer Treated	• Treatment of patients with CLL
Burden of Illness	• Most common leukemia in western countries • Primarily affects an older population and has a long natural history
Current Standard Treatment	• Fludarabine, cyclophosphamide and rituximab (FCR) is the standard of care for medically-fit patients • Chlorambucil most commonly used for less medically-fit patients
Limitations of Current Therapy	• Limited effectiveness or tolerability of available treatment options, especially in older or less medically-fit populations

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. Sunil Desai, Dr. Bill Evans and Dr. Tallal Younis who were not present at this meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

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 of bendamustine (Treanda) for first line CLL, through their declarations, five members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, but 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*. 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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