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 indolent Non-Hodgkin Lymphoma and Mantle Cell Lymphoma (first line and relapsed/ refractory)

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	The pCODR Expert Review Committee (pERC) recommends funding bendamustine (Treanda) as a first-line therapy in patients with indolent CD20 positive Non-Hodgkin Lymphoma (iNHL) and Mantle Cell Lymphoma (MCL) with an ECOG performance status of less than or equal to 2, when used in combination with rituximab. pERC made this recommendation because it considered that there is a net clinical benefit of bendamustine in this setting and that it is likely to be cost-effective. The pERC also recommends funding bendamustine (Treanda) in the relapsed/refractory setting in patients with iNHL and MCL when used in combination with rituximab, where the combination of fludarabine-rituximab would previously have been the therapeutic option. pERC made this recommendation because it considered that there is a net clinical benefit of bendamustine in this setting and that it is likely to be cost-effective. There is no clinical trial evidence available on the clinical benefit of combination bendamustine-rituximab in patients who have either received prior maintenance therapy with rituximab or who are refractory to rituximab. pERC was unable to make an informed recommendation on funding bendamustine in the broader patient population with relapsed or refractory disease.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility for Resubmission to Support Broader Funding in Relapsed/Refractory Setting** There is an ongoing study which will provide information on the use of bendamustine in rituximab refractory disease. This study, the ROBIN trial, will assess the efficacy of bendamustine in comparison to physician's choice in the relapsed/refractory setting and could lead to a broader recommendation if a resubmission were made to pCODR.

SUMMARY OF pERC DELIBERATIONS

pERC discussed that in the first-line setting, comparator therapies include both R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) and R-CVP (rituximab, cyclophosphamide, vincristine and prednisolone). However, R-CVP is often preferred given the toxicity of doxorubicin in the R-CHOP regimen. Maintenance therapy with rituximab is also considered standard practice for most patients. pERC also discussed that in the relapsed/refractory setting, there is no standard approach to treatment. pERC noted that in both settings there are limitations of current therapies with respect to effectiveness and tolerability and that new treatment options addressing these factors are needed.

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 evaluating bendamustine plus rituximab (B-R) compared with R-CHOP in the first-line setting (STiL NHL1, Rummel 2009) and one randomized controlled trial evaluating B-R compared with fludarabine plus rituximab (F-R) in the relapsed/refractory setting (STiL NHL2, Rummel 2010) were included in the pCODR systematic review. Both of these studies are currently only available in abstract-form and have not been published as full journal articles. However, considering the available details on study design and the type of information included in these abstracts, pERC accepted that in the review of bendamustine for indolent Non-Hodgkin Lymphoma (iNHL) and Mantle Cell Lymphoma (MCL), the abstract data were sufficient to evaluate the clinical benefit of bendamustine.

pERC deliberated upon the results of the STiL NHL1 study, which was conducted in the first-line setting. pERC considered that the magnitude of the progression-free survival benefit for B-R compared with R-CHOP was substantial and statistically significant (54.8 months versus 34.8 months, respectively). pERC also considered reports of grade 3 and grade 4 adverse events and noted that, in most cases, adverse events were similar or greater in the R-CHOP group compared with the B-R group. pERC discussed that comparing B-R with R-CHOP, which has known toxicities, may bias the results in favour of bendamustine and it is not certain how B-R compares with R-CVP. However, overall, pERC considered that the adverse event profile of bendamustine appeared tolerable in this setting and that the ongoing BRIGHT study would provide more details on B-R versus R-CVP. Therefore, pERC determined that there is a net clinical benefit of bendamustine in combination with rituximab in the first-line setting.

pERC also deliberated upon the results of the STiL NHL2 study, which was conducted in the relapsed/refractory setting. pERC considered that the magnitude of the progression-free survival benefit for B-R compared with F-R was substantial and statistically significant (30 months versus 11 months, respectively). pERC also noted that serious adverse events were similar between B-R and F-R, which satisfied pERC that bendamustine was no more toxic than fludarabine in this patient population and setting. pERC discussed whether F-R was the most appropriate comparator and noted that although this is one possible comparator, there are other treatments used in the relapsed/refractory setting and it is not clear how B-R would compare with those other therapies. pERC also discussed the patient population that was included in STiL NHL2 and considered that, although there is sufficient evidence to suggest a net clinical benefit, it would be important to limit the use of bendamustine to the patients in whom it had been studied. pERC further noted that rituximab-refractory patients were specifically excluded from the STiL NHL2 study, and therefore the clinical benefit of bendamustine in this population is unknown.

In both studies, pERC considered that the impact of rituximab maintenance therapy on the apparent effectiveness of bendamustine was unclear given that it was not used in STiL NHL1 and given that the proportion of patients in STiL NHL2 who had previously received rituximab maintenance therapy was not reported. pERC noted this to be an important limitation given that rituximab maintenance therapy is now considered standard care, which limits the generalizability of the bendamustine results to broader clinical settings. pERC noted that the ongoing BRIGHT study may provide more information on this point.

pERC also deliberated on the alignment of bendamustine with patient values. pERC noted that bendamustine has a progression-free survival advantage, may be less toxic than currently available therapies and would provide patients with another treatment option. This aligns with patients' expressed values of having additional treatment choices that have a clinical benefit over current therapies. However, neither the STiL NHL1 study or the STiL NHL2 study reported quality of life data. Therefore, it is uncertain how bendamustine treatment would align with the patient value of improving or maintaining quality of life.

pERC deliberated upon the cost-effectiveness of bendamustine in patients with iNHL and MCL. In both of the submitted analyses, one for the first-line setting and the other in the relapsed-refractory setting, pERC acknowledged that there were serious limitations in the economic evaluations that were submitted and that there was considerable uncertainty in the cost-effectiveness estimates provided by pCODR's Economic Guidance Panel (EGP). However, pERC noted that the face validity of the economic models was not questioned by the EGP. This led pERC to suggest that in both the first-line setting and the relapsed/refractory setting, the incremental cost-effectiveness ratio is probably acceptable. However, pERC acknowledged that these estimates should be interpreted with caution.

pERC considered the feasibility of implementing a recommendation for bendamustine for patients with iNHL and MCL. It was noted that drug wastage could be an important issue that may limit feasibility, if the 25 mg vials of bendamustine are ever 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 that might require treatment, which could also have a substantial budget impact. pERC also discussed that because bendamustine was evaluated in combination with rituximab in both the STiL NHL1 and STiL NHL2 studies, the feasibility of implementing a recommendation could be challenging given the significant variation in access to rituximab and rituximab maintenance therapy in different jurisdictions.

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 (Leukemia and Lymphoma Society of Canada; Lymphoma Foundation Canada) 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:

- Previously untreated indolent Non-Hodgkin Lymphoma (iNHL) or Mantle Cell Lymphoma (MCL).
- iNHL or MCL that has relapsed or refractory to treatment that included rituximab.

Studies included

The pCODR systematic review included two open-label randomized controlled trials:

- Study StiL NHL1 (Rummel 2009), compared B-R to R-CHOP in 549 patients with previously untreated NHL or MCL. In the B-R group, patients received bendamustine 90 mg/m^2 on days 1 and 2; rituximab was administered at a dose of 375 mg/m^2 on day 1 and every 4 weeks for 6 cycles. In the R-CHOP group, every 3 weeks for 6 cycles, patients received cyclophosphamide 750 mg/m^2 on day 1; doxorubicin 50 mg/ m^2 on day 1, vincristine 1.4 mg/m^2 on day 1; prednisone 100 mg orally on days 1 to 5 and rituximab 375 mg/ m^2 on day 1.
- Study StiL NHL2 (Rummel 2010), compared B-R to F-R in 219 patients with previously treated relapsed follicular, NHL and MCL. In the B-R group, patients received bendamustine 90 mg/m^2 on days 1 and 2 plus rituximab 375 mg/m^2 on day 1, every 4 weeks for a maximum of 6 cycles. In the F-R group, patients received fludarabine 25 mg/m^2 on days 1 to 3 plus rituximab 375 mg/ m^2 on day 1, every 4 weeks for a maximum of 6 cycles.

Although neither study has been published as a full journal article at the time of this review, pERC considered the available details on study design and the type of information included in the abstracts, and concluded that the quality of the information was sufficiently high that the abstract data was adequate to evaluate the clinical benefit of bendamustine in iNHL and MCL.

- In the STiL NHL1 study, pERC noted that the sample size was relatively large (n=549), that six-year follow-up data were provided and that the results were consistent with previous analyses of bendamustine in NHL.
- In the STiL NHL2 study, pERC noted that the sample size was reasonable (n=219) and that the presented analysis was consistent with earlier analyses.

Therefore, pERC was confident that it could assess the clinical benefit of bendamustine with this abstract evidence in these specific circumstances.

Patient populations: impact on patients receiving rituximab maintenance or who are refractory to rituximab unclear

Both the StiL NHL1 and STiL NHL2 study included patients with a WHO Performance Status ≤2 and histologically verified CD20-positive B-cell lymphomas, MCL, lymphocytic lymphoma (CLL without leukemic characteristics) and nonspecified/classified lymphomas of low malignancy.

In STiL NHL1 (Rummel 2009), patients did not receive prior therapy with cytotoxics, interferon, or monoclonal antibodies.

In STiL NHL2, as reported in the abstract (Rummel 2010), patients had:

- recurrent disease (remission duration greater than 3 months), independent of type or quantity of prior therapies, except for treatment consisting of rituximab containing regimens; or
- recurrent disease where remission duration was >1 year after rituximab containing regimen; or
- disease refractory to prior therapy (progression on therapy or within 3 months of completion of initial therapy), except for refractory disease to purine analogs or bendamustine.

Patients refractory to rituximab were excluded from the study, therefore, pERC considered that there is no information on the clinical benefit of bendamustine in this population. pERC noted that the ongoing ROBIN study may provide more information on this point.

In both studies, pERC considered that the impact of rituximab maintenance therapy on the apparent effectiveness of bendamustine was unclear given that it was not used in STiL NHL1 and given that the proportion of patients in STiL NHL2 who had previously received rituximab maintenance therapy was not reported. pERC noted this to be an important limitation as rituximab maintenance therapy is now considered standard care and could limit the generalizability of the bendamustine results to broader clinical settings.

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

The key efficacy outcomes deliberated upon by pERC were progression-free survival, the primary outcome in both studies, and response rate.

- In the first-line setting (StiL NHL1 Study), a statistically significant benefit was demonstrated for B-R compared to R-CHOP (median 54.8 versus 34.8 months, respectively; HR=0.58, 95% confidence interval (95% CI) 0.43 to 0.77, P=0.0002). The proportion of patients with a complete response was statistically significantly higher in the B-R compared to the R-CHOP group (40.1% vs. 30.8%, respectively p=0.0323).
- In the relapsed/refractory setting (StiL NHL2 Study) a statistically significant benefit in progression-free survival was demonstrated for B-R compared to F-R (median 30 months versus 11 months, respectively; HR =0.51, 95% CI 0.34 to 0.67, P<0.0001). The proportion of patients with a complete response (38.5% versus 16.2%, respectively, P=0.0004) or with an overall response (83.5% vs. 52.5%, respectively p<0.0001) was statistically significantly higher in the B-R group compared to the F-R group.

Quality of life: No information available
pERC noted that from a patient perspective treatment options that allow them to maintain quality of life while controlling their disease and extending life is important. However, pERC noted that neither study, StiL NHL1 or StiL NHL2 evaluated the effect of bendamustine on quality of life.

Safety: toxicity similar or less than R-CHOP (first-line) or F-R (relapsed/refractory)
pERC discussed the safety of bendamustine in both settings.

- In the StiL NHL1 Study (untreated), a higher proportion of patients experienced Grade 3 or 4 neutropenia and leukopenia in the R-CHOP arm than in the B-R arm (69% and 72% vs. 29% and 37%, respectively); however, more patients in the B-R arm experienced Grade 3 or 4 lymphopenia than in the R-CHOP arm (74% vs. 34%, respectively). Similar rates of Grade 3 or 4 anemia and thrombocytopenia were reported for both arms.
- In the StiL NHL2 Study (relapsed/refractory setting) the rates of the following adverse events were similar in both study arms serious adverse events (17.4% for B-R vs. 22.2% for F-R), grade 3/4 neutropenia (8.9% vs. 9.1%), and grade 3/4 leukopenia (11.8% vs. 12.4%). No additional data on adverse events were reported.

Ongoing trials: BRIGHT Study will provide clarity on comparative benefits of B-R vs R-CVP
Two ongoing RCTs evaluating bendamustine in patients with iNHL may provide additional relevant information on the clinical benefit of bendamustine

- The BRIGHT study comparing bendamustine hydrochloride and rituximab (BR) with R-CVP or R-CHOP in the first-line treatment of patients with advanced iNHL or MCL
- The ROBIN study comparing the efficacy of bendamustine with physicians therapy of choice (without bendamustine) in patients with NHL refractory to rituximab.

Need: Treatment options with improved tolerability and effectiveness
Despite the use of R-CVP and R-CHOP in the first-line setting, these therapies are limited in their ability to extend length of life and improve quality of life. The use of R-CHOP is further limited by doxorubicin-associated toxicity. Therefore, there is a need for treatment options that reduced toxicity, improve progression free and/or overall survival, and improve quality of life. Similarly, there is no established treatment in the relapsed/refractory setting and effective treatment options are needed for patients. pERC considered the limitations of the current therapies in iNHL and MCL and acknowledged that there is a need for more tolerable agents that demonstrate a clinical benefit relative to current treatments.

PATIENT-BASED VALUES

Values of patients with NHL: Disease stabilization and improved quality of life
Patient advocacy group input highlighted that NHL is a common cancer and that iNHL may recur many times, becoming less responsive to treatment over time. pERC noted that bendamustine has a progression-free survival advantage and would provide patients with another treatment option. This would align with patients' expressed values of having additional treatment choices that have a clinical benefit over current therapies.

Patient values on treatment: treatment alternatives, improved quality of life, disease stabilization and resistance to therapy
From a patient perspective, patients with NHL are seeking more treatment options or choices for their condition. In addition, patients want treatment options that will control their disease and extend their life, while maintaining quality of life. Most patients indicate that they would be willing to tolerate the side effects of a new therapy, even significant side effects, if the therapy is able to control their disease or if the side effects disappear after treatment is complete with an improvement in their quality of life for a substantial length of time. In addition, patients also express a desire to have a treatment option to which the disease does not develop resistance. Data from the STiL NHL1 and STiL NHL2 studies suggest that bendamustine may be similar or less toxic than currently available therapies, which may be a benefit to patients. However, pERC noted that neither the STiL NHL1 study or the STiL NHL2 study reported quality of life data. Therefore, it is uncertain how bendamustine would align with the patient value of improving or maintaining quality of life.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility

The economic analysis submitted by Lundbeck Canada Inc. evaluated the cost-utility and cost-effectiveness of bendamustine in both the first-line setting (compared with R-CHOP or R-CVP) and the relapsed/refractory setting (compared with either radioimmunotherapy, best supportive care or fludarabine).

Basis of the economic model: clinical and economic inputs

Costs included were drug costs, costs associated with progression free survival, rituximab maintenance therapy and costs associated with progressive NHL, adverse events and subsequent chemotherapy.

Key clinical effects included progression-free survival and overall survival estimates. However, the Submitter did not have access to the individual patient-level clinical data for these outcomes to allow for appropriate extrapolation and validation of the economic model, which limited the Economic Guidance Panel's confidence in the submitted estimates.

Drug costs: wastage due to use of 100 mg vial could increase drug costs

At the list price, bendamustine costs $312.50 per 25 mg vial and $1,250.00 per 100 mg vial. At the recommended dose in first-line NHL of 120 mg/m^2 IV on days 1, 2 and every 21 days, the average cost per day in a 28-day course is $182.12 and the average cost per 28-day course is $5,100.00.

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 could increase, leading to substantially greater drug costs associated with bendamustine.

Cost-effectiveness estimates: substantial uncertainty but likely cost effective

In various scenarios in both the first-line setting and the relapsed/refractory setting, the Economic Guidance Panel (EGP) provided a wide range of estimates for the incremental cost-effectiveness ratios. For the first line setting, the range suggested by the EGP was from $35,081 to $155,000 per QALY. For the relapsed/refractory setting, the range suggested by the EGP was $41,613 to $81,107 per QALY. However, the EGP considered that their best estimates were seriously limited by the submitted models and uncertainty in the data given the lack of individual patient level data and clinical trials with appropriate direct comparisons to inform them. The EGP was critical of their best estimates and noted that these estimates were subject to substantial uncertainty and may, in fact, be higher. In addition, the EGP noted that assumptions around the time horizon and bendamustine dose had a significant impact on the cost-effectiveness of bendamustine and needed to be adjusted by the Economic Guidance Panel.

pERC noted the limitations of the submitted analyses and the resultant uncertainty in the EGP estimates, but considered that the true cost-effectiveness ratios for both the first-line and relapsed/refractory settings were likely in the mid to lower end of the ranges presented by the EGP. As such, pERC considered that bendamustine was likely to be cost-effective but acknowledged that there was significant uncertainty which reduced their confidence in the ICER estimates.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: drug wastage, prevalent populations and rituximab accessibility

pERC considered the feasibility of implementing a recommendation for bendamustine for patients iNHL and MCL. 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 noted that indolent NHL is a large patient population and that some patients have already had experience with bendamustine. 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. pERC also discussed that because bendamustine was evaluated in combination with rituximab in both the STiL NHL1 and STiL NHL2 studies, feasibility of implementing a recommendation could be challenging given the significant variation in access to rituximab and rituximab maintenance therapy in different jurisdictions.

DRUG AND CONDITION INFORMATION

Drug Information	• Alkylating agent • 25 mg/vial and 100 mg/vial as a lyophilized powder, reviewed by pCODR • Health Canada recommended dose in relapsed setting is 120 mg/m^2 IV on Days 1 and 2 of a 21 day-cycle to a maximum of 8 cycles; Dose used in STiL2 relapsed /refractory study was 90 mg/m^2 on days 1 and 2 of a 28-day-cycle to a maximum of 6 cycles
Cancer Treated	• Indolent Non-Hodgkin Lymphoma and Mantle Cell Lymphoma
Burden of Illness	• Fifth most common malignancy in Canada, with 7800 new cases and 2800 deaths from this diagnosis expected in 2012. • Advanced stage iNHL is incurable and associated with reduced life expectancy. • MCL, while less common than other indolent lymphomas, has a poorer prognosis.
Current Standard Treatment	• R-CVP and R-CHOP are the most commonly used front line chemotherapy regimens. • In Canada, R-CVP is more frequently prescribed due to toxicity of doxorubicin in the R-CHOP regimen. • No preferred treatment in second line setting; options include re-treatment with CVP (+/- rituximab), CHOP (+/- rituximab) and fludarabine-containing regimens (+/- rituximab).
Limitations of Current Therapy	• Currently available first line treatments for iNHL can induce temporary remissions but do not control iNHL indefinitely • Toxicity associated with doxorubicin in the R-CHOP regimen • New treatments that can improve remission with acceptable or improved toxicity profiles are needed in both first-line and relapsed/refractory settings

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 iNHL/MCL, 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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