PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review

# Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

# Bendamustine (Treanda) for Chronic Lymphocytic Leukemia

**November 29, 2012**

## INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

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# 3 Feedback on pERC Initial Recommendation

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|---|---|
| Name of the Drug and Indication(s): | Bendamustine (TREANDA) for chronic lymphocytic leukemia |
| Role in Review (Submitter and/or Manufacturer): | Submitter and Manufacturer |
| Organization Providing Feedback | Lundbeck Canada Inc. |

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

## 3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees __**X**_ agrees in part ____ disagree

*Lundbeck Canada Inc. agrees in part with the initial recommendation related to the following statements made in the pERC initial recommendation:*

**pERC RECOMMENDATION - NEXT STEPS (First-line CLL): *"Deferral of Recommendation in First-Line Setting Until Appropriate Economic Evaluation Provided."***
The manufacturer is currently working with the pCODR secretariat to address the economic questions.

**EVIDENCE IN BRIEF (OVERALL CLINICAL BENEFIT): *"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…In the relapsed/refractory setting, the pCODR systematic review included one randomized study… 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."(Page 3, paragraphs 1 & 2 of the Overall clinical benefit section).***
The scope of review in the relapse or refractory setting appears to be broader than the manufacturer's request for funding (e.g. for patients for whom Fludarabine-based therapy is not appropriate). In the context of this funding request, the manufacturer believes that other phase II studies, such as the submitted Fisher 2011, should be considered during deliberation along with the Medgenberg 2009 study. According to the initial recommendation, only the Medgenberg 2009 trial was considered for deliberation.

**SUMMARY OF pERC DELIBERATIONS: *"pERC discussed that there is a need for***

***new treatments in patients with relapsed or refractory CLL... However, because of 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." (Page 2, paragraph 2)***

The primary objective of the Medgenberg 2009 study was to determine if progression-free survival (PFS) was comparable between the Bendamustine and Fludarabine arms. Based on the reported results, the study suggests that Bendamustine single agent (100 mg/m$^2$ d 1–2 q 28 days) until best response or a maximum of 8 cycles can be considered as a reasonable alternate to Fludarabine. This conclusion supports the role of Bendamustine as a reasonable option for patients for whom Fludarabine-based therapy is not appropriate.

It is also generally accepted that the addition of anti-CD-20 monoclonal antibodies Fludarabine-based therapy is becoming a common regimen in the relapse CLL setting as per the NCCN and ESMO guidelines. The submitted Fisher trial, evaluated the efficacy and safety of the addition of Bendamustine (70mg/m2 d1-2 q 28 days) to rituximab for up to 6 cycles. The Fisher study, although a single-arm, provides evidence on the efficacy and the safety of the combination in this high-risk CLL population for whom little if no therapeutic options are available. The Fisher trial included:

- A significant number of Fludarabine (F) refractory patients (28%)
- 81% patients previously exposed to F (mono or combo)
- High rate of unmutated IGHV (67%), poor prognosis
- Almost half of patients Binet C and renally impaired
- 1/3 elderly (above 70 years)

Therefore, the manufacturer believes that Bendamustine in this particular context could be considered as an option (e.g. patients for whom Fludarabine-based therapy is not-appropriate including Fludarabine-refractory patients).

**ADOPTION FEASABILITY:** ***"… pCODR's PAG indicated that the use of bendamustine in relapsed/refractory CLL should be considered given the potential for indication creep in this setting…."(Page 5, paragraph 1)***

Considering the high unmet need in CLL relapsed/refractory, the limitation of the data in this setting and that there are no ongoing phase III trials to confirm the promising results of Bendamustine, we hope the pERC could recommend to stakeholders areas for future research such as funding with evidence development or alike mechanisms.

**ADOPTION FEASABILITY:** ***"pERC also discussed that for relapsed/refractory CLL, there may be a large prevalent population requiring treatment, which could have a substantial budget impact."(Page 5, paragraph 2)***

The manufacturer submitted a budget impact analysis evaluating the potential net financial impact to provinces should they fund Bendamustine in the relapsed CLL patients population for whom Fludarabine-based therapy is not appropriate. This patient population represents only a subset of the total CLL relapse/refractory population. The majority of pCODR participating provinces currently fund Rituximab+/- Fludarabine.

Hence, the most appropriate dosing for cost comparison is Bendamustine (70mg/m$^2$ d 1-2 q 28 days) when used in combination with Rituximab. For provinces who do not currently reimburse rituximab in the relapsed CLL setting, the most appropriate dosing for cost comparison is Bendamustine single agent (100mg/m$^2$ d 1-2 q 28 days).

**ECONOMIC EVALUATION (Drug costs: wastage due to use of 100 mg vial could increase drug costs): *" pERC noted that bendamustine is currently available in two-vial sizes, 25 mg and 100 mg vials… if 25 mg were not available. Drug wastage would increase, leading to substantially greater drug costs associated with bendamustine."(Page 4, paragraph 2 of drugs costs section)***
The manufacturer has already made available the two strengths of 100 mg and 25 mg vials in Canada and plans to continue to do so. The pricing structure is also attractive where the 25mg/vial price is a quarter of the 100mg/vial. Hence, we do not believe that this question should represent a barrier for adoption.

**ECONOMIC EVALUATION (Cost-effectiveness estimates: fundamental flaws, unable to estimate cost effectiveness): *"pERC deliberated upon the cost-effectiveness of Bendamustine and discussed the EGP critique of the manufacturer's submitted economic evaluation in the relapsed/refractory setting." (Page 4, 1st paragraph of cost-effectiveness estimates section)***
The manufacturer is currently addressing the economic questions that were also raised during the review and should be able to provide the clarifications at the same time as for the first-line CLL economic evaluation.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____ Support conversion to final recommendation.
Recommendation does not require reconsideration by pERC.

_**X**_ Do not support conversion to final recommendation.
Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

| Page Number | Section Title | Paragraph, Line Number | Comments and Suggested Changes to Improve Clarity |
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### 3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR Secretariat.

| Page Number | Section Title | Paragraph, Line Number | Comments related to Submitter or Manufacturer-Provided Information |
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### 3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

| Page Number | Section Title | Paragraph, Line Number | Additional Comments |
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# 1 About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

# 2 Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer of the

drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½″ by 11″ paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

***Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.***