pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Bendamustine (Treanda) for Chronic Lymphocytic Leukemia

November 29, 2012

****Please note that sections pertaining to the use of Bendamustine (Treanda) for First Line Chronic Lymphocytic Leukemia in this report are superceded by the Clinical Guidance Report on Bendamustine (Treanda) for First Line Chronic Lymphocytic Leukemia which can be found at:** Bendamustine (Treanda) First Line CLL**

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Lundbeck Canada Inc.** compared bendamustine (Treanda) to chlorambucil as a first line monotherapy for patients chronic lymphocytic leukemia (CLL) and compared bendamustine (Treanda) plus rituximab to best supportive care for patients with relapsed CLL at high risk. The first line analysis reflects the phase 3 trial population in the 02CLLIII study. For relapsed CLL the analysis reflects an indirect comparison of a single-arm phase 2 study (Fischer et al 2011) and retrospective case series (Keating et al. 2002).

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate, however, the CGP noted that when possible the first line treatment for CLL is FCR (fludarabine, cyclophosphamide plus rituximab). For less fit patients who might not tolerate FCR chlorambucil alone is an acceptable first line treatment. In the relapsed/refractory setting there are no clearly established treatments.

Patient advocacy groups considered the following factors important in the review of bendamustine:

- Increased choice of treatments
- Willingness to experience side effects for long term improvements in quality of life

The **pCODR Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for bendamustine, and which are relevant to the economic analysis:

- Comparison to a combination of rituxmab, fludarabine and cyclophosphamide should be incorporated
- Consideration of the use of bendamustine for relapsed/refractory CLL should be given

At the list price, bendamustine costs $1,250 per 100mg. For first line therapy, at the recommended 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. 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.

1.2 Summary of Results

The manufacturer's economic model has major methodological flaws. The EGP is not able to correct the model to provide meaningful results with respect to cost effectiveness. Therefore, the EGP cannot provide a best estimate of the incremental cost-effectiveness ratio.

According to the economic analysis that was submitted by the manufacturer, when bendamustine was compared with chlorambucil as a first line monotherapy:

- The extra cost (ΔC) of bendamustine is $28,155. Incremental costs for bendamustine (Treanda) are based on a model which extrapolates data from the clinical trial to estimate long terms survival and progression.
- The extra clinical effect (ΔE) of bendamustine is 0.65 QALYs. This was largely driven by the assumptions relating to progression and survival and assuming a different quality of life of patients with progression between bendamustine (Treanda)and chlorambucil.

So, the Submitter reports that the incremental cost-effectiveness ratio (ΔC / ΔE) was $43,023 per QALY. This differed from the actual model results where the calculated incremental cost-effectiveness ratio (ΔC / ΔE) was $59,713 per QALY. The EGP was unable to replicate these results using the same assumptions as the submitter.

According to the economic analysis that was submitted by the manufacturer, when bendamustine plus rituximab was compared with Best Supportive Care (BSC) for relapsed CLL:

- The extra cost (ΔC) of bendamustine plus rituximab is $37,481. Incremental costs for bendamustine plus rituximab are based on a model which extrapolates data from a phase II study and then assumes its comparability to a an earlier case series study for BSC.
- The extra clinical effect (ΔE) of bendamustine is 0.52 QALYs. Incremental QALYs for bendamustine plus rituximab are based on a model which extrapolates data from a phase II study and then assumes its comparability to a an earlier case series study for BSC.

So, the Submitter reports that the incremental cost-effectiveness ratio (ΔC / ΔE) was $72,504 per QALY. EGP was able to replicate these results using the same assumptions as the manufacturer.

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

The EGP is unable to provide an estimate of cost effectiveness given the substantial methodological flaws within the manufacturer's submitted model. Requested re-analysis, while not addressing the methodological flaws, did provide alternative ICUR estimates that assumed no vial sharing ($[redacted]/QALY), equal utility in PFS ($[redacted]/QALY) and a restricted time (limited of trial data at 36 months) time horizon ($[redacted]/QALY) or all 3 of these factors ($[redacted]). *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).* The inability to resolve the methodological flaws in the submitted model led the Economic Guidance Panel to consider the limited information available from other economic reviews. The Scottish Medicines Consortium (SMC) and the National Institute for Health and Clinical Excellence (NICE) reported an ICURs of £10, 621/QALY and £11,960/QALY (bendamustine vs chlorambucil) respectively for the first line treatment of CLL in patients in whom fludarabine combination therapy is not appropriate and major structural flaws were not reported in these models.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

No. The submitted analysis is of poor quality and therefore concerns of the patients cannot be addressed.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

No. Due to substantial methodological flaws the submitted economic model is inadequate.

The major flaw relates to the modelling of survival. Given the short term nature of the clinical trial it is necessary to use mathematical techniques to extrapolate from the clinical trial duration. The manufacturer used incorrect mathematical techniques to model survival. This is best illustrated by the model forecasting that 103% of patients in the bendamustine arm being progression free at 1 month. Therefore, the modelling used for survival is inappropriate. To properly analyze survival data to allow for extrapolation, the manufacturer must have access to the patient level data.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

No exploration of key variables can be conducted due to the major methodological flaws within the submitted economic models.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

Due to the major methodological flaws and the lack of clarity in the reporting of the economic study, this issue could not be explored.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

Capture rates are unknown. Clearly, higher rates will have a major impact on budgets.

Bendamustine is assumed to capture the market of combination therapies for which no economic data are provided supporting such comparisons.

What are the key limitations in the submitted budget impact analysis?

The analysis is well done in terms of technical quality. The major limitation is the lack of data to support the assumptions made. In particular this applies to:

- Analysis assumes no wastage of vials – inclusion of wastage will increase the additional costs of funding
- Analysis assumes a dose of 70mg/m^2 – it is not clear what the dose would be in the relapsed setting
- The analysis is heavily based on assumptions especially capture rate but this is similar as for other BIAs.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

For the analysis of first line use of bendamustine:

- Justification for the use of the particular functional forms for survival is required. Sensitivity analysis exploring alternate functional forms should be provided.
- The progression free survival functions must be estimated properly. They are incorrectly specified and lead to illogical results – i.e. survival of 103%.
- When partitioning transition out of the progression free state, the model should have an explicit method of calculating the proportion who die versus the proportion who progress.
- Survival post progression should be a function of the time in the post progression state not the time since the start of treatment as currently.
- Utility values in progression free state should be assumed the same for both treatments.

For the analysis of bendamustine in relapsed CLL:

- Justification for the use of the particular functional forms for survival is required. Sensitivity analysis exploring alternate functional forms should be provided.
- The progression free survival functions must be estimated properly. They are incorrectly specified and can lead to illogical results.
- When partitioning transition out of the progression free state, the model should have an explicit method of calculating the proportion who die versus the proportion who progress.
- Survival post progression should be a function of the time in the post progression state not the time since the start of treatment as currently.
- Survival post progression should be the same for both treatment alternatives.

Is there economic research that could be conducted in the future that would provide valuable information related to bendamustine?

A revised economic model addressing the above concerns is essential – the EGP cannot use the current model for assessing cost effectiveness.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3. ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Leukemia Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of Bendamustine (Treanda) for CLL. A full assessment of the clinical evidence of Bendamustine (Treanda) for CLL is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, which was provided to pERC for their deliberations and has been redacted in this publicly available Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the *pCODR Nomination/Application Information Package* and *the Economic Guidance Panel Terms of Reference*, which are available on the pCODR website (www.pcodr.ca). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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pan-Canadian Oncology Drug Review Manufacturer Submission: Treanda (bendamustine hydrochloride): Lyophilized powder for injection, for intravenous infusion: 25 mg and 100 mg. Company: Lundbeck Canada Inc. Montreal (QC): Lundbeck Canada Inc.; 2012 Apr 24.