PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Bendamustine (Treanda) for First Line Chronic Lymphocytic Leukemia

February 19, 2013

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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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 with chronic lymphocytic leukemia (CLL). The analysis reflects the phase 3 trial population in the 02CLLIII study.

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 FC (R) fludarabine, cyclophosphamide plus rituximab. For less fit patients who might not tolerate FD(R) chlorambucil is an acceptable first line treatment.

The updated economic analysis incorporates additional information requested by pCODR from the Submitter. The current report deals with the use of bendamustine in the first line treatment setting alone. The following changes were made by the Submitter:

- Development of new parametric curves for transition from PFS to Progression
- Partitioning transition from PFS to progression from the transition from PFS to death
- Using age-specific, all-cause mortality adjusted for a higher risk of death for patients with progressive CLL to derive the transition from Progression to Death.

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. 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.

1.2 Summary of Results

The manufacturer's economic model has major methodological flaws. The EGP was able to correct many of these failings but due to concerns with the handling of withdrawals from the clinical trials, the EGP cannot provide a reliable best estimate of the incremental cost-utility ratio. However, the results from the reanalysis are provided for information.

The Economic Guidance Panel's estimate of the incremental cost-utility ratio based on reanalysis is $98,321 per quality-adjusted life year (QALY), when bendamustine was compared with chlorambucil as a first line monotherapy**. This estimate is based on reanalyses conducted by the Economic Guidance Panel and using the model submitted by Lundbeck Canada Inc.** The result may be biased as it does not allow for the exclusion of a high number of bendamustine treated patients from the clinical trial due to toxicity.

The incremental cost-utility ratio (ICUR) was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔQALY). The **Economic Guidance Panel's** estimate is based on:

- An extra cost (ΔC) of bendamustine of $27,467. Costs included drug costs, healthcare costs associated with routine follow-up for patients receiving active treatment, disease progression and routine health care resources involved in best supportive care. Costs associated with management of serious adverse events were also considered.
- An extra clinical effect (ΔQALY) of bendamustine of 0.28 QALYs. The biggest influence on QALYs was the estimate of extended progression free survival.

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 $27,501. Incremental costs for bendamustine are based on a model which extrapolates data from the clinical trial to estimate long term survival and progression.
- The extra clinical effect (ΔE) of bendamustine is 0.52 QALYs. This was largely driven by the assumptions relating to progression and survival and assuming a different [redacted] of patients with progression between bendamustine and chlorambucil. *(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 clinical guidance report does not support a difference in quality of life between bendamustine and chlorambucil.

So, the Submitter estimated that the incremental cost-utility ratio (ΔC / ΔE) was $52,606 per QALY.

1.3 Summary of Economic Guidance Panel Evaluation

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

The EGP is unable to provide a reliable estimate of cost effectiveness given the substantial methodological flaws within the manufacturer's submitted model.

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 ICER 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. However, the EGP does not have access to these models and it is unclear whether the models used in these analyses

may have the same methodological failings as the currently considered model especially in relation to the exclusion of patients with toxicities.

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

No. Given the concerns with the submitted analysis, the 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 the 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.

Progression free survival is modelled using a digitized Kaplan Meier curve. This method is highly unreliable. It is unclear that the analysts allowed for the differential sample size at different points along the survival curve. Furthermore, survival analysis excludes patients who experienced toxicity in the clinical study, which will clearly bias results in favour of bendamustine. In addition, the model is not properly designed as a Markov model with transition probabilities – this leads to the illogical finding of a negative probability of patients being in certain states.

There are two further failings with the technique adopted. First, the mechanism of choosing which curve to include in the analysis does not follow accepted practice. Secondly, analysts assume that the proportion of patients who die from the progressive free state are a function of the general public's mortality rates and are deductible from the proportion of patients progressing as identified by the PFS curve. This assumption is not justified.

Therefore, the model used for survival is inappropriate. To properly analyze survival data to allow extrapolation, the manufacturer must have access to the raw clinical 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.

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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 to the extent that the EGP would like. The limited reanalysis possible gave very different results than the manufacturer's estimates.

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
- 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. This requires exploration of both AIC and clinical validity.
- The progression free survival functions must be estimated properly. This requires access to the original raw data. When partitioning transition out of the progression free state, the model should have an explicit method of calculating the proportion that die versus the proportion who progress. The current method does not allow for this.
- The progression free survival functions must include data from those withdrawn from the clinical study due to toxicity.
- Analysis requires proper specification of transition probabilities.
- Survival analysis should not exclude patients with toxicities as this biases' the results in favour of bendamustine.
- Utility values in the progression-free state should be assumed the same for both treatments.

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

A revised survival analysis of the clinical data is required before any inferences from the economic model can be made. This requires analysis incorporating the 23 patients total (18 or 11.2% from the bendamustine and five or 3.3% from the chlorambucil group) who withdrew from the study due to toxicity.

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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.

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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 first line CLL. A full assessment of the clinical evidence of bendamustine (Treanda) for first line 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 Clinical 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, therefore, this information was redacted from 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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