



# pan-Canadian Oncology Drug Review Final Economic Guidance Report

## Ibrutinib (Imbruvica) for Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

March 5, 2015

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## **FUNDING**

The pan-Canadian Oncology Drug Review is funded collectively by the province 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 Janssen compared ibrutinib to a standard of care treatment mix for patients with chronic lymphocytic leukemia/small lymphocytic leukemia with or without del 17p who had received at least one prior therapy and are not considered appropriate for treatment or retreatment with purine analog. Ibrutinib is administered orally. As the comparator is a standard of care treatment mix, the administration varied.

According to the pCODR Clinical Guidance Panel (CGP), the proportion of treatments in the standard of care treatment mix is not appropriate and does not reflect clinical care across Canada. The Clinical Guidance Panel considered that rituximab plus chlorambucil may be a more clinically relevant comparator. The Submitter did include this comparison in a modification to the main economic analysis; however, only the costs of this comparator were considered and the effectiveness of this comparator was not considered. The EGP was unable to provide conclusions on the results of this analysis with the limited information. As the efficacy was based on the comparator arm of the clinical trial (ofatumumab), this may be a conservative assumption.

Patients considered the following factors important in the review of ibrutinib, which are relevant to the economic analysis: disease control, improved quality of life and decreased toxicity. These factors were incorporated into the economic model through survival, quality of life and adverse events.

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

Enablers to the implementation of ibrutinib include:

- A new class of drug that fills the gap in therapy for CLL patients; and
- Oral therapy with once daily dosing.

Key barriers to the implementation of ibrutinib include:

- Potentially large budget impact; and
- Possible use in first-line treatment or other indications.

PAG also noted the Health Canada indication for ibrutinib includes front-line treatment of patients with CLL with del(17)p. The indication states that clinical effectiveness in the front-line setting is based on the benefit observed in previously treated CLL patients with del(17)p.

Ibrutinib costs \$90.65 per tablet of 140 mg. At the recommended dose of 420 mg, the daily cost of ibrutinib is \$271.95. The cost of ibrutinib is based on a list price submitted by the manufacturer.

## 1.2 Summary of Results

The EGP's best estimate of the incremental cost-effectiveness ratio ( $\Delta C / \Delta E$ ) is between \$80,941 and \$382,134 per QALY when ibrutinib is compared with the standard of care treatment mix. This large range of ICERs provided by the EGP reflects

a large amount of uncertainty present in the incremental benefit against the standard of care treatment mix. This range is based on the most optimistic and pessimistic scenarios of the analysis submitted by the submitter as well as reanalyses by the EGP. However, within this range, the EGP best estimate would most likely be \$199,368 per QALY.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost ( $\Delta C$ ) and the extra clinical effect ( $\Delta E$ ). The EGP's best estimate of:

- the extra cost of ibrutinib is between \$117,601 and \$185,089. The main factor that influences the change in cost for the best estimate is the hazard ratio for progression-free survival. Other cost drivers in the model include the cost of ibrutinib and the standard of care treatment mix, as the cost of the standard of care treatment mix increases, the change in cost decreases.
- the extra clinical effect of ibrutinib is between 0.31 and 1.94 ( $\Delta E$ ). The main factors that influence the change in effect for the best estimate is the hazard ratio for overall survival and a shortened time horizon (from 10 years to 5 years). Other effect drivers in the model include utilities.

The EGP based these estimates on the model submitted by Janssen and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that, for the lower bound of the best estimate, when:

- The lower bound of the 95% confidence intervals for the hazard ratio for overall survival is examined, the extra cost of ibrutinib is \$149,326 ( $\Delta C_1$ ), and the extra clinical effect is 1.84 ( $\Delta E_1$ ), which decreases the estimated incremental cost-effectiveness ratio to \$80,941 (from \$124,954).
- The lower bound of the 95% confidence interval for the hazard ratio for progression-free survival is examined, the extra cost of ibrutinib is \$183,933 ( $\Delta C_2$ ), and the extra clinical effect is 1.29 ( $\Delta E_2$ ), which increases the estimated incremental cost-effectiveness ratio to \$143,138 (from \$124,954). This increase in cost is driven by the increase in progression-free survival, which increases the time on therapy, thereby increasing the cost of the drugs.
- The best case estimate of the above two parameters are examined, the extra cost of ibrutinib is \$185,089 ( $\Delta C$ ), and the extra clinical effect is 1.94 ( $\Delta E$ ), which decreases the estimated incremental cost-effectiveness ratio to \$95,257 (from \$124,954).
- The time horizon is set to 5 years (from 10 years), the extra cost of ibrutinib is \$147,741 ( $\Delta C_3$ ), and the extra clinical effect is 0.74 ( $\Delta E_3$ ), which increases the estimated incremental cost-effectiveness ratio to \$199,368 (from \$124,954). **The EGP estimates that this is the most likely point estimate of the ICER within the lower and upper range.**
- The best case estimate of the above three parameters, the extra cost of ibrutinib is \$183,495 ( $\Delta C$ ), and the extra clinical effect is 1.09 ( $\Delta E$ ), which increases the estimated incremental cost-effectiveness ratio to \$167,721 (from \$124,954).

The reanalysis conducted by the EGP using the submitted model showed that, for the upper bound of the best estimate, when

- The upper bound of the 95% confidence intervals for the hazard ratio for overall survival is examined, the extra cost of ibrutinib is \$146,701 ( $\Delta C_4$ ), and the extra

- clinical effect is 0.48 ( $\Delta E_4$ ), which increases the estimated incremental cost-effectiveness ratio to \$303,551 (from \$124,954).
- The upper bound of the 95% confidence interval for the hazard ratio for progression-free survival is examined, the extra cost of ibrutinib is \$118,889 ( $\Delta C_5$ ), and the extra clinical effect is 1.11 ( $\Delta E_5$ ), which decreases the estimated incremental cost-effectiveness ratio to \$107,452 (from \$124,954).
  - The best case estimate of the above two parameters are examined, the extra cost of ibrutinib is \$117,730 ( $\Delta C$ ), and the extra clinical effect is 0.40 ( $\Delta E$ ), which increases the estimated incremental cost-effectiveness ratio to \$291,593 (from \$124,954).
  - The time horizon is set to 5 years (from 10 years), the extra cost of ibrutinib is \$147,741 ( $\Delta C_6$ ), and the extra clinical effect is 0.74 ( $\Delta E_6$ ), which increases the estimated incremental cost-effectiveness ratio to \$199,368 (from \$124,954). **The EGP estimates that this is the most likely point estimate of the ICER within the lower and upper range.**
  - The best case estimate of the above three parameters, the extra cost of ibrutinib is \$117,601 ( $\Delta C$ ), and the extra clinical effect is 0.31 ( $\Delta E$ ), which increases the estimated incremental cost-effectiveness ratio to \$382,134 (from \$124,954).

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Janssen when ibrutinib is compared with the standard of care treatment mix:

- the extra cost of ibrutinib is \$148,364 ( $\Delta C$ ). Costs considered in the analysis included drugs, disease management, and adverse events.
- the extra clinical effect of ibrutinib is 1.19 quality-adjusted life years and 1.75 life years gained ( $\Delta E$ ). The clinical effect considered in the analysis was based on progression-free survival, overall survival, incidence of adverse events, dose intensity, and utilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio ( $\Delta C / \Delta E$ ) was \$124,954 per QALY and \$84,804 per LYG.

### 1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of  $\Delta C$ ,  $\Delta E$  and the ICER differ from the Submitter's, what are the key reasons?

The EGP wanted to examine the lower and upper bounds of the 95% confidence intervals for the hazard ratios for progression-free survival and overall survival as the data from the trial is immature. This provided a large range for the ICER. Further, the EGP wanted to examine a shortened time horizon in this relapsed/refractory setting, as the data in the economic model relied heavily on extrapolation; this further increased the range for the ICER.

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

Yes, factors that are important to patients were incorporated into the economic model. These factors were survival, quality of life and adverse events.

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

The model structure was adequate, however, a model that allows for the modification of progression-free survival would permit the ascertainment of uncertainty. The model also did not incorporate wastage or subsequent lines of therapy, which are important costs to consider when examining an economic model with a time horizon of 10 years. Further, the clinical trial data is immature, and the model relied heavily on extrapolation of this data to derive the needed inputs. Extrapolation introduces additional uncertainty. Reducing the time horizon is one way of limiting the uncertainty, by limiting the reliance on extrapolated 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?**

The largest cost drivers in the model were the hazard ratio for progression-free survival, the cost of ibrutinib and the standard of care treatment mix. The largest effect drivers in the model were the hazard ratio for overall survival, utilities for responders and time horizon. As the clinical trial data was immature, the 95% confidence intervals around the hazard ratio for overall survival were explored and were considered part of the best estimate. In order to account for the immaturity of the clinical trial data and the lack of inclusion of subsequent therapies which affect costs and effects over a long term period, a shortened time horizon of 5 years was considered as well. Further, this shortened time horizon was deemed appropriate by the CGP in the relapsed/refractory setting. Utilities were not collected in the clinical trial, and alternate plausible values were explored in modifications to the main analysis. The relative dose intensity was taken from the clinical trial and was deemed a reasonable assumption.

**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?**

For economic inputs, the majority of inputs used in the submitted economic model were similar to what the EGP would have chosen. However, the standard of care treatment mix did not reflect clinical care across Canada as per the CGP. The mix chosen in the main analysis, however, was a conservative approach in terms of costs. Choosing a costlier regimen in the comparator arm for the standard of care would decrease the ICER. For the clinical inputs, the EGP most likely would have chosen different inputs due to the immaturity of the clinical trial data and the heavy reliance on the extrapolation of this data. However, alternative clinical inputs are not available. Therefore, other than waiting for updated data, the inputs chosen are partially adequate, despite the uncertainty around them and the results from this economic model should be interpreted with caution.



## 1.4 Summary of Budget Impact Analysis Assessment

### **What factors most strongly influence the budget impact analysis estimates?**

The inputs that have the largest impact the budget impact analysis are the eligibility for public reimbursement, the cost of the drug, the number of CLL patients and the market share of ibrutinib. PAG did identify the potentially large budget impact as a concern. As noted by PAG, the greatest barriers to implementation would be the unknown number of patients to be treated, duration of treatment and high cost.

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

The submitted budget impact analysis did examine modifications to the main analysis, but as ibrutinib is but one of several new drugs entering the Canadian market for CLL, it is difficult to determine with certainty the market share and the number of CLL patients that would benefit from this therapy.

## 1.5 Future Research

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

This economic model could benefit from incorporating both wastage and use of subsequent therapies. Further, in order to reduce the uncertainty around estimates, the use of immature clinical trial data should be avoided.

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

Utilities could be collected along the disease continuum, from pre-progression to post-progression for both comparators of interest.

## 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 [Tumour Group] 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 [drug name and indication]. A full assessment of the clinical evidence of [drug name and indication] 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](http://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*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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.

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](http://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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