pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Ibrutinib (Imbruvica) for Waldenström's Macroglobulinemia

November 3, 2016

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FUNDING

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INQUIRIES

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

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: requests@cadth.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

DISCLAIMER ii
FUNDING ii
INQUIRIES iii
TABLE OF CONTENTS iv
1 ECONOMIC GUIDANCE IN BRIEF 1
1.1 Submitted Economic Evaluation 1
1.2 Clinical Considerations 2
1.3 Submitted and EGP Reanalysis Estimates 2
1.4 Evaluation of Submitted Budget Impact Analysis 5
1.5 Conclusions 5
2 DETAILED TECHNICAL REPORT 6
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 7
REFERENCES 8

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Janssen[2]** compared ibrutinib in patients with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy to a standard of care patient group derived from a chart review who received a mixture of standard treatment regimens.

Table 1. Submitted economic model[2]

Funding Request	*Matches patient population in clinical trial and economic model*
Type of Analysis	*CEA and CUA*
Type of Model	*Markov cohort*
Comparator	*Standard care represented by a mixture of treatments (identified through a review of 454 charts of European patients with WM). A smaller match adjusted cohort of 175 patients was selected from the charts reviewed and used as the comparator arm.*
Time Horizon	*20 years*
Perspective	*Government payer*
Cost of ibrutinib	*Ibrutinib costs $90.65 per 140 mg capsule* *At the recommended dose of 420 mg once daily, ibrutinib costs:* • *$271.95 per day* • *$7614.60 per 28-day course*
Cost of standard care *A standard of care treatment mix* was used as the comparator arm*	Based on a weighted average, the annual drug cost for the mix of standard of care treatments used in the economic model was $32,411
Model Structure	*A Markov model with health states defined as lines of treatments. When the WM progressed, patients transition to the next line of therapy until reaching the final state of best supportive care. See Figure 1 below.*
Key Data Sources	*Single arm clinical trial (PCYC 1118E)* *Patient chart review* *Canadian clinical expert*
*Standard of care treatment mix: R-CVP = rituximab + cyclophosphamide + vincristine + prednisone; CVP = cyclophosphamide + vincristine + prednisone; FCR = fludarabine + cyclophosphamide + rituximab; FC = fludarabine + cyclophosphamide; FR = fludarabine + rituximab; R-CHOP = rituximab + cyclophosphamide + doxorubicin +vincristine + prednisone; CHOP = cyclophosphamide + doxorubicin +vincristine + prednisone; BR = bendamustine + rituximab; Bort-R = bortezomib + rituximab; B = bendamustine; F = fludarabine; Chl = chlorambucil;	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), a comparison to a standard of care (SOC) treatment mix is appropriate, given the lack of a gold standard for patients in this setting. It should be noted that treatment practice patterns across Canada vary and the treatments and proportion of the drugs utilized as the standard of care may differ from one jurisdiction to the next, affecting the costs in the economic model.

Relevant issues identified included:

- *The key clinical data for the economic analysis came from a single arm clinical trial for the ibrutinib arm and a European patient chart review (n=454) for the comparator arm. A match adjusted cohort of 175 patients was selected from the chart review to represent the SOC treatment mix. Due to missing data in nearly 50% of charts, imputations were done to adjust for missing data.*
- *Lack of comparative safety and efficacy data in both short and long term inputs resulted in substantial uncertainty in the clinical inputs and resulting cost effectiveness estimates of ibrutinib for this patient population.*

Summary of patient input relevant to the economic analysis
Patients considered

- The physical and emotional impact of living with WM was varied. Most respondents reported that the impact of WM on their quality of life was moderate; however, there was a sizeable minority who reported that their quality of life was significantly impacted due to symptoms of WM.
- Symptoms having the most impact were tiredness/lack of energy, tingling or numbness in feet or legs, weakness, shortness of breath, joint or muscle pain, swollen lymph nodes, heavy night sweats, and frequent infections.
- Desire for new treatment that results in remission, control of disease symptoms, allows for longer survival, improves quality of life, and improves blood counts.
- Fewer side effects with ibrutinib than other therapies, significant improvement in symptom when taking ibrutinib. Top symptoms controlled by ibrutinib include weakness, tiredness or lack of energy and shortness of breath.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for ibrutinib, which are relevant to the economic analysis:

Clinical factors:

- Standard of care is intravenous chemotherapy
- New treatment option that is an oral drug

Economic factors:

- Very small number of patients relative to other cancers
- Long duration of treatment
- High cost of treatment

1.3 Submitted and EGP Reanalysis Estimates

The EGP noted a high level of uncertainty regarding the inputs for long term overall survival. The PCYC-1118 trial, after a follow up of 24 months, reported 3 deaths. In the absence of data to model long term OS, the Submitter has assumed that, in the pre-progression state where the majority of benefit is accrued, patients who receive ibrutinib have the same mortality risk as patients in the general population (after adjusting for age), which the CGP and EGP feel is a very strong assumption that is not justifiable. The CGP indicated that this is an unrealistic assumption as those with WM are likely to have increased mortality compared to the general population, and especially patients who have progressed on two lines of treatment. In the absence of

alternative data source for long term OS and lack of input within the model to directly alter this variable, the EGP was unable to explore this uncertainty in a re-analysis. Therefore the EGP was unable to provide a best estimate and only provided one way sensitivity analyses to demonstrate the impact of individual parameters on the ICER.

The main assumptions and limitations with the submitted economic evaluation were:

- Source of data: Source of data for ibrutinib was from a single arm clinical trial *(PCYC 1118E)*; source of data for the standard of care was from a chart review, where more than 50% of the data were missing.
- Mortality: Since there were only three deaths observed during the trial in the progression-free state, the age-adjusted life table of the Ontario general population was used as a proxy for the mortality risk of ibrutinib patients. Essentially, this assumes that patients at this stage of disease have the same mortality risk as a healthy population during the progression-free state. The CGP indicated that this very likely underestimates the mortality risk of a patient population with WM, who have failed at least one line of therapy (as is the case in the economic model).
- Time Horizon: The submitted funding request for ibrutinib is for those who have failed at least one prior line of therapy. Within the PCYC-1118 trial, patients had failed a median of two lines of therapies. In the submitted economic model, these patients can receive up to three more lines of therapy plus best supportive care, over a time horizon of 20 years. The CGP indicated that this time horizon is not clinically justifiable given the poor prognosis of patients with progressed WM. Patients in both the ibrutinib group and the standard of care group were modeled to receive the same subsequent treatments with same associated costs and effectiveness inputs in the post-progression state. The EGP was therefore concerned that the longer the time horizon, the cost effectiveness profile of ibrutinib appears to be more favourable for ibrutinib as the cost is ammortized over a long time.
- Utilities were not derived from a population with WM but from patients with CLL and may not truly reflect the WM population that has previously failed at least one line of therapy. In the absence of an alternative data source and to explore the impact of change in the utilities, the EGP examined a 50% reduction in utilities as suggested by the CGP.

Table 2. Submitted and EGP Reanalysis Estimates

Estimates (range/point)	Submitted	EGP Reanalysis
ICER estimate ($/QALY)	$140,106	*Unknown*
ΔE (QALY)	2.02	-
Progression-free	1.50	-
Post-progression	0.52	-
ΔE (LY)	2.63	*Unknown*
Progression-free	1.87	-
Post-progression	0.75	-
ΔC ($)	$283,515	*Unknown*

In the absence of alternative data source for long term OS and inability to directly alter risk of mortality in the model, the EGP was unable to explore this uncertainty in the re-analysis. Therefore the EGP provided one way sensitivity analysis to demonstrate the impact of individual parameters on the ICER and was unable to provide a best estimate.

EGP Reanalysis

The EGP conducted the following one way sensitivity analysis:

- **Time horizon**: Based on feedback from the CGP, and given that the patient population modeled consists of patients with WM who have already progressed on a median of two lines of therapy, a time horizon of 5 years was felt to be more appropriate and reflective of what is seen in clinical practice. Further, a 5-year time horizon would address some of the uncertainty around extrapolation of the short trial follow-up.
- **Mortality risk of ibrutinib**: Due to the lack of long term data, there is a high degree of uncertainty in the survival estimates of patients who receive ibrutinib. While the submitter used the mortality risk of the general Ontario population to approximate that of patients with WM who received ibrutinib, the CGP agreed that the mortality risk of patients on ibrutinib would not be similar to the general age-adjusted Ontario population and it very likely underestimates the mortality risk of a patient population with WM, who have failed at least one line of therapy. As an example, studies using ibrutinib in other indications (relapsed/refractory chronic lymphocytic leukemia/small lymphocytic leukemia), demonstrate a mortality risk of 57% (HR for OS, 0.43)[3]. In the absence of direct and/or comparative data to reasonably estimate the long term survival of patients treated with ibrutinib, the EGP was unable to provide a re-analysis estimate exploring this uncertainty. Additionally, despite the considerable uncertainty in the estimates of long term OS, an input was not available in the model to explore the impact of changing the risk of mortality on the ICER. The EGP was able to provide one way sensitivity analysis in Table 3 by making structural changes to the model by making incremental changes to the risk of mortality with ibrutinib relative to the SOC group. Therefore a risk of mortality that is 10%, 25%, 50% and 75% relative to the risk of mortality of SOC was presented to demonstrate the impact of this input on the ICER. The EGP acknowledges that there are limitations in exploring the impact that relative changes of the mortality risk of ibrutinib compared with SOC have on the ICER due to the structural design of the submitted model. However, the EGP noted that this approach was the best available method for the panel to demonstrate the impact of changes in the mortality risk. Therefore the EGP felt that this approach should be considered a sensitivity analysis and that due to limitations of the available data and in the submitted model, the EGP could not provide a range of reanalysis estimates The EGP noted that a model that had functionality to explore different values for the relative mortality risk of ibrutinib compared with SOC would have allowed the EGP to better explore the impact that the uncertainty in the mortality risk of ibrutinib compared with SOC has on the ICER. Despite this limitation, there is a high degree of uncertainty in the survival of patients who receive ibrutinib compared with SOC, and changes to the model structure will not overcome this.
- **Utilities:** The utility inputs used in the economic model were not derived from WM patients. The CGP indicated that the utilities used in the economic model could be high for a population of patients with WM who have failed at a median of two prior lines of therapy. As the utility data was not derived from a population of WM patients, the EGP reduced the all utilities in the submitter's model by 10% for the upper bound estimate.

Table 3. One-way Sensitivity Analysis of Key Model Inputs

Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
Submitted base case	**$283,215**	**2.02**	**$140,106**	----
Time horizon - 5 years	$230,872	1.03	$224,809	$84,703
Utility reduction 10%	$283,315	1.82	$155,676	$15,570
Mortality risk of ibrutinib (10% of that of SOC)	$281,325	1.90	$148,045	$7,939
Mortality risk of ibrutinib (25% of that of SOC)	$275,682	1.55	$177,468	$37,362
Mortality risk of ibrutinib (50% of that of SOC)	$266,277	0.98	$273,013	$132,907
Mortality risk of ibrutinib (75% of that of SOC)	$259,376	0.55	$470,459	$330,353

1.4 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include prevalence of WM in Canada and the market share in the projected three-year time frame.

Key limitations of the BIA model include the estimates of prevalent WM cases and projected market shares of ibrutinib. These parameters were able to be modified and explored by the EGP.

1.5 Conclusions

Due to the considerable uncertainty in the long term survival data, lack of comparative efficacy results and inability to alter the risk of mortality for ibrutinib, the EGP was unable to provide a re-analysis estimate. However, the EGP agreed that a lower bound of the ICER range would be higher than the Submitter's base case. Furtheremore, a one way sensitivity analyses that made alterations to the time horizon to align with the expected clinical outcome of patients demonstrated that just reducing the time horizon alone (5 years from 20 years in the base case), produced a ΔC of $230,872 and a ΔE of 1.03 QALY, resulting in an ICER of $224,809/QALY, an increase of $84,703/QALY from the base case results.

- The EGP noted that it is difficult to estimate the ICER as long term survival data are not available and it is unlikely the mortality risk of patients who receive ibrutinib will be similar to an age adjusted Ontario population.
- Given the absence of comparative data, there is considerable uncertainty in the efficacy and safety inputs used for on the comparative efficacy of ibrutinib in relation to the standard of care.

Overall conclusions of the submitted model:

- The submitted model is limited by the lack of both a direct and an indirect comparison to SOC to evaluate the comparative efficacy of ibrutinib.
- There is considerable uncertainty in the cost-effectiveness of ibrutinib compared to the standard of care, due to uncertainty around the benefits in survival provided by ibrutinib. There is a lack of high quality comparative evidence to inform this uncertainty, therefore any estimate of the ICER would be based on clinical assumptions of the relative benefit of ibrutinib compared with SOC. While a model with functionality to explore the uncertainty in the relative survival of ibrutinib compared with SOC would have been preferable, such a model would not have overcome the limitations of the available clinical data and the need to make assumptions that would only be verifiable with additional clinical data.

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 ibrutinib (Imbruvica) for Waldenström's macroglobulinemia 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.cadth.ca/pcodr).

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. 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.cadth.ca/pcodr). 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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