pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Ibrutinib (Imbruvica) for Mantle Cell Lymphoma

July 19, 2016

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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 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Janssen Inc. compared ibrutinib to a standard of care treatment mix for patients with relapsed or refractory mantle cell lymphoma (MCL). Ibrutinib is administered orally. As the comparator is a standard of care treatment mix where the administration varied. Table 1.1 summarizes the submitted economic model.

Table 1.1 Submitted Economic Model	
Funding Request/Patient Population Modelled	Patients with relapsed or refractory MCL
Type of Analysis	Cost Utility Analysis and Cost Effectiveness Analysis
Type of Model	Partitioned-survival model
Comparator	Standard of care treatment mix (SOC)
Year of costs	2015 Canadian dollars (CAD)
Time Horizon	10 year time horizon
Perspective	Perspective of the Canadian publicly funded healthcare system using Ontario as a reference

Cost of Ibrutinib^	• $90.65 Per Capsule (140 mg)
	• At the recommended dose of 560 mg daily, ibrutinib costs
	  • $362.60 per day
	  • $9,776 per 28-day course
	  • $127,526.14 per Year

Cost of Temsirolimus*	• $1,278.91 per 1.2mL vial
	• Temsirolimus is not funded in any province and not used in Canada for MCL, the dose per trial is 175 mg on Days 1, 8, and 15 of the first cycle; and 75 mg on Days 1, 8, and 15 of each subsequent 21 day cycle, at this dose temsirolimus costs
	  • $609.00 per day
	  • $17,052.1333 per 28-day course

Cost of Standard care mix*	• Bendamustine costs $1,250.00 per 100 mg vial • Rituximab costs $45.72 per 10 mg • Cyclophosphamide costs $52.06 per 1000 mg vial • Vincristine costs 31.00 per mg • Doxorubicin costs $5.60 per mg • Prednisone costs $9.19 per 50 mg tablet • Gemcitabine costs $308.35 per 1000 mg vial • Dexamethasone costs $0.30 per 4 mg tablet • Cisplatin costs $4.45 per mg • Fludarabine costs $255 per 50 mg vial • Mitoxantrone costs $54.81 per 2 mg Bendamustine-Rituximab • Bendamustine dosed at 90mg/m^2 on days 1 & 2, every 28 days and rituximab dosed at 375mg/m^2 on day 1, every 28 day; bendamustine-rituximab costs: ○ $240.61 per day

Table 1.1 Submitted Economic Model	
	○ $6,739.53 per 29-day course R-CHOP • Rituximab dosed at 375mg/m^2 on Day 1, every 21 days; cyclophosphamide dosed at 750mg/m^2 on Day 1, every 21 days; vincristine dosed at 1.4mg/m^2 on Day 1, every 21 days; doxorubicin dosed at 50mg/m2 on Day 1, every 21 days; and prednisone dosed at 100mg daily on Days 1-5, every 21 days; R-CHOP costs: ○ $168.23 per day ○ $4,710.54 per 28-day course R-CVP • Rituximab dosed at 375mg/m^2 on Day 1, every 21 days; cyclophosphamide dosed at 750mg/m^2 on Day 1, every 21 days; vincristine dosed at 1.4mg/m^2 on Day 1, every 21 days; and prednisone dosed at 100mg daily on Days 1-5, every 21 days; R-CVP costs: ○ $145.05 per day ○ $4,061.39 per 28-day course R-GDP • Rituximab dosed at 375mg/m^2 on Day 1, every 21 days; gemcitabine dosed at 1000mg/m2 on Days 1, 8, every 21 days; dexamethasone dosed at 40mg on Days 1 to 4, every 21 days; and cisplatin dosed at 75mg/m^2 on Day 1, every 21 days, R-GDP costs: ○ $241.29 per day ○ $6,756.07 per 28-day course FR • Fludarabine dosed at 25mg/m^2 on Days 1 - 3, every 28 days and rituximab dosed at 375mg/m^2 on day 1, every 28 days, FR costs: ○ $127.31 per day ○ $3,564.78 per 28-day course FC • Fludarabine dosed at 25mg/m^2 on Days 1 - 3, every 28 days and cyclophosphamide dosed at 750mg/m^2 on Day 1, every 21 days, FC costs: ○ $25.59 per day ○ $716.63 per 28-day course FCM • Fludarabine dosed at 25mg/m^2 on Days 1 - 3, every 28 days and cyclophosphamide dosed at 750mg/m^2 on Day 1, every 21 days; and mitoxantrone dosed at 6mg/m^2 on Day 1, every 28 days, FCM costs: ○ $35.58 per day ○ $996.18 per 28-day course
Model Structure	• A partitioned survival approach with a state transition model was developed in 2007 Microsoft Excel. • The model was comprised of three health states: Pre-progression; Post-progression; and Death. • PFS and OS curves were used to inform the transitions between model health states.

Table 1.1 Submitted Economic Model	
Key Data Sources	<u>Efficacy data from trials</u> • MCL-3001[1] • OPTIMAL[2] ITC used to link results between the MCL-3001 (ibrutinib versus temsirolimus) and OPTIMAL (temsirolimus versus investigator's choice) trials <u>Cost data</u> Drug costs from ODB Drug admininstration cost from a published Canadian study AE costs from expert opinion <u>Utility</u> Baseline utility from MCL-3001 trial[1] increment / decrement % are from public literature[3-5] and adjusted to MCL-3001 trial
^ *Cost based on the current list price in the Ontario Exceptional Access Program (Ontario Ministry of Health and Long-term Care, 2015). Mark-up and dispensing fees have not been included.* ***Drug costs for the comparator in this table are based on costing information obtained under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the effectiveness of ibrutinib for relapsed or refractory (R/R) mantle cell lymphoma (MCL) was established in the randomized phase III clinical trial comparing ibrutinib to temsirolimus (MCL-3001 trial[1]), which was chosen as a reasonable comparator based on a lack of a well-defined treatment for relapsed MCL and prior demonstration that temsirolimus induced better control of MCL than investigator's choice in an earlier clinical trial (OPTIMAL trial[2]). As temsirolimus is not approved to treat R/R MCL in Canada, the submitter did not include this comparison in the main economic analysis. Instead, the submitter conducted an indirect treatment comparison using an indirect treatment comparison to compare the standard of care treatment mix (SOC) with ibrutinib indirectly.

- Relevant issues identified included:
  - *The make-up of the treatment mix used in the economic analysis is different than the mix of treatments that was reported in the OPTIMAL trial. The CGP noted the proportion of included comparators such as bendamustine-rituximab (BR) may be too high and not reflective of Canadian clinical practice. Otherwise, the mix of treatments was appropriate.*

Summary of patient input relevant to the economic analysis

Two patient advocacy groups provided input on ibrutinib for the treatment of patients with R/R MCL. Most of the patients agreed that ibrutinib improved their quality of life compared to previous therapies that they have used. More than 50% of patients reported that ibrutinib manages or managed MCL symptoms better than previous therapies in the areas of loss of

appetite, weight loss, and fatigue. Patients also noted that ibrutinib brought their disease under control and made them feel better again.

The submitted economic model did consider factors that were important and relevant to patients: quality of life and adverse events.

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

Enablers to implement of ibrutinib include:

- New treatment option that is an oral drug.

Key barriers to implement of ibrutinib include:

- Small number of patients relative to other cancers but potentially large number of prevalent patients;
- Unknown treatment duration and number of patients eligible for treatment;
- High cost of ibrutinib.

These factors relevant to PAG were considered in the economic analysis.

1.3 Submitted and EGP Reanalysis Estimates

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

- The extra cost of ibrutinib is $173,687 (ΔC). Costs considered in the analysis included drugs, disease management, and adverse events.
- The extra clinical effect of ibrutinib is 0.86 quality-adjusted life years and 1.10 life years gained (ΔE). The clinical effect considered in the analysis was based on progression-free survival, overall survival, incidence of adverse events, and utilities.

The submitter estimated that the incremental cost-effectiveness ratio was $201,671 per QALY.

The submitter also provided another approach (using the efficacy of temsirolimus as a proxy for the efficacy of SOC, instead of efficacy for SOC using the indirect comparison). With this approach, the submitter estimated that the incremental cost-effectiveness ratio was $173,165 per QALY. The EGP considered both approaches and determined that the indirect comparison approach provide a more reasonable comparison in the Canadian context.

The EGP used the economic model submitted by Janssen Inc. and performed reanalyses. Detailed highlights of the EGP Reanalysis is provided in Section 1.4. The EGP estimates differed from the submitted estimates. A comparison between the submitted model and the EGP reanalysis results is provided in Table 1.3.

Table 1.3. Submitted and EGP Estimates		
Estimates	Submitted	EGP Reanalysis
ICER estimate ($/QALY), range/point	$201,671	$264,142
ΔE (QALY), range/point	0.86	0.646
ΔE (LY), range/point	1.10	0.730
ΔC ($), range/point	$173,687	$170,716

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

- ***Standard of care treatment mix (comparators and proportion of patients treated with each comparator):*** The efficacy data calculated from the ITC is based on a different set of treatment mix than what was used in the economic evaluation submitted. The economic evaluation treatment mix was based on clinical expert opinion. The CGP noted the proportion of included comparators such as bendamustine-rituximab (BR) may be too high and not reflective of Canadian clinical practice. As the proportion of BR decreases in the SOC, the ICER increases.
- ***Wastage not included:*** Wastage could be an issue for some of the treatments in the standard of care arm. Ibrutinib, as an orally administered drug, has very minimal risk of wastage even though it is expensive. Including the cost of wastage of treatments in the standard of care arm would decrease the ICER.
- ***Disease management cost:*** Not included in the model, the CGP noted that ibrutinib may involve higher monitoring cost than SOC. The impact on the ICER was uncertain.
- ***Subsequent therapies:*** Not included in the model, the rate at which patients would incur costs from subsequent lines of therapy may differ, and would impact results but not significantly. The impact on the ICER was uncertain.
- ***Treatment duration not modeled separately:*** treatment duration was modelled using either the extrapolated PFS curve or time to treatment discontinuation curve. There is a possibility that patients will be on ibrutinib for longer than what was modelled. The impact on the ICER was uncertain.
- ***Post-progression survival:*** based on extrapolation of data (42.5% of QALY gain was based on this assumption). The impact on ICER was uncertain.
- ***Adverse Events cost for SOC:*** Estimated based on clinical expert opinion. Increasing the cost of AE in the standard of care arm would decrease the ICER.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

The EGP re-conducted several one-way sensitivity analyses. The EGP considered the following important factors after consulting with the CGP:

- **SOC mixture (*proportion of patients treated with each comparator)***: The CGP identified that the proportion of patients treated with standard of care treated with BR (30%) was quite high and that 10-20% may be more reasonable.
- **Time horizon:** The CGP identified the 10 year time horizon was high for the R/R MCL setting where median survival is around 2 or 3 years. A 5 year time horizon was considered more appropriate.
- **Survival hazard ratios:** 95% Cr.I. for the HR for OS (ibrutinib vs. SOC) was not statistically significant which may indicate there is no survival benefit for ibrutinib.

- **Response rate of SOC:** The CGP identified the 2% response rate for SOC is very low and suggested a response rate of 40%.

A range for the ICER with a lower and upper bound is provided in Table 1.4, the EGP also reran the probabilistic sensitivity analysis to determine the estimated point estimate of the ICER for the following scenario:

- Time horizon of 5 years
- 10% distribution for BR
- 40% response rate for SOC
- 95% Cr.I. of the HR for OS (ibrutinib vs. SOC), with the maximum HR assumed to be 1
- Keeping all other parameters in the economic model as set by the submitter

Based on 10,000 iterations, the estimated point estimate of the ICER is $264,142/QALY.

Table 1.4 EGP Reanalysis

Description of Reanalysis	Change to cost/effect inputs	ΔC	ΔE (LYs)	ΔE (QALYs)	ICER	Δ from baseline submitted ICER
Baseline		$173,687	1.10	0.86	$201,671	--
Lower bound						
Response rate for SOC - 2%	--	$173,687	1.10	0.86	$201,671	--
Time horizon - 10 years	Time horizon - 5 years	$166,532	0.68	0.63	$265,861	$64,190
SOC Comparator Proportion - BR 30%	SOC Comparator Proportion - BR 20%. Average SOC Treatment cost changed from $17,117 to $15,052.	$175,736	1.10	0.86	$204,051	$2,380
Hazard Ratio for OS - 0.61	Lower 95% Cr.I. of HR for OS - 0.34	$171,830	2.02	1.36	$126,547	-$75,124
Hazard Ratio for PFS - 0.19	Lower 95% Cr.I. of HR for PFS - 0.10	$177,847	1.10	0.89	$200,863	-$808
Upper bound						
Response rate for SOC - 2%	Response rate for SOC - 40%	$173,687	1.10	0.85	$203,738	$2,067
Time horizon - 10 years	Time horizon - 3 years	$147,395	0.40	0.45	$330,776	$129,105
SOC Comparator Proportion - BR 30%	SOC Comparator Proportion - BR 10%. Average SOC Treatment cost changed from	$177,829	1.10	0.86	$206,481	$4,810

Description of Reanalysis	Change to cost/effect inputs	ΔC	ΔE (LYs)	ΔE (QALYs)	ICER	Δ from baseline submitted ICER
	$17,117 to $12,944.					
Hazard Ratio for OS - 0.61	Hazard Ratio for OS - 1.00	$176,889	0.00	0.27	$650,508	$448,837
Hazard Ratio for PFS - 0.19	Upper 95% Cr.I. of HR for PFS - 0.36	$170,172	1.10	0.82	$208,147	$6,476

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include drug cost, prevalence of MCL, patient adherence, duration of therapy, and market share. The CGP noted that a potentially large number of patients with R/R MCL may be waiting for treatment, which would have a potentially large budget impact.

Key limitations of the BIA model include the way in which the prevalence of MCL was estimated, duration of therapy, and market share. It is difficult to determine with certainty the prevalence of MCL, duration of therapy, and market share at this point in time. However, these parameters were able to be modified in the submitted BIA and explored by the EGP.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for ibrutinib when compared to standard of care treatment mix is:

- Lower bound ΔC = $165,930
- Upper bound ΔC = $175,384
- Lower bound ΔE = 0.256 QALY
- Upper bound ΔE = 1.554 QALY
    - Which produced an ICER between $106,774/QALY and $686,165/QALY

- 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.
- Within this range, the best estimate would likely be:
    - ΔC = $170,716
    - ΔE = 0.646 QALY
    - ΔC/ΔE = $264,142/QALY

- The extra cost of ibrutinib is between $165,930 and $175,384. The main factor that influences the ΔC is the HR for PFS. Other cost drivers in the model include the cost of ibrutinib and SOC, as the cost of the SOC mix increases, the ΔC decreases.

- The extra clinical effect of ibrutinib is between 0.256 QALY and 1.554 QALY. The main factor that influences the ΔE is the 95% Cr.I. of HR for OS (ibrutinib vs. SOC) as

the OS results were not statistically significant (the CI crossed 1.0); and a shortened time horizon (from 10 years to 5 years). Other minor effect drivers in the model include utilities.

Overall conclusions of the submitted model:

- **Model Structure**
  - The economic model provided is adequate, however, the model did not consider inputs such as wastage, disease management costs, and subsequent therapies.
- **Data Inputs**
  - The make-up of the standard of care treatment mix used in the economic model is different from the investigator choice treatment mix in the OPTIMAL trial. The make-up of the treatment mix used in the economic analysis is different than the mix of treatments that was reported in the OPTIMAL trial. The CGP noted the proportion of included comparators such as bendamustine-rituximab (BR) may be too high and not reflective of Canadian clinical practice. Otherwise, the mix of treatments was appropriate.
- **Patient Input**
  - The factors relevant to patients were taken into consideration in the economic model.
- **Overall**
  - Overall, the model is adequate, however, there is some degree of uncertainty present. For example, there exists uncertainty in the HR for OS; and the choice of time horizon due to extrapolation of OS and PFS data beyond the trial follow-up period.

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 Lymphoma & Myeloma 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 relapsed or refractory mantle cell lymphoma. A full assessment of the clinical evidence of ibrutinib (Imbruvica) for relapsed or refractory mantle cell lymphoma 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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