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PAN-CANADIAN  
ONCOLOGY DRUG REVIEW

## pan-Canadian Oncology Drug Review Final Economic Guidance Report

### Venetoclax (Venclexta) for Chronic Lymphocytic Leukemia

March 2, 2018

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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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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 <i>pCODR Disclosure of Information Guidelines</i> , this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.	
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# 1 ECONOMIC GUIDANCE IN BRIEF

## 1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by AbbVie compared venetoclax monotherapy to rituximab monotherapy or rituximab plus high-dose methyl-prednisolone for patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-cell Receptor Inhibitor (BCRi). The model addresses the cost-effectiveness of venetoclax in patients with del(17p), which contains the TP53 tumor suppressor (TP53), who are unsuitable or have failed a BCRi and secondly, those who are non-del(17p)/TP53, and have received at least one prior therapy and have failed a BCRi.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	The funding request is in alignment with the patient population modeled.
Type of Analysis	<i>CUA &amp; CEA</i>
Type of Model	<i>Partitioned-survival</i>
Intervention	<i>Venetoclax, once daily, using five-week dose ramp up protocol</i>
Comparator	<i>Standard of care: Rituximab monotherapy (50%) Rituximab plus high-dose methylprednisolone (50%).</i>  <i>Note that the submitter stated that idelalisib and ibrutinib were not included as comparators due to the lack of comparative data in the appropriate population.</i>
Year of costs	2017
Time Horizon	<i>5 years</i>
Perspective	<i>Government</i>
Cost of venetoclax	Venetoclax costs \$6.80 per 10 mg, \$33.99 per 50 mg and \$67.99 per 100mg  The recommended ramp up dose for venetoclax includes: <ul style="list-style-type: none"> <li>• Week 1: 2 x 10 mg daily</li> <li>• Week 2: 1 x 50 mg daily</li> <li>• Week 3: 1 x 100 mg daily</li> <li>• Week 4: 2 x 100 mg daily</li> </ul> All subsequent doses are: <ul style="list-style-type: none"> <li>• Week 5 &amp; onward: 4 x 100 mg daily</li> </ul> At the recommended ramp-up and subsequent doses, venetoclax costs: <ul style="list-style-type: none"> <li>• \$62.89 per day and \$1,760.88 per 28-day course for first cycle (ramp up)</li> <li>• \$271.95 per day and \$7,614.60 per 28-day course for subsequent cycles</li> </ul>
Cost of high dose methylprednisone <i>* Price Source: IMS Brogan accessed October 31, 2017</i>	Methylprednisone costs 0.0722 per mg. At the recommended dose of 1g/m <sup>2</sup> daily for 5 consecutive days every 21 days x 6 cycles, methylprednisone costs: <ul style="list-style-type: none"> <li>• \$5.85 per day</li> </ul>

	<ul style="list-style-type: none"> <li>• \$163.65 per 28-day course</li> </ul>
<p>Cost of rituximab</p> <p>* Price Source: IMS Brogan accessed October 31, 2017</p>	<p>Rituximab costs 4.71 per mg.</p> <p>When used as combination therapy and at the recommended dose of 375mg/m<sup>2</sup> on day 1 of cycle 1; 500mg/m<sup>2</sup> on day 1 and 5 of cycle 2 and 3; then 500mg/m<sup>2</sup> on day 1 cycles 3 to 6, every 21 days, rituximab costs:</p> <ul style="list-style-type: none"> <li>• \$190.45 per day</li> <li>• \$5332.54 per 28-day cycle</li> </ul> <p>When used as a single agent and at the recommended dose of 375mg/m<sup>2</sup> on day 1 of cycle 1; 500mg/m<sup>2</sup> on day 1 cycles 2 to 7, every 28 days x 6 cycles, rituximab costs:</p> <ul style="list-style-type: none"> <li>• \$142.84 per day</li> <li>• \$3999.40 per 28 day cycle</li> </ul>
Model Structure	<i>A partitioned survival model was constructed in Excel to simulate the disease pathway for BCRI-F CLL patients undergoing treatment with venetoclax or standard of care. Extrapolation techniques were used taking data from relevant clinical trials. Health states included were progression free, progressed and dead.</i>
Key Data Sources	<i>M14-032 clinical trial<sup>6</sup>: an open-label, non-randomized, phase 2 study NICE TA359<sup>1</sup>: idelalisib: used for data for comparator arm (rituximab monotherapy)</i>
<p><i>* Drug costs for all comparators in this table are based on costing information 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. Quintile IMS DeltaPA- accessed on October 31, 2017 All calculations are based on = 70kg and BSA = 1.7m<sup>2</sup></i></p>	

## 1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate.

Relevant issues identified included:

- The current data establishes venetoclax as the most effective agent yet discovered for the treatment of patients in this setting and demonstrates that venetoclax provides better disease control than any currently available chemotherapy or immunotherapy, including possible use of alternative BCRI treatments.
- These results have been achieved in a population that currently has no well-defined treatment options and an expected median overall survival of less than 6 to 12 months. An effective, well-tolerated agent can be expected to have a major health impact in this population.
- Although not demonstrated in the trial, the CGP feels it reasonable to expect that at least a 1-2 year OS benefit is likely to be observed. This is based on clinical opinion.
- Based on clinical opinion and results from the Mato et al 2017 data, the CGP agree that patients who are intolerant to a BCRI should qualify for venetoclax treatment. The CGP agree that a substantial portion of the patients who switch from a BCRI to venetoclax will do so because of BCRI intolerance; however, such patients will have an even higher response rate and longer durability of response than those patients who make the switch because of disease progression. That is both clinical opinion and what was seen in the Mato studies.

### Summary of registered clinician input relevant to the economic analysis

- Registered clinicians considered the availability of venetoclax as an additional effective therapy for this patient population.
- Registered clinicians noted that the risk of tumour lysis syndrome (TLS) is increased, and those on venetoclax should be monitored at tertiary care centres or by an experienced hematologist.
- Acknowledging that CLL is a common hematological malignancy, the clinicians noted that the proportion of patients who have failed a TKI, and have exhausted all other treatment options, is currently small. Also, not all patients receiving TKIs would qualify for venetoclax in their lifetime as a number of patients succumb to their disease in the interim.
- It was also noted that there was considerably higher response rates after TKI failure when compared with alternate TKIs. For example responses to venetoclax after ibrutinib failure are higher than responses to idelalisib in patients who have failed on ibrutinib.

### Summary of patient input relevant to the economic analysis

Patients considered increased effectiveness and decreased toxicity as important factors for additional choices in therapy. These factors were incorporated into the economic model.

### Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

PAG considered the following factors important to consider if implementing a funding recommendation for venetoclax which are relevant to the economic analysis:

- There would be a potentially large budget impact given the prevalent number of patients with relapsed/refractory CLL who have received at least one prior therapy.
- PAG noted that the high incidence of neutropenia requiring supportive therapy would be additional costs associated with venetoclax therapy. Additional health care resources for monitoring of tumour lysis syndrome and the high incidence of neutropenia. PAG noted that venetoclax may need to be restricted to dispensing from pharmacies in cancer centres with the expertise and resources to monitor and treat the severe adverse effects associated with venetoclax.
- Cost of venetoclax treatment is a barrier.
- Venetoclax may need to be restricted to dispensing from pharmacies in cancer centres with the expertise and resources to monitor and treat the severe adverse effects associated with venetoclax.

## 1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
$\Delta E$ (LY)	1.885	3.375	-0.074
Progression-free	1.548	3.309	0.469
Post-progression	0.337	0.066	-0.543
$\Delta E$ (QALY)	1.486	2.585	0.047
Progression-free	1.279	2.563	0.373
Post-progression	0.212	0.026	-0.321
$\Delta C$ (\$)	\$184,319	\$359,461	\$69,893
ICER estimate (\$/QALY)	\$124,050	\$139,074	\$1,474,649

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

- *Given that the M14-032 trial was non-comparative, data for the comparator arm was taken from published survival curves from NICE submissions for idelalisib in the relapsed/refractory CLL setting. Covariance was not reported in the NICE submission and precluded the ability to explore uncertainty. It was not possible to use patient-level data from the clinical trial as this was not adjusted for crossover.*
- *Though the comparator of choice in the economic model are not potential treatment options, according to the CGP, there is no standard of care that would be effective in this patient population.*
- *Median overall survival data has not been reached in the trial, as there have been only 14 overall survival events recorded at the 240-day data cut off.*
- *Treatment duration data is based on the progression-free survival curve in the trial, where nearly 74% of patients have not progressed. The EGP was unable to modify treatment duration in the economic model.*

#### 1.4 Detailed Highlights of the EGP Reanalysis

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

- **Source of utilities:** To reflect consistency with other CLL reviews for similar indications, which used utility values lower than what is used in the current base case analysis, the EGP elected to use lower estimates for utilities based on the Dretzke et al., data. The CGP concurred that this would be more reflective of clinical reality where patients at this stage of disease would have lower utilities than what is modeled in the base case.
- **Survival estimates:** Given that the clinical inputs are not based on a comparative trial, and the available evidence from M14-032 trial is immature (not all progression events were reported and median OS was not reached), the EGP and CGP agreed that there is uncertainty in the estimates for comparative effectiveness. Further, the data in the economic model is based on a data cut-off of 240 days from the trial and is extrapolated to 5 years. In the absence of alternative inputs for these data to help explore this uncertainty, the EGP explored the lower and upper bounds of the 95% confidence intervals as part of the EGP's best estimate for venetoclax. Though the CGP agreed that venetoclax is expected to provide an OS benefit, the magnitude of benefit is unclear. The CGP agreed that it would not be as not as high as what is captured by the lower bound of the 95%CI nor as low as the upper bound of the 95%CI. Based on the CGP input the anticipated benefit is likely somewhere in the middle.
- **Treatment duration:** Treatment duration in the economic model was based on the progression-free survival curve in the trial. Though the intended treatment of venetoclax is to treat until progression, in the absence of data on the median PFS there is uncertainty on the duration of treatment. Estimates for 12 month PFS indicate nearly 74% of patients have not progressed. The model time on treatment was predicted to be 25.1 months, and the EGP was unable to modify this parameter without modifying PFS and the resulting impact on survival. As PFS is a proxy for treatment duration, any exploration of uncertainty regarding PFS explores uncertainty related to treatment duration. The lower 95% CI of PFS (i.e. better survival for venetoclax) increases the time on therapy for venetoclax, increase the incremental cost, and QALYs, and increasing the ICER. The upper 95% CI of PFS (i.e. worse survival for venetoclax), results in lower costs as patients are on venetoclax for less time (progressing faster), and though the QALYs are also less, the resulting ICER is lower.



Following the posting of the pERC initial recommendation, the submitter provided feedback regarding the EGP's use of the 'lower' and 'upper' bound of the 95% CI for OS and PFS to present a deterministic reanalysis. The submitter felt this method to be inappropriate given current CADTH guidelines which specify the use of a probabilistic analysis to assess parameter uncertainty.

In response to this feedback, the EGP concur that under most circumstances “uncertainty about the true value of parameters included in the economic evaluation (inputs) should be expressed using probability distributions.” (CADTH Guidelines) In the current review, however, the EGP note that the PSA simulations provided in the submitted model do not appear to fully capture the uncertainty in the estimated PF and OS survival curve parameters. Furthermore, the lack of robust comparative data and long term follow-up (are sources of uncertainty that are not directly quantifiable in the submitted model, given the available data) provides limited data with which to measure and estimate the uncertainty in the model. The EGP recognizes the chosen method to present a re-analysis is not ideal, but in order to attempt to capture the uncertainty in the available data (captured within the lower and upper bound of the 95% CI's) as well as the uncertainty from the non-comparative nature of the available data, presenting a series of scenario analyses around the 95% confidence intervals was the best alternative with the submitted model.

**Table 3. Detailed Description of EGP Reanalysis**

	$\Delta C$	$\Delta E$ QALYs	ICUR (QALY)	$\Delta$ from baseline submitted ICER
<b>Base case results</b>	\$184,319	1.486	\$124,050	-----
<b>EGP's Reanalysis for the Best Case Estimate - Lower Bound</b>				
<i>Source of utilities - Dretzke et al.</i>	\$184,319	1.40	\$132,061	\$8,011
<i>Progression-free survival - venetoclax, lower 95% CI</i>	\$286,139	1.65	\$173,075	\$49,025
<i>Overall survival - venetoclax, lower 95% CI</i>	\$192,043	2.45	\$78,352	-\$45,698
<b>Best case estimate - lower bound</b>	\$359,461	2.585	\$139,074	\$15,024
<b>EGP's Reanalysis for the Best Case Estimate - Upper Bound</b>				
<i>Source of utilities - Dretzke et al.</i>	\$184,319	1.40	\$132,061	\$8,011
<i>Progression-free survival - venetoclax, upper 95% CI</i>	\$80,427	1.32	\$61,162	-\$62,888
<i>Overall survival - venetoclax, upper 95% CI</i>	\$91,483	0.06	\$1,523,007	\$1,398,957
<b>Best case estimate - upper bound</b>	\$69,893	0.047	\$1,474,679	\$1,350,629

## 1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include discontinuation rates of BCRIs, market share of venetoclax and discontinuation rates of venetoclax.

- Increasing the discontinuation rate of BCRIs after 12 months increases the budget impact.
- Increasing the market share of venetoclax increases the budget impact.
- Decreasing the discontinuation rate of venetoclax increases the budget impact.

Key limitations of the BIA model include the assumptions and unconventional use of discontinuation rates for both venetoclax and the comparator arm. The BIA model

provided was difficult to perform sensitivity analyses on by the EGP (ie. modifying the percent of patients eligible for public reimbursement). This was not one of the scenario analyses provided as the EGP was unable to modify this input in the given model.

Notably, the CGP indicated that the majority of patients qualifying for treatment with venetoclax will likely be those that have discontinued treatment with a BCRI due to intolerance rather than failure (the population under consideration in this BIA). Should the market share be changed to include both patients who have failed and who are intolerant to a previous BCRI, then the BIA will likely be impacted significantly; the number of patients who are intolerant to a BCRI is expected to be larger than the number of patients who fail a BCRI.

## 1.6 Conclusions

The EGP's best estimate of  $\Delta C$  and  $\Delta E$  for venetoclax when compared to standard of care is:

- Between \$139,074/QALY and \$1,474,679/QALY
- Within this range, the best estimate would likely be somewhere in the middle. The CGP estimated that venetoclax provides an approximate extra 1-2 years of life when compared to the standard of care.
- The extra cost of venetoclax is between \$69,893 and \$359,461 ( $\Delta C$ ). *The main factors that influence  $\Delta C$  include the lower and upper 95% CI of both progression-free and overall survival. As the duration of treatment is dependent on the progression-free survival curve, modifying the progression free survival curve impacts the cost due to treatment duration. The lower 95% CI of PFS (i.e. better survival for venetoclax) increases the time on therapy for venetoclax, increase the incremental cost, and QALYs, and increasing the ICER. The upper 95% CI of PFS (i.e. worse survival for venetoclax), results in lower costs as patients are on venetoclax for less time (progressing faster), and though the QALYs are also less, the resulting ICER is lower.*
- The extra clinical effect of venetoclax is between 0.047 and 2.585 QALY ( $\Delta E$ ). *The factors that most influence  $\Delta E$  are the time horizon and the 95% CIs of overall survival. Notably, depending on the magnitude of long term benefit gained with the use of venetoclax, the ICER may change substantially in either direction.*

Overall conclusions of the submitted model:

- *Given that a significant amount of costs in the venetoclax arm are due to active treatment, treatment duration is an important parameter to explore. Further, not all patients have progressed in the clinical trial and the product monograph states that venetoclax should be given until disease progression or unacceptable toxicity. The uncertainty around the 95% confidence intervals for PFS reflects the impact of treatment duration on the model.*
- *The CGP highlighted that though the magnitude of overall survival benefit is unknown with venetoclax, there is a benefit in survival. This survival benefit would most likely result in an incremental gain of approximately 1-2 years of life and would therefore be around the mid=point of the lower and upper bound of the EGP re-analysis estimates.*

## 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 Initial 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 venetoclax (Venclexta) for chronic lymphocytic leukemia. A full assessment of the clinical evidence of venetoclax (Venclexta) for chronic lymphocytic leukemia 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](http://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](http://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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