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CADTH DRUG REIMBURSEMENT REVIEW

# Pharmacoeconomic Report

## Venetoclax (VENCLEXTA)

## (AbbVie Corporation)

**Indication:** in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL) who are fludarabine ineligible.

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**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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# Abbreviations

| | |
|---|---|
| **BCRi** | B-Cell receptor inhibitor |
| **BEN-RIT** | bendamustine plus rituximab |
| **CLB-OBI** | chlorambucil plus obinutuzumab |
| **CLB-RIT** | chlorambucil plus rituximab |
| **CLL** | chronic lymphocytic leukemia |
| **FCR** | fludarabine plus cyclophosphamide and rituximab |
| **HC** | Health Canada |
| **ICER** | incremental cost-effectiveness ratio |
| **IGVH** | immunoglobulin heavy chain variable region genes |
| **ITC** | indirect treatment comparison |
| **IV** | intravenous |
| **OS** | overall survival |
| **PFS** | progression-free survival |
| **PPS** | post-progression survival |
| **PSM** | partitioned survival model |
| **QALY** | quality adjusted life-year |
| **TOT** | time on treatment |
| **TTNT** | time to next treatment |
| **WTP** | willingness-to-pay |
| **Ven** | venetoclax |
| **VEN-OBI** | venetoclax plus obinutuzumab |

# Executive Summary

## Table 1: Summary of Economic Evaluation

| Item | Description |
|---|---|
| Drug product | Venetoclax (Venclexta) in combination with obinutuzumab;<br>Venetoclax is administered orally (tablet) and obinutuzumab is administered intravenously |
| Submitted price | Venetoclax, tablet, 10 mg: $7 per tablet<br>Venetoclax, tablet, 50 mg: $35 per tablet<br>Venetoclax, tablet, 100 mg: $70 per tablet |
| Indication | In combination with obinutuzumab for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). |
| Health Canada approval status | Approved |
| Health Canada review pathway | Standard |
| NOC date | April 29, 2020 |
| Reimbursement request | Venetoclax in combination with obinutuzumab for the treatment of adult patients with previously untreated CLL who are fludarabine ineligible. |
| Sponsor | AbbVie Corporation |
| Submission history | Previously reviewed: Yes<br>Drug/combination: Venetoclax (Venclexta)<br>Indication: Patients with CLL who have received at least one prior therapy and who have failed a BCRi<br>Recommendation date: March 2, 2018<br>Recommendation: Reimburse with conditions (including price reduction) |
| | Previously reviewed: Yes<br>Drug/combination: Venetoclax (Venclexta) in combination with Rituximab<br>Indication: Adult patients with CLL who have received at least one prior therapy, irrespective of their 17p deletion status.<br>Recommendation date: May 31, 2019<br>Recommendation: Reimburse with conditions (including a price reduction) |

CLL = Chronic Lymphocytic Leukemia, NOC = Notice of Compliance; BCRi = B-cell Receptor Inhibitor

## Table 2: Summary of Economic Evaluation

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost utility analysis<br>Partitioned survival model |
| **Target populations** | Base case analysis: All previously untreated CLL patients (aligned with the Health Canada-approved indication)<br>Scenario analysis: Previously untreated CLL patients who are considered fludarabine ineligible (aligned with sponsor's reimbursement request) |
| **Treatment** | Venetoclax in combination with obinutuzumab (VEN-OBI) |
| **Comparators** | Base case: Chlorambucil plus Obinutuzumab (CLB-OBI), Bendamustine plus Rituximab (BEN-RIT), Chlorambucil plus Rituximab (CLB-RIT), Ibrutinib, Fludarabine plus Cyclophosphamide and Rituximab (FCR)<br>Scenario analysis: CLB-OBI, BEN-RIT, CLB-RIT, Ibrutinib |
| **Perspective** | Canadian publicly funded health care system |
| **Outcome** | Quality adjusted life-years (QALYs) |
| **Time horizon** | 10 years |
| **Key data sources** | • CLL14 trial (comparison of VEN-OBI and CLB-OBI) and ITC (comparative efficacy for BEN-RIT, CLB-RIT, Ibrutinib and FCR; relative to VEN-OBI) were used to inform PFS, OS, TTNT and TOT. Separate ITCs were used to inform the base case population and reimbursement request population. |
| **Submitted results for base case and key scenario analyses** | • In previously untreated CLL patients, VEN-OBI is dominant (i.e. resulted in lower costs and greater QALYs (0.285 to 0.860) compared to all comparators (CLB-OBI, BEN-RIT, CLB-RIT, Ibrutinib and FCR).<br>• The probability of VEN-OBI being cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained compared to all comparators was 97%. VEN-OBI was dominant in 63% of iterations.<br>• In previously untreated CLL patients who are fludarabine ineligible, VEN-OBI remained dominant compared to all comparators. |
| **Key limitations** | • The key clinical evidence for VEN-OBI was derived from a population reflective of the reimbursement request population. The clinical experts consulted by CADTH considered that the data from the CLL14 trial in previously untreated CLL patients considered fludarabine ineligible was not generalizable to the broader Health Canada-indicated population. Due to this gap in the clinical evidence, the cost-effectiveness of VEN-OBI in the full Health Canada population is unknown.<br>• The comparative clinical efficacy of VEN-OBI to all comparators except CLB-OBI was uncertain as it was derived from a fixed effects ITC which was identified to have substantial heterogeneity in the populations included, differences in effect modifiers, and in the design of included studies. The PFS hazard ratios resulting from the ITC, which are the key driver of the model results, were deemed to have questionable face validity and the clinical experts consulted by CADTH agreed that the hazard ratios were higher than expected in clinical practice, though the magnitude of impact is unclear.<br>• CADTH also identified limitations relating to how the ITC data were applied in the model. The decision to apply HRs that are dependent on the VEN-OBI curves restrains the explanatory power of the model, and underestimates the variability of the potential treatment outcomes. These constraints tend to bias the results in accordance with the HRs reported from the ITC. |
| **CADTH reanalysis results** | • CADTH reanalyses focused on the fludarabine-ineligible population. The cost-effectiveness of VEN-OBI in fludarabine-eligible patients is unknown.<br>• While CADTH revisions based on best available data indicated that VEN-OBI remained dominant versus all comparators and reported similar findings to the sponsor's base case (97% probability at a WTP of $50,000 per QALY that VEN-OBI is cost-effective), there is significant structural and parameter uncertainty that is left unaddressed due to the nature of the model design and the identified limitations with the submitted clinical evidence. As such, CADTH's reanalysis based on best available data doesn't capture the full extent of clinical uncertainty.<br>• CADTH undertook several scenario analyses assessing parameter uncertainty. Alternate assumptions to two key drivers – PFS and time on subsequent treatment – indicate greater |

| Component | Description |
|---|---|
| | uncertainty in the cost-effectiveness estimate. If the PFS HR for any comparator treatments relative to VEN-OBI is 1.5, then the probability that VEN-OBI is cost-effective at a willingness to pay of $50,000 per QALY is 71%, while if TTNT post-progression is assumed the same across treatments, the probability that VEN-OBI is cost-effective at a willingness to pay of $50,000 per QALY is 79%. |

ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life-year; OS = overall survival; PFS = progression-free survival; QALY= quality-adjusted life-year; TTNT: time to next treatment; TOT: time on treatment.

## Conclusions

The cost-effectiveness of VEN-OBI in patients with previously untreated CLL who are fludarabine-eligible is unknown, given the lack of clinical evidence for the use of VEN-OBI in that patient population.

While revisions based on best available data suggest that VEN-OBI is cost-effective compared to currently funded treatments for patients with previously untreated CLL who were fludarabine-ineligible, there is significant structural and parameter uncertainty that is left unaddressed due to the nature of the model design and the limitations identified with the submitted clinical evidence; particularly the clinical and methodological heterogeneity observed in the ITC, leading to concerns of the validity in the PFS HRs. As such, although VEN-OBI has been shown to improve PFS compared to CLB-OBI based on the CLL14 trial, the incremental benefit of VEN-OBI relative to other comparators is uncertain due to the limitations identified with the submitted ITC and the uncertain validity of the resulting hazard ratios.

Due to the design of the model, including the asserted dependence of treatment effects to favor VEN-OBI, it was structurally difficult to differentiate, test, and validate the sponsor's clinical assertions. As a result, while CADTH's reanalysis using best available data is relatively similar to that of the sponsor's, CADTH scenario analyses assessing parameter uncertainty highlighted the volatility of the model to alternate assumptions for the PFS hazard ratios and subsequent treatment assumptions. Based on CADTH's revised and scenario analyses, VEN-OBI is likely to be a cost-effective treatment option for previously untreated CLL patients who were fludarabine-ineligible if the PFS HR for comparators versus VEN-OBI is equal to or greater than 1.5 and the OS HR is close to 1.

Based on the sponsor's submitted budget impact model, CADTH reanalyses suggest that the estimated budget impact of introducing VEN-OBI to the market is uncertain due to uncertainty in the estimation of the population size and is sensitive to different ibrutinib market share displacement assumptions. CADTH considered that the three-year budget impact of introducing VEN-OBI to the market may range from $8,087,572 to $18,805,174 in this population. If the population is expanded to all previously untreated CLL patients, the budget impact is assumed to roughly double.

## Stakeholder Input Relevant to the Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

## Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

# Appendix 1: Cost Comparison Table

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

# Appendix 2: Submission Quality

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

# Appendix 3: Additional Information on the Submitted Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

# Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

# Appendix 5: Submitted BIA and CADTH Appraisal

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

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