pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Vemurafenib (Zelboraf) for Advanced Melanoma

June 1, 2012
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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis submitted to pCODR by Hoffmann-La Roche Limited was a cost-utility and cost-effectiveness analysis that compared vemurafenib to dacarbazine in untreated patients (i.e., first-line setting) with BRAF V600 mutation-positive unresectable or metastatic melanoma. Vemurafenib is administered orally and dacarbazine is administered intravenously.

According to the pCODR Melanoma Clinical Guidance Panel, this comparison is appropriate as dacarbazine is considered the standard of care of patients with advanced melanoma.

A cost-minimization analysis was submitted that compared vemurafenib to relevant comparators in previously treated patients (i.e., second-line setting) with BRAF V600 mutation-positive unresectable or metastatic melanoma. The analysis was conducted over a seven-month timeframe based on available information from BRIM-2.

The following factors were considered by patient advocacy groups to be important in the review of vemurafenib and were relevant to the economic analysis: life expectancy and ease at managing side effects. A full summary of patient advocacy group input is provided in the pCODR Clinical Guidance Report. Factors important to patients were addressed in the economic analysis by including estimates of life-years gained and side effects of treatments in the economic model.

The Provincial Advisory Group (PAG) considered that the following factors would be important to consider if implementing a funding recommendation for vemurafenib, and are relevant to the economic analysis: the role and cost-effectiveness of vemurafenib in first-line and second-line settings, differences in costs and cost-effectiveness between vemurafenib and ipilimumab in the second-line setting, and costs associated with implementing BRAF mutation-testing. A full summary of PAG input is provided in the pCODR Clinical Guidance Report. Factors relevant to PAG were addressed as follows:

- The Submitter provided analyses of vemurafenib in both the first and second-line setting, however, the analysis in second-line was limited as an economic model was not provided and only a comparison of drug prices for relevant comparators was included.
- The Economic Guidance Panel was unable to provide an estimate of the cost-effectiveness of vemurafenib compared with ipilimumab in the first-line or the second-line setting, however, drug prices were compared over a seven-month time frame.
- The Economic Guidance Panel identified factors associated with BRAF mutation testing that would impact cost-effectiveness, and a best-estimate of the cost-effectiveness of vemurafenib if BRAF-mutation testing was considered. However, due to uncertainty in some of the costs associated with testing assumptions around testing costs would need to be further validated.

At the list price, vemurafenib costs $46.54 per 240 mg tablet. At the recommended dose of 960 mg twice daily (8 tablets per day), the cost of vemurafenib is $372.32 per day. The average cost per 28-day course is $10,425.34.
The list price of dacarbazine, the most commonly used first-line therapy for advanced melanoma, is $200.20 per 600 mg/mL vial. At the recommended dose of 200 to 250 mg/m², administered intravenously on days one to five every 21 to 28 days, and assuming a body mass of 70 kg and a body surface area of 1.7 m², the average cost of dacarbazine per day is between $20.26 and $33.76 in a 28-day course. The average cost per 28-day course of dacarbazine is between $567.230 and $945.39.

1.2 Summary of Results

When vemurafenib is compared to dacarbazine in untreated patients and when any costs associated with BRAF-mutation testing costs are excluded, the Economic Guidance Panel’s best estimate of the incremental cost-effectiveness ratio is between $221,668 per QALY and $275,707 per QALY.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔQALY). The Economic Guidance Panel’s best estimate of:

- The extra cost of vemurafenib is approximately $73,995. Costs include costs of treatment with vemurafenib and comparators, medical resource utilization per health state, costs for treatment of adverse events and the cost of infusion. No costs associated with BRAF-mutation testing were included.
- The extra clinical effect of vemurafenib is between 0.268 and 0.339 QALYs or between 0.202 and 0.438 life-years gained. Effects were primarily based upon progression-free survival estimates and mortality rates from the BRIM-3 trial and utility values derived from the literature. The biggest influence is the mean time in the progression-free survival state and the utility value for progression-free survival. Assuming no difference between treatments in the mortality rates following progression leads to a higher estimate of benefit with vemurafenib.

When vemurafenib is compared to dacarbazine in untreated patients and when an estimate of costs associated with BRAF-mutation testing is included, the EGP’s best estimate of the incremental cost-effectiveness ratio is between $227,571 per QALY and $279,433 per QALY.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔQALY). The EGP’s best estimate of:

- The extra cost of vemurafenib is between $73,995 and $74,995. Including an estimate of the costs per BRAF test leads to increased costs associated with vemurafenib. All other costs remained the same compared with the analysis excluding BRAF-mutation testing costs.
- The extra clinical effect of vemurafenib did not change compared with the analysis excluding BRAF-mutation testing costs and is between 0.268 and 0.339 QALYs or between 0.202 and 0.438 life-years gained.

The EGP provided a range of estimates of the incremental cost-effectiveness ratio between $227,571 per QALY and $279,433 per QALY (ΔC / ΔQALY) or between $171,425 per life-year gained and $247,785 per life-year gained (ΔC / ΔLYG) when vemurafenib is compared to dacarbazine. The EGP based these estimates on the model submitted by
Hoffman La Roche and reanalyses conducted by the EGP. Reanalyses conducted by the EGP using the submitted model showed that:

- If an assumed cost of $500 for a BRAF test was included, the incremental cost of vemurafenib is increased to $74,995, which increases the estimated incremental cost-effectiveness ratio.

- Assuming the same mortality rates post progression, the incremental clinical effect of vemurafenib is 0.339 QALYs (or 0.438 life years), which decreases the estimated incremental cost-effectiveness ratio.

In addition a secondary analysis was submitted evaluating vemurafenib in the second-line setting, i.e. in previously treated patients. This analysis simply compared the drug price of vemurafenib with relevant comparators in this clinical setting, given the lack of head-to-head trials in this patient population. Median progression-free survival from BRIM-2 (i.e. 7 months) was used to calculate the duration and cost of therapies for vemurafenib and other potential comparators. The EGP noted that ipilimumab is a relevant comparator in the second-line setting and that PAG was interested in the cost-effectiveness of ipilimumab compared with vemurafenib. The EGP estimated that, over a seven month period, based on drug price alone, the cost of treatment with vemurafenib would be approximately $78,187.20 compared with approximately $118,000 for ipilimumab. The ipilimumab price was estimated based on receiving one course of ipilimumab (four doses at 3 mg/kg) and assuming international ipilimumab pricing, drug wastage and a body mass of 70 kg. However, as no economic model was submitted for this comparison, and only drug prices were compared, best estimates by the EGP are limited and an appropriate estimation and critical review of the cost-effectiveness of vemurafenib compared with [redacted] and other relevant comparators cannot be conducted. (Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).

The cost-effectiveness estimates submitted to pCODR by Hoffman-LaRoche Limited for untreated patients (i.e., first-line setting) were within the range of EGP estimates. The EGP could not provide a best estimate of the cost-effectiveness of vemurafenib in previously treated patients (i.e., second-line setting).

According to the economic analysis that was submitted by Hoffmann-LaRoche Limited, when vemurafenib is compared with dacarbazine in untreated patients:

- The extra cost of vemurafenib was $[redacted]. (The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from guidance reports provided to pERC and has been redacted in this publicly available guidance report. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).

- The extra clinical effect of vemurafenib was [redacted] QALYs. (The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from guidance reports provided to pERC and has been redacted in this publicly available guidance report. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).
So, the incremental cost required for one QALY was $\text{[redacted]}$. *(The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from guidance reports provided to pERC and has been redacted in this publicly available guidance report. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.)*

### 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?

Overall, the Submitter’s estimates were similar to the Economic Guidance Panel’s estimates and represent a good estimate of the cost-effectiveness of vemurafenib. The key reasons why the Economic Guidance Panel estimates of ICER may differ from the submitted ICERs are because the Economic Guidance Panel conducted analyses where:

- BRAF mutation testing costs were assumed and included, which increased the extra costs associated with vemurafenib and the resulting ICER. The assumed costs for the BRAF test were based on the costs of the EGFR mutation test which may not be reflective of the true costs of the BRAF test (Medical Devices Secretariat 2010). The EGP assumed a test cost of $500 and that 50% of patients tested will not have the mutation so the cost of the test per person with the mutation identified is $1000.

- It was assumed there was no difference between treatments in survival following disease progression, which increased the extra clinical effects associated with vemurafenib and decreases the ICER.

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

To some extent. The submitted model addresses the desire for increased life expectancy and the manageability of side effects. The primary analysis is cost per QALY gained but there are additional analyses which deal with increased life expectancy, i.e. life-years gained. The costs of certain adverse events are included but not all adverse events. Differences in utilities based on side effects are not included.

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

Yes, the model structure was adequate and no changes in structure are needed.

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 Submitter assumed a greater mortality rate with vemurafenib following disease progression than with dacarbazine, which decreases the clinical benefit associated with vemurafenib. This is a conservative assumption by the Submitter and biases the results against vemurafenib.

While pCODR does not require cost-effectiveness analyses of a companion diagnostic test, BRAF mutation testing is required to appropriately identify candidates for vemurafenib and
having no BRAF-mutation testing costs associated with vemurafenib is unlikely in a real-world setting. Because the Submitter assumed zero costs of the BRAF-mutation test, costs associated with vemurafenib are lower than would occur in a real-world setting and biased the results in favour of vemurafenib. However, the impact of the test cost on overall cost-effectiveness is small compared with the impact of the drug costs.

Extrapolation of clinical benefits beyond the trial period also has an important effect on estimates of vemurafenib’s cost-effectiveness. In the submitted analysis, benefits were extrapolated over a five year period, which the Economic Guidance Panel considered appropriate in consultation with the pCODR Melanoma Clinical Guidance Panel.

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?

Yes. This is a well designed study with mostly appropriate estimates in the submitted analysis. There are concerns only with the characterization of uncertainty around parameters (costs and utilities) not their base values. Adverse events which were a major focus of the patient submission were only incorporated to a limited extent but further incorporation would likely have limited impact on the study results.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

Variables included in the budget impact analysis include the cost of vemurafenib and other comparators, market share, the overall population and proportion covered by public plans, the prevalence of melanoma, the proportion of unresectable and metastatic melanoma cases, the proportion of patients receiving first-line therapy and second-line therapy and the proportion of BRAF-mutation positive patients. The key factors influencing the budget impact analyses are the vemurafenib capture rate, the derived market share and the prevalence of melanoma.

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

There were no limitations to the structure of the budget impact analysis or the variables considered. For provinces, more evidence based estimates of market share and prevalence could improve the accuracy of budget impact analysis results.

In general, BRAF mutation testing costs were not considered in the budget impact analysis, therefore, provinces may need to consider additional factors associated with diagnostic testing for the BRAF mutation when determining budget impact.
1.5 Future Research

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

While pCODR does not require cost-effectiveness analyses of a companion diagnostic test, a proper estimation of the costs of BRAF-mutation testing is essential before the real-world cost effectiveness of vemurafenib can be determined. This would require a detailed costing exercise which would involve estimation of the following variables:

- Acquisition costs of hardware
- Annual costs of upkeep and maintenance
- Expected number of patients per year
- Expected number of sites acquiring the test
- Volume of tests run at each time
- How long hardware is expected to last
- Variable costs of using test including labour

The economic evaluation of vemurafenib in the second-line setting, which compared drug prices of relevant comparators, was insufficient. Ideally there would be an economic model comparing vemurafenib with second-line treatment alternatives, including ipilimumab.

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

- Costing of the BRAF test, as detailed above that would allow for cost-effectiveness analyses that include both vemurafenib costs and BRAF-mutation testing costs.

- A more developed economic model in previously treated patients that evaluates the cost-effectiveness of vemurafenib relative to ipilimumab in this second-line setting. Ideally the economic model would be supported by head-to-head clinical trials directly comparing ipilimumab and vemurafenib in the second-line setting.
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 Melanoma 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 vemurafenib. A full assessment of the clinical evidence of vemurafenib for advanced melanoma 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).

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. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from the Guidance Report provided to pERC for their deliberations and has been redacted in this publicly available Guidance Report.

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.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.
REFERENCES


PIVINA Consulting Inc. ZELBORAF TM (vemurafenib) Health Economic Model. ZELBORAF for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma (manufacturer’s submission)