pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Vemurafenib (Zelboraf) **Funding Request:** Treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma	
Submitted By: Hoffmann-La Roche Limited	**Manufactured By:** Hoffmann-La Roche Limited
NOC Date: February 15, 2012	**Submission Date:** December 6, 2011
Initial Recommendation: March 29, 2012	**Final Recommendation:** June 1, 2012

RECOMMENDATION	The pCODR Expert Review Committee (pERC) **recommends funding vemurafenib (Zelboraf) conditional on the cost-effectiveness of vemurafenib being improved to an acceptable level.** Funding should be as a first-line therapy for patients presenting with BRAF V600 mutation-positive unresectable stage IIIC or IV melanoma or for patients who develop metastatic disease. Patients should have good performance status (ECOG ≤ 1), and, if brain metastases are present, the metastases must have been previously treated and be stable. Treatment may be continued until disease progression. The Committee made this recommendation because they were satisfied that, despite some limitations in the clinical trial design, there is an overall clinical benefit of vemurafenib compared with dacarbazine. However, at the submitted price and the Economic Guidance Panel's best estimates of the incremental cost-effectiveness ratio, vemurafenib could not be considered cost-effective compared with dacarbazine.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given pERC was satisfied, despite some limitations in the clinical trial design, that there is a net clinical benefit of vemurafenib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of vemurafenib to an acceptable level. **Implementation of Vemurafenib and BRAF Mutation Testing** Because use of vemurafenib requires patients to have BRAF V600 mutation positive melanoma, diagnostic testing for BRAF V600 mutations should be made available with funding for vemurafenib. **Time-Limited Need for Vemurafenib in Second-Line Setting** At the time of implementing a funding recommendation for vemurafenib, jurisdictions may consider addressing the short-term, time-limited need for vemurafenib in the second-line setting in the small subset of BRAF V600 mutation positive patients who progressed after receiving treatment in the first-line setting, prior to vemurafenib being available, while recognizing the lack of robust cost-effectiveness analyses submitted for vemurafenib in the second-line setting.

SUMMARY OF pERC DELIBERATIONS

pERC noted that currently there is no standard treatment for metastatic melanoma and there is a need for effective therapies that demonstrate an improvement in overall survival. It was discussed that the most commonly used first-line therapy in untreated patients with metastatic melanoma is dacarbazine and that, until recently, therapies in the second-line setting have been largely ineffective. The one open-label randomized controlled trial (BRIM-3, Chapman 2011) comparing vemurafenib with dacarbazine, which was included in the pCODR systematic review, was, therefore, considered appropriate in the first-line setting.

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of the BRIM-3 study, which evaluated the oral administration of vemurafenib in a dose of 960 mg twice daily (8 tablets per day) as a first-line therapy for metastatic melanoma. pERC concluded that there is a net clinical benefit associated with vemurafenib, despite some limitations observed in the BRIM-3 study. pERC noted that there was a statistically significant improvement in the hazard ratios for overall survival at the planned interim analysis conducted at approximately six months and at exploratory analyses of overall survival conducted at three months and 10 months after the planned interim analysis. pERC also considered the median overall survival results that were obtained at the third analysis and considered that these were clinically significant. However, pERC noted that the trial was not blinded, which may have affected the integrity of the trial results and the magnitude of the observed benefit. pERC discussed that while overall survival may not be directly affected in an unblinded trial, the supportive care management of patients in the trial may have been affected and biased the overall trial results. In addition, it was noted that a larger proportion of patients in the dacarbazine group withdrew from the trial compared with the vemurafenib group. It was recognized that blinding of the BRIM-3 study would have been challenging because an orally administered drug (vemurafenib) was compared with a drug that is administered intravenously (dacarbazine), however, the Committee noted that randomized double-blind trials are considered the gold standard and should be attempted whenever possible; double dummies may be used when oral and IV treatments are compared.

pERC noted that the BRIM-3 study only included untreated patients and that there is no randomized controlled trial evidence evaluating vemurafenib in previously treated patients. pERC considered feedback from the manufacturer on evidence for the use of vemurafenib in the second-line setting and further deliberated upon the results of BRIM-2, a single-arm study conducted in previously treated patients. pERC discussed the limitations of non-randomized studies and considered that the quality of evidence supporting vemurafenib in the second-line setting was not robust and that stronger study designs could have been used. pERC considered that, given the absence of a comparator arm in BRIM-2, the magnitude of vemurafenib response is uncertain and likely overestimates the magnitude of clinical benefit associated with vemurafenib in previously treated patients. Despite the limitations in evidence, pERC discussed whether or not there is a need for vemurafenib in the second-line setting in patients who are BRAF V600 mutation positive. pERC considered feedback from the Provincial Advisory Group that there may be BRAF V600 mutation positive patients who had received an alternative agent in the first-line setting prior to vemurafenib being made available. These patients, therefore, would not be eligible for vemurafenib funding in the first-line setting and would not be able to access vemurafenib unless it were available as a second-line treatment. pERC considered that prior to the availability of vemurafenib, there were limited treatment options in the first-line setting and that for a time-limited period it would be clinically reasonable for patients who are BRAF V600 positive and who progressed after first-line therapy (e.g. dacarbazine, treatment in a clinical trial) to have access to vemurafenib in the second-line setting. pERC noted that the Provincial Advisory Group considered this to be a potential implementation issue that would need to be addressed at a jurisdictional level, while recognizing that pERC did not consider vemurafenib cost-effective.

pERC considered that the effectiveness of vemurafenib is dependent upon patients having BRAF V600 mutation positive melanoma. It was discussed that diagnostic testing for BRAF V600 mutations should be

available with funding for vemurafenib. pERC discussed possible challenges associated with testing such as appropriate tissue sampling, gaining access to testing across the country and additional costs associated with diagnostic testing that may affect the feasibility of adoption of a recommendation for funding.

pERC discussed the toxicity profile of vemurafenib based on the serious adverse events observed in the BRIM-3 study. pERC noted that nonfatal serious adverse events occurred in a greater proportion of vemurafenib patients compared with dacarbazine patients. pERC also noted that over one-quarter of patients in the vemurafenib group experienced cutaneous squamous cell carcinomas, new primary malignant melanomas and other cutaneous lesions, compared with less than 1% of dacarbazine patients. pERC noted that these adverse events were manageable through excision or the use of local therapies; however, the Committee expressed concern over possible long-term effects of vemurafenib. pERC determined that because of the short trial follow-up (approximately 7 months) the long-term safety of vemurafenib is unknown and long-term survivors should be monitored for adverse events that may appear after continuous, long-term administration of vemurafenib.

pERC also deliberated upon patient advocacy group input that indicated that patients have a high tolerance for side effects from new treatments if the treatment has the possibility of extending life and the side effects can be managed effectively. pERC also noted that patients who had received vemurafenib indicated that side effects were milder than those experienced with other treatments for advanced melanoma such as dacarbazine. pERC also noted that patient advocacy group input indicated that an oral therapy would be desirable for patients and could provide better access to treatment. However, it was further noted that vemurafenib accessibility and budget impact would vary across the country because funding for oral drugs varies across jurisdictions. Given the patient advocacy group input, pERC considered that vemurafenib aligns with patient values. However, pERC also noted that quality of life was a patient-expressed value and that the pCODR Melanoma Clinical Guidance Panel considered that quality of life data from the BRIM-3 study was not robust and, therefore, the impact of vemurafenib on quality of life could not be assessed. pERC discussed that quality of life is an important outcome and that trial sponsors, including manufacturers, should collect good quality data in clinical trials on this outcome, which is so important to patients. In reviewing the patient advocacy group input, pERC noted that it was based upon responses from a small number of patients. While recognizing the difficulty patient advocacy groups may have in accessing a large number of patients, pERC considered that it would be helpful to get input from a larger number of patients who may have had both positive and negative experiences with vemurafenib.

pERC discussed the burden of illness of metastatic melanoma. It was noted that although this affects a small patient population, it is not a rare disease and the incidence is increasing. Despite the small population, when considering budget impact, pERC also noted that the affordability of vemurafenib is unknown given that there is no defined duration of treatment. pERC also considered patient advocacy group input and noted that melanoma patients are often young and the ability to work and financially support their family can be negatively impacted.

pERC deliberated upon the cost-effectiveness of vemurafenib in untreated patients. It was concluded that vemurafenib is not cost-effective based on the Economic Guidance Panel's best estimates, which were consistent with the manufacturer's estimates. In order for it to be cost-effective, pERC considered that the price of vemurafenib would need to be reduced substantially. pERC expressed concern that the manufacturer would not publicly disclose their estimates of cost-effectiveness; however, pERC noted that because it was known that the manufacturer's estimates were within the range of the Economic Guidance Panel's best estimates, this reduced the challenges pERC had in interpreting the redacted cost-effectiveness information. pERC noted that the time horizon used in the submitted economic evaluation and in the Economic Guidance Panel's best estimates was five years. pERC discussed this in light of the short follow-up period for the BRIM-3 study and the uncertainty of long-term outcomes. As a result, pERC noted that the incremental cost utility ratios associated with vemurafenib could potentially be even higher than what was estimated by the Economic Guidance Panel.

pERC noted that a cost minimization analysis had also been attempted by the manufacturer that evaluated the cost-effectiveness of vemurafenib in previously treated patients. However, pERC considered that this approach was not appropriate since there is no evidence to suggest that the efficacy of vemurafenib is similar to other second-line therapies. In addition, pERC noted that because the magnitude of clinical benefit of vemurafenib is uncertain in previously treated patients, it was

challenging to estimate cost-effectiveness. Therefore, pERC considered that these estimates of cost-effectiveness in previously treated patients were not robust.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review,
- other literature in the Clinical Guidance Report providing clinical context,
- an evaluation of the manufacturer's economic model and budget impact analysis,
- guidance from pCODR clinical and economic review panels,
- input from one patient advocacy group (Melanoma Network of Canada) and input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group who provided input at the beginning of the review (Melanoma Network of Canada)
- pCODR's Provincial Advisory Group
- the Submitter (Hoffman-La Roche Ltd.)

The pERC Initial Recommendation was to consider funding vemurafenib, if the cost-effectiveness of vemurafenib was improved to an acceptable level, as a first-line therapy for patients with BRAF V600 mutation-positive unresectable stage IIIC or IV melanoma or with metastatic disease. Patients should have good performance status (ECOG ≤ 1), and, if brain metastases are present, they must have been previously treated and be stable. Feedback on the pERC Initial Recommendation indicated that the Melanoma Network of Canada and pCODR's Provincial Advisory Group agreed with the recommendation and that Hoffman-La Roche Ltd. agreed with the recommendation in part.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the use of vemurafenib compared with standard treatment, placebo, or best supportive care for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Studies included

The pCODR systematic review included one open-label randomized controlled trial (BRIM-3, Chapman 2011) comparing vemurafenib (960 mg twice daily, i.e., 8 tablets per day) with dacarbazine in patients with unresectable, previously untreated, BRAF V600E mutation-positive, stage IIIC or IV melanoma. The co-primary outcomes of BRIM-3 were overall survival and progression-free survival. Based on statistically significant results at a planned interim analysis, the Data and Safety Monitoring Board recommended to close accrual into the trial after approximately six months and patients treated with dacarbazine were able to crossover to receive vemurafenib.

The pCODR review also provided contextual information on BRAF mutation testing and on BRIM-2 (Sosman 2012), a single-arm, non-randomized study evaluating vemurafenib in previously treated patients that was not included in the systematic review because it lacked a comparator treatment group.

Patient population: Untreated patients with good performance status and BRAF V600 mutation positive melanoma

pERC noted that in the BRIM-3 study, treatment groups were generally balanced with respect to demographic and disease characteristics at study entry. pERC also noted that the BRIM-3 study only included patients with an ECOG score of 0 or 1, representing patients with good performance status. pERC also recognized that BRIM-3 excluded patients with prior treatment. pERC noted that there is no randomized controlled trial evidence evaluating vemurafenib in previously treated patients but that a

non-randomized single-arm study, BRIM-2 (N = 132) had evaluated vemurafenib in previously treated patients.

It was noted that BRAF V600 mutations were identified using the manufacturer's diagnostic test, the Cobas 4800 BRAF V600 Mutation Test. Because the clinical effect of vemurafenib is limited to patients with V600 mutation, pERC recognized that diagnostic testing is essential and implementation of a funding recommendation for vemurafenib would need to occur side-by-side with implementation of diagnostic testing.

Key efficacy results: Overall survival benefit for vemurafenib

The key efficacy outcome deliberated on was overall survival. Overall survival was a co-primary endpoint in BRIM-3, along with progression-free survival. pERC noted that patients treated with vemurafenib had a statistically significant improvement in overall survival compared with dacarbazine at the six month planned interim analysis (hazard ratio=0.37; 95% CI: 0.26 to 0.55). pERC also noted that median survival estimates were obtained at the third analysis, approximately 10 months after the interim analysis. At this time point, the median survival times were estimated to be 13.2 months and 9.6 months for the vemurafenib and dacarbazine groups, respectively (hazard ratio=0.62; 95% CI: 0.49 to 0.77), when data were censored for cross-over. pERC noted that at this third analysis, a total of 81 dacarbazine patients had crossed over from the dacarbazine group to receive vemurafenib.

Duration of therapy: Vemurafenib treatment duration unknown

pERC discussed that in the BRIM-3 study there was no fixed duration of treatment and patients were allowed to continue treatment until they experienced tumour progression, unacceptable toxicity, death or study discontinuation for other reasons. It was noted that the median duration of treatment among the vemurafenib group was 4.2 months compared with 0.8 months among the dacarbazine group. Therefore, pERC considered that the effects of long-term continuous administration of vemurafenib are unknown and that the affordability and budget impact of treatment is also unknown.

Quality of life: Quality of life data not robust

The effect of vemurafenib on quality of life was a pre-specified secondary outcome evaluated in the BRIM-3 study. However, because patients were only required to complete the questionnaire until disease progression, few patients completed all quality of life assessments and these data were not considered sufficiently robust to draw concrete conclusions as to the impact of vemurafenib on quality of life in advanced melanoma. pERC considered this and noted that quality of life is important to patients and that it is important to be able to determine the impact of vemurafenib on quality of life. pERC considered that trial investigators and manufacturers should collect good quality data for this outcome in clinical trials.

Safety: Increase in secondary skin malignancies manageable but long-term safety unknown

pERC noted that serious non-fatal adverse events occurred in 43% of patients receiving vemurafenib versus 18% of dacarbazine patients. pERC also considered that over one-quarter of patients in the vemurafenib group experienced cutaneous squamous cell carcinomas, new primary malignant melanomas and other cutaneous lesions compared with less than 1% of dacarbazine patients. pERC noted that these are clinically significant adverse events; however, they were manageable through excision or the use of local therapies. pERC considered that being able to manage adverse events is important to patients and also noted that patients who had experience with vemurafenib indicated that side effects were milder than those experienced with standard treatments such as dacarbazine.

pERC expressed concerns over the possible long-term effects of vemurafenib. The Committee was concerned that because of the short trial follow-up (approximately seven months) the long-term safety of vemurafenib is unknown and that long-term survivors should be monitored for adverse events, including squamous cell carcinomas in other sites, that may appear after continuous, long-term administration of vemurafenib.

Limitations: Lack of blinding and short follow-up period

While deliberating upon the net clinical benefit of vemurafenib, pERC expressed concerns over limitations associated with the available evidence from BRIM-3. BRIM-3 was an unblinded study, which may have

resulted in observer bias and contributed to a higher dropout rate in the dacarbazine group. pERC discussed that while overall survival may not be directly affected in an unblinded trial, the supportive management of patients in the trial may have been compromised and indirectly affected overall trial results. In addition, it was noted that approximately 11% patients in the dacarbazine group withdrew from the trial compared with none in the vemurafenib group. It was recognized that blinding of the BRIM-3 study would have been challenging because a drug that is administered orally (vemurafenib) was compared with a drug that is administered intravenously (dacarbazine); however, the Committee noted that randomized double-blind trials are considered the gold standard and should be attempted whenever possible.

pERC also discussed that the short follow-up period of BRIM-3 (approximately seven months) limits the conclusions that can be drawn on the long-term safety and effectiveness of vemurafenib as well as drug utilization and treatment duration.

Previously treated patients: Evidence not robust and magnitude of benefit uncertain
pERC considered feedback from the manufacturer on evidence for the use of vemurafenib in the second-line setting and further deliberated upon the results of BRIM-2, a single-arm study involving previously treated patients. pERC discussed the limitations of non-randomized studies and considered that the quality of evidence supporting vemurafenib in the second-line setting was not robust and that stronger study designs could have been used such as a comparison with best supportive care or the use of a historical control group. pERC noted that a 53% best overall response rate (95% confidence interval: 44% to 62%) was achieved, of which 6% of patients had a complete response. pERC considered that, given the lack of comparator arm, the magnitude of vemurafenib response is uncertain and likely overestimates the magnitude of clinical benefit associated with vemurafenib in previously treated patients.

Need: New treatment options available that improve overall survival
pERC noted that there is a need for effective therapies to treat metastatic melanoma. It was discussed that there is no evidence that dacarbazine, the most commonly used first-line therapy, improves overall survival and has associated side effects that patients sometimes find difficult to tolerate. pERC also noted that patients with metastatic melanoma are often young and while this cancer may affect a small patient population, incidence is increasing and it cannot be considered a rare disease.

PATIENT-BASED VALUES

Values of patients with advanced melanoma: Extending life and improving quality of life
Patient advocacy group input indicated that there are limited therapies available for patients with advanced melanoma and new therapies which could extend their life expectancy are very important. pERC considered that patients receiving vemurafenib in the BRIM-3 study had an approximately 3.6 month improvement in overall survival compared to patients receiving dacarbazine.

pERC also noted that quality of life was a patient-expressed value and that the pCODR Melanoma Clinical Guidance Panel considered that quality of life data from the BRIM-3 study were not robust and, therefore, the impact of vemurafenib on quality of life could not be assessed. pERC noted that quality of life is an important outcome and that trial investigators and manufacturers, should collect good quality data in clinical trials on this patient-important outcome.

Patient values on treatment: Oral therapy preferred and willing to tolerate side effects
pERC discussed that patient advocacy group input indicated that an oral therapy would be desirable for patients and could potentially provide patients with better access to treatment.

Although vemurafenib may be associated with side effects, input from patient advocacy groups indicated that patients would be willing to tolerate certain side effects if a new therapy extends their life expectancy. pERC noted that the most common serious adverse event associated with vemurafenib is an increase in second skin malignancies but that this side effect can be managed through either excision or other local therapies. pERC also noted that patients who had experience with vemurafenib indicated that side effects were milder than those experienced with other treatments for advanced melanoma such as dacarbazine.

In reviewing the patient advocacy group input, pERC noted that it was based upon responses from a small number of patients. While recognizing the difficulty patient advocacy groups may have in accessing a large number of patients, pERC considered that it would be helpful to get input from a larger number of patients who may have had both positive and negative experiences with vemurafenib.

pERC reviewed feedback from one patient advocacy group on the pERC initial recommendation for vemurafenib and noted that there was agreement with the pERC recommendation. pERC was sensitive to the needs of BRAF mutation positive patients who may have progressed after first-line therapy (e.g., dacarbazine, treatment in a clinical trial) before vemurafenib was available as a first-line treatment. pERC considered that, for a time-limited period, it would be clinically reasonable for these BRAF V600 mutation positive patients to have access to vemurafenib even though they had been previously treated and that this would align with patient identified values.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis in untreated patients

The pCODR Economic Guidance Panel assessed an economic evaluation looking at the cost-effectiveness and cost-utility of vemurafenib compared to dacarbazine in untreated patients (i.e., first-line setting) with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Basis of the economic model: Clinical and economic inputs

Costs include costs of treatment with vemurafenib and comparators, medical resource utilization in each distinct health state, costs for treatment of adverse events and the costs of administration.

No costs associated with BRAF-mutation testing were included. pERC noted that costs of testing would need to be considered when implementing a funding recommendation for vemurafenib. However, pERC also considered that the impact of the test cost on overall cost-effectiveness would be small compared with the impact of the drug costs.

Key clinical 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 was the mean time in the progression-free survival state and the utility value for progression-free survival. Assuming no difference in the mortality rates between the two treatment arms following progression would lead to a higher estimate of benefit with vemurafenib. pERC considered it a limitation that good quality of life data were not available from BRIM-3 to inform the economic evaluation and so utility values had to be derived from the literature.

Drug costs: Treatment duration uncertain

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 for a 28-day course is $10,425.34. pERC noted that the duration of vemurafenib treatment is unknown and, therefore, affordability and the long-term budget impact of vemurafenib is unknown.

pERC also considered that this cost is substantially more than dacarbazine, which is the most commonly used first-line therapy in patients with advanced melanoma. Dacarbazine costs $200.20 per 600 mg/vial. At the recommended dose of 200 to 250 mg/m^2 administered intravenously on days one to five every 21 to 28 days and a body surface area of 1.7 m^2 and no wastage, the average cost of dacarbazine per day is between $20.26 and $33.76 in a 28-day course. The average cost for a 28-day course of dacarbazine is between $567.230 and $945.39.

Cost-effectiveness estimates: Cost-effectiveness based on long-term data unknown

pERC considered that the Economic Guidance Panel's best estimate of the incremental cost-utility ratio in untreated patients is between $221,668 per quality-adjusted life year (QALY) and $275,707 per QALY when the costs of BRAF mutation testing are not included. pERC considered that vemurafenib is not cost-effective within this range and that the price of vemurafenib would need to be reduced substantially in order for it to be cost-effective.

pERC considered that the Economic Guidance Report indicated that the manufacturer's cost-effectiveness estimates were within the range of the Economic Guidance Panel's best estimates. pERC expressed concern that the manufacturer would not publicly disclose their cost-effectiveness estimates and this information was redacted from the Economic Guidance Report provided to pERC. However, pERC noted that because the manufacturer's estimates were consistent with the Economic Guidance Panel's best estimates, the challenges pERC faced in interpreting the redacted cost-effectiveness information were reduced.

pERC noted that the time horizon used in the submitted economic evaluation and in the Economic Guidance Panel's best estimates was five years. pERC discussed this in light of the short follow-up period for the BRIM-3 study and uncertainty of long-term outcomes. As a result, pERC noted that the incremental cost utility ratios associated with vemurafenib could potentially be even higher than what was estimated by the Economic Guidance Panel.

Economic evaluation in previously treated patients: Cost-effectiveness unknown in second-line setting

pERC noted that a cost-minimization analysis had also been attempted by the manufacturer to evaluate the cost-effectiveness of vemurafenib in previously treated patients. However, pERC considered that this approach was not appropriate since there is no evidence to suggest that the efficacy of vemurafenib is similar to other second-line therapies. In addition, pERC noted that because the magnitude of clinical benefit of vemurafenib in previously treated patients is uncertain, it was challenging to estimate cost-effectiveness. Therefore, pERC considered that these estimates of cost-effectiveness in previously treated patients were not robust.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: BRAF mutation testing and time-limited access in the second-line setting

The Cobas® 4800 BRAF V600 Mutation Test has been developed by the manufacturer to detect BRAF V600E mutation positive melanoma. pERC discussed possible challenges associated with testing that may affect the feasibility of adoption such as appropriate tissue sampling, gaining access to testing across the country and additional costs associated with diagnostic testing. pERC also noted that in the future, there may be other validated testing options available to identify the BRAF V600 mutation.

pERC noted that vemurafenib accessibility and budget impact would vary across the country because funding for oral drugs varies across jurisdictions.

pERC considered feedback from the Provincial Advisory Group that there may be patients who had received an alternative agent in the first-line setting prior to vemurafenib being made available who would not be eligible for vemurafenib funding in the first-line setting. pERC considered that prior to the availability of vemurafenib, there were limited treatment options in the first-line setting and that for a time-limited period it would be clinically reasonable for BRAF V600 mutation positive patients who progressed after first-line therapy (e.g. dacarabazine, treatment in a clinical trial) to have access to vemurafenib in the second-line setting. pERC noted that this need was likely to diminish once vemurafenib becomes an established first-line treatment option for BRAF V600 mutation positive patients and that the Provincial Advisory Group considered this to be an implementation issue that may need to be addressed at a jurisdictional level.

DRUG AND CONDITION INFORMATION

Drug Information	• BRAF inhibitor • 240 mg tablet reviewed by pCODR • Recommended dosage of 960 mg administered orally twice daily • Validated diagnostic test for BRAF V600 mutation required
Cancer Treated	• Unresectable or metastatic melanoma, BRAF V600 mutation positive, untreated and previously treated.
Burden of Illness	• Small proportion of patients but incidence increasing. Affects a young patient population.
Current Standard Treatment	• Dacarbazine, a systemic therapy and intravenous alkylating agent, is a commonly used first-line therapy. Other chemotherapeutic and immunologic therapies may also be used as first or second-line therapies.
Limitations of Current Therapy	• Complete responses rare and survival improvement has not been demonstrated with dacarbazine. Has side effects but generally tolerated.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist;
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Lister, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Dr. Maureen Trudeau, Dr. Chaim Bell, Dr. Scott Berry and Dr. Sunil Desai who were not present
- Carole McMahon who did not vote due to her role as a patient member alternate

All members participated in deliberations and voting on the final recommendation except:

- Dr. Chaim Bell and Jo Nanson who were not present

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of vemurafenib for advanced melanoma, through their declarations, six members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, however, no members were excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

The pERC Final Recommendation may also be informed by feedback on the pERC Initial Recommendation from pCODR's Provincial Advisory Group, patient advocacy groups that provided input at the beginning of the review and the Submitter and/or the manufacturer of the drug under review if they were not the Submitter. Feedback on the pERC Initial Recommendation that was considered is posted on the pCODR website.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Hoffmann-LaRoche Limited, 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 recommendation and publicly available guidance reports, as needed.

Use of this recommendation

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