pan-Canadian Oncology Drug Review Final Economic Guidance Report

Vismodegib (Erivedge) for Basal Cell Carcinoma

January 10, 2014

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Hoffmann-La Roche Ltd.** compared vismodegib 150mg to best supportive care (BSC) for patients with histologically confirmed metastatic basal cell carcinoma (mBCC) or locally advanced basal cell carcinoma (laBCC) inappropriate for surgery or radiotherapy. The patient population reflects patients from the ERIVANCE study (Sekulic, 2012). The ERIVANCE was a phase II singe-arm study, open label trial designed to assess the safety and efficacy of vismodegib in laBCC and mBCC patients. Vismodegib is an orally administered drug. According to the Submitter there is currently no standard treatment option in Canada for patients with mBCC or laBCC inappropriate for surgery or radiotherapy. For these patients chemotherapy is sometimes considered an alternative option although its effectiveness is uncertain.

According to the pCODR Clinical Guidance Panel (CGP), comparison of vismodegib to BSC is appropriate as there are currently no approved treatment options in Canada for mBCC and laBCC patients.

Patient advocacy groups considered the following factors important in the review of vismodegib, which are relevant to the economic analysis: improvement in quality of life and physical appearance, improvements with respect to disease progression, side effects and the fact that vismodegib is available in a convenient means of administration (oral). A full summary of patient advocacy group input is provided in the pCODR Clinical Guidance Report (CGR). The submitter made an effort to address the impact of vismodegib on quality of life disease progression and short-term side effects in the economic analysis however there were limitations to these analyses.

The **Provincial Advisory Group (PAG)** suggested that the following factors would be important to consider if implementing a funding recommendation for vismodegib, and which are relevant to the economic analysis: vismodegib being only available in one dose and vismodegib's impact on clinical resources due to treating a new population of patients and increased workload for pharmacies and clinics. A full summary of PAG input is provided in the pCODR CGR.

Based on the list price, vismodegib costs $294.22 per 150mg. At the recommended dose of 150mg per day, the cost of vismodegib is $294.22 per day or $8,238.24 per 28 day cycle.

1.2 Summary of Results

The submitted economic analysis analyzed separately the two populations (laBCC inappropriate for surgery or radiotherapy and mBCC). The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) for the laBCC population was between $161,370 and $497,864 per quality-adjusted life year (QALY) gained when vismodegib is compared with BSC. The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) for the mBCC population is between $147,860 and $656,314 per QALY gained when vismodegib is compared with BSC. The wide range of the economic results can be attributed mainly to the substantial uncertainty around the utility estimates for the study populations.

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

- the extra cost of vismodegib for patients with laBCC is between $168,446 and $193,238. The factors that mainly influence incremental cost are the unit price of vismodegib and the weekly supportive care cost after progression.
- the extra cost of vismodegib for patients with mBCC is between $117,090 and $136,374. The factors that mainly influence incremental cost are the unit price of vismodegib and the weekly supportive care cost after progression.
- the extra clinical effect of vismodegib, measured in ΔQALYs, for patients with laBCC is between 0.363 and 1.264 (ΔE). The factors that mainly influence incremental effect are the utility estimates for the health states and the assumption of the difference overall survival between the progression-free and progressed state.
- the extra clinical effect of vismodegib, measured in ΔQALYs, for patients with mBCC is between 0.169 and 0.794 (ΔE). The factors that mainly influence incremental effect are the quality of life estimates and the assumption on difference in overall survival between the two arms.

This range is based on the most optimistic and most pessimistic scenarios of the analysis submitted by **Hoffmann-La Roche Ltd** as well as the reanalysis done by the EGP.

In the reanalysis by the EGP, the assumptions around the cost of wound care and the time horizon of the model were evaluated:

Wound care costs

In the economic analysis the submitter made the assumption that the cost of wound care for progressed patients is $7,116.58 per 3 months. Based on input from the pCODR Clinical Guidance Panel, the EGP considered this as an overestimate of the wound care cost and conducted a reanalysis using an estimate that is 50% the value used by the submitter ($3,558.30 per 3 months). Under this assumption

- in the laBCC population the extra cost of vismodegib is $192,309 (ΔC) and the extra clinical effect is between 0.403 and 0.679 QALYs, which increases the incremental cost-effectiveness ratio.
- in the mBCC population the extra cost of vismodegib is $129.924 (ΔC) and the extra clinical effect is between 0.729 and 0.773 QALYs, which increases the incremental cost-effectiveness ratio.

The Submitter additionally assumed that patients in the progression-free state experience no wound care costs. The EGP, using input from a clinical expert, conducted a reanalysis where 25% of the progression-free patients experience wound care costs. Under this assumption

- in the laBCC population the extra cost of vismodegib is $191,792 (ΔC) and the extra clinical effect is between 0.403 and 0.679 QALYs, which increases the estimated incremental cost-effectiveness ratio.
- in the mBCC population the extra cost of vismodegib is $136,374 (ΔC) and the extra clinical effect is between 0.729 and 0.773 QALYs, which increases the estimated incremental cost-effectiveness ratio.

Time horizon

The EGP conducted a reanalysis where the time horizon of the model was changed from the baseline lifetime horizon of 40 years) to 10 years, taking into consideration input from the pCODR Clinical Guidance Panel and the trial duration. This 10 year time horizon was

considered appropriate for the mBCC population as the expected survival of these patients is <10 years. For the laBCC patients, although their expected survival may be longer, the time horizon was limited since based on extrapolation from the clinical trial data, at 10 years, almost all patients have progressed (only 0.2% progression-free), therefore, no additional benefit is expected from vismodegib after this point.

- The extra cost of vismodegib in laBCC patients is $168,445.77 ($\Delta C_2$) and the extra clinical benefit is between 0.380 and 0.640 QALYs, which increases the estimated incremental cost-effectiveness ratio.
- the extra cost of vismodegib in mBCC patients is $124,213.36 ($\Delta C$) and the extra clinical benefit is between 0.675 and 0.733 QALYs, which increases the estimated incremental cost-effectiveness ratio

According to the economic analysis that was submitted by **Hoffmann-La Roche Ltd**, when vismodegib is compared with BSC:

- the extra cost of vismodegib for laBCC patients is $178,692 ($\Delta C$). Costs included treatment with vismodegib, wound care and healthcare visit costs.
- the extra cost of vismodegib for mBCC patients is $125,741 ($\Delta C$). Costs included treatment with vismodegib, wound care and healthcare visit costs
- the extra clinical effect of vismodegib is between 0.403 and 0.679 QALYs (ΔE) for patients with laBCC and between 0.729 and 0.773 QALYs for patients with mBCC.
- So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was between $263,141 and $443,613 for the laBCC patients and between $162,646 and $172,464 for the mBCC patients.

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

Although, the range of EGP estimates was broad, they were not considerably different from those provided by the submitter. The variation in the ICER due to the EGP-altered model inputs (time horizon and cost of wound care in the progression free and progressed states) is relatively small compared to the degree of uncertainty related to the quality of life data. However, this uncertainty of the quality of life data was illustrated in the submitter's report already. The EGP was not able to reanalyze the model with quality of life data that were collected alongside the clinical trial, due to limitations of the quality of life instrument used (lack of sensitivity for this indication, ceiling effect for relatively healthy individuals at baseline) and the small size of the sample.

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

Partially. The manufacturer made an effort to address the impact of vismodegib on quality of life. However the quality of life data collected alongside the clinical trial could not be used in the economic model because of the limitations described above. Quality of life estimates from the literature were used instead. The analysis did not explicitly focus on physical appearance although some components of the tool used to measure quality of life (SF-36) are sensitive to physical appearance. The analysis took into account disease progression and side effects although under the limitation of the non-comparative nature

of the data. The submitter incorporated some short-term side effects in the model. There is very limited information on the long-term side effects of vismodegib and therefore it was not possible to incorporate these side effects in the economic model.

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 required

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?

A number of assumptions had to be made from the submitter. Some of these assumptions were due to the fact that the economic analysis was based on a single-arm non-comparative trial. The submitter assumed that every patient in the control arm will by default be in a progressed disease state and any response can only be experienced by patients on treatment with vismodegib.

The submitter presented two scenario analyses regarding the quality of life of patients with laBCC and mBCC. In the first scenario the submitter assumed that that quality of life of patients with partial or complete response and progressed laBCC and mBCC is similar to the quality of life of patients with metastatic melanoma (MM) and partial or complete response or disease progression. In the second scenario the submitter used utilities of advanced BCC (aBCC) patients from a UK study that were estimated through a time trade-off (TTO) method. It was assumed that the patient's utility is a function of tumour size and number of tumours. The final utilities were calculated based on a weighted average of the utilities for each health state (Stable Disease, Partial Response, Complete Response and Progression) and the proportion of patients within each range of tumour sizes. These two scenarios resulted in significantly different results in the economic analysis for both the mBCC and the laBCC populations. Additionally the submitter made the assumption of reduced survival after disease progression for the mBCC population. Without the assumption of a survival benefit the resulting ICERs are much higher ($308,632 or $656,314).

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?

Most of the cost data were adequate, although the cost of wound care was overestimated for patients with disease progression and underestimated for those that were progression-free. There were a number of limitations with the quality of life data. Given that the bulk of clinical benefit originates from the change in quality of life, relying on estimates from a different population introduces uncertainty to the accuracy of the cost effectiveness estimates. Utility estimates that are more representative of the study populations would have been preferable. The quality of life data collected alongside the clinical trial could have provided such an estimate but a number of limitations related to the small sample of the study and the lack of sensitivity of the instrument used (SF-36) for this indication did not allow the EGP to use these data in the economic analysis. On the basis of this limited information, the overall quality of life observed in the ERIVANCE trial for both laBCC and mBCC populations was inconclusive.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

A budget impact analysis (BIA) was submitted to determine the impact from the public payer's perspective of the introduction of vismodegib over a three year time horizon. The variables involved in the BIA were the epidemiology of (locally advanced and metastatic) BCC, the cost of vismodegib, the underlying population size, the proportion of patients covered by a drug plan and the market share of vismodegib. The most important of these factors were: the disease prevalence (including the proportion of BCC being mBCC or laBCC) the proportion of patients covered by a drug plan, the market share and the price of vismodegib.

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

The model structure of the BIA was appropriate. The key limitations of the submitted budget impact analysis relate to the limited literature on the epidemiology of the disease in Canada and the uncertainty regarding the proportion of eligible patients who would be covered by a drug plan. It should be noted that, given the high cost of vismodegib, small deviations from the current assumptions can have significant implications on the budget impact estimations. Finally, due to the between-province variation on drug coverage plans in Canada, the proportion of eligible patients across provinces might be significantly different with, again, large implications on the budget.

1.5 Future Research

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

The current model could be improved through the application of Canadian specific estimates of quality of life collected from the literature (e.g. from Hogg (2010)). The EGP identified this alternative source of utility estimates for advanced melanoma patients during the review. Unfortunately the EGP was unable to incorporate these utility estimates due to the current structure of the model. However, the Canadian utility estimates were less favourable for vismodegib, implying that the cost-effectiveness estimate with the Canadian utility estimates would be higher than the one provided by the submitter.

Is there economic research that could be conducted in the future that would provide valuable information related to vismodegib for treatment of laBCC and mBCC?

Valuable information could be provided by an economic analysis that is based on a randomized clinical trial in which the efficacy and safety of vismodegib would be compared against a control intervention. In addition, a study collecting utilities for the populations of interest (laBCC/(mBCC), potentially through a disease specific instrument rather than a generic tool such as SF-36 (as was done in ERIVANCE), would provide the necessary input utility parameters for an economic analysis. Finally, long term follow-up data could provide information on the effect of vismodegib on mortality and long-term side effects for the laBCC and mBCC populations.

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 Final 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 vismodegib (Erivedge) for basal cell carcinoma A full assessment of the clinical evidence of vismodegib (Erivedge) for basal cell carcinoma 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 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.

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