PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Aflibercept (Zaltrap) for Metastatic Colorectal Cancer

September 5, 2014

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TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis submitted to pCODR by Sanofi-Aventis Canada Inc. compared aflibercept + FOLFIRI to placebo + FOLFIRI in patient with metastatic colorectal cancer (mCRC) who had been previously treated with oxaliplatin. The patient population reflects patients from the VELOUR trial (Van Custem et al. 2012). Aflibercept is administered intravenously. There is some regional variability in practice patterns in Canada in the treatment of mCRC however patients are often first treated with FOLFIRI with or without bevacizumab.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate however the Clinical Guidance Panel considered that bevacizumab + FOLFIRI may be a clinically relevant comparator. The Submitter included this comparison in modifications to the main economic analysis at pCODRs request.

Patients considered the following factors important in the review of aflibercept, which are relevant to the economic analysis: quality of life, progression-free survival, overall survival.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for aflibercept, and which are relevant to the economic analysis: provinces where FOLFOX is not the current funded first-line treatment or standard of care, drug wastage, and management of toxicities (neutropenia) associated with this therapy.

At the list price, aflibercept costs $500.00 per 100mg vial and $1000.00 per 200mg vial. At the recommended dose of 4mg/kg every two weeks, for a 70 kg patient, aflibercept costs $100.00 per day and $2800.00 per 28 day course.

Bevacizumab cost $125.00 per 25mg vial at the list price. At the recommended dose of 5 mg/kg every two weeks, for a 70 kg patient, bevacizumab costs $125.00 per day and $3500.00 per 28 day course.

FOLFIRI (Irinotecan, Leucovorin, Fluorouracil) costs $10.00, $0.50 and $1.50 per 20mg/ml, 10mg/ml and 50mg/ml vials, respectively. At the recommended dose of 180 mg/m^2 (Irinotecan), 400 mg/m^2 (Leucovorin) and 400 mg/m^2 (Fluorouracil) every two weeks, for a 70 kg patient, FOLFIRI costs $14.38 per day and $402.56 per 28-day course.

1.2 Summary of Results

The EGP has presented two sets of results: the first using placebo + FOLFIRI as the comparator, the second using bevacizumab + FOLFIRI as the comparator. Direct evidence for the placebo + FOLFIRI comparison is available through the results of the VELOUR trial. Only indirect evidence is available for the bevacizumab + FOLFIRI comparison, and this evidence has been obtained from a network meta-analysis (NMA) conducted by the manufacturer (see pCODR Clinical Guidance Report, section 7).

<u>Placebo + FOLFIRI as the comparator:</u>

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is $140,370/QALY when aflibercept + FOLFIRI is compared with placebo + FOLFIRI.

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

- the incremental cost of aflibercept + FOLFIRI is $17,069. Factors affecting this estimate include modelling assumptions (time horizon, a calibration factor on the number of treatment cycles, assumptions regarding the therapeutic effect of aflibercept + FOLFIRI in the post-trial period) and the consideration of drug wastage.
- the incremental effect for aflibercept + FOLFIRI is 0.1216 QALYS. This was lower than the submitted model, due to modelling assumptions (i.e., reducing the post-progression benefit) and the choice of lower utility values used by the EGP in the model.

For the comparison with placebo + FOLFIRI, the EGP based these estimates on the original model submitted by Sanofi-Aventis Canada Inc. and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when the following adjustments are made, the ICER increases due to an increase in the incremental costs (by $4,251 compared with the submitted analysis) and a decrease in the incremental clinical effect (by 0.0791 QALYs compared with the submitted analysis):

Analysis	Incremental Costs	Incremental Effects (QALYs)	ICUR
Submitted Analysis	**$12,818**	**0.2007**	**$63,850**
EGP's reanalysis estimates			
Time Horizon decreased from 16 to 5 years	$12,571	0.137	$91,665
Utility values decreased *	$12,571	0.122	$102,891
Calibration factor removed*	$16,111	0.137	$117,479
Wastage considered*	$13,296	0.137	$96,955
Post-progression impact of aflibercept decreased by 50%*	$12,539	0.129	$97,172
All factors combined (EGP Best Estimate)	**$17,069**	**0.1216**	**$140,370**

*Estimates based on 5-year time horizon.

The EGPs estimates differed from the submitted estimates. The main reasons for the difference in estimates were assumptions regarding the time horizon, the utility values used, a calibration factor on the number of treatment cycles, drug wastage, and the impact of treatment with aflibercept + FOLFIRI on overall survival after treatment discontinuation.

According to the primary economic analysis that was submitted by Sanofi-Aventis Canada Inc., when aflibercept + FOLFIRI is compared with placebo + FOLFIRI:

- the extra cost of aflibercept + FOLFIRI is $12,818. Costs considered in the analysis included drug and drug administration, disease management costs, subsequent treatment options, and adverse events.
- the extra clinical effect of aflibercept + FOLFIRI is 0.2007 QALYs (0.3207 life years). The clinical effect considered in the analysis was based on progression free survival and overall survival obtained from the VELOUR trial (Van Cutsem et al. 2012) and utility values reported in the literature.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC/ΔE) was $63,850/QALY ($39,968/LY).

Bevacizumab + FOLFIRI as the comparator:

The EGP's best estimate of the incremental cost of aflibercept + FOLFIRI when compared with bevacizumab + FOLFIRI is that there are potential cost savings ranging from $3021.11 to $3518.24 (ΔC) associated with aflibercept+FOLFIRI and that the difference in the incremental effect (ΔE) could be between -0.0047 (approx. 2 days less benefit) **and 0.00006 QALYs** (approx. 30 minutes extra benefit) **based on the submitted NMA results. However, in the absence of a head-to-head trial and with limitations in the submitted NMA, the true difference in incremental effect is unknown and these should only be considered rough estimates to be used with extreme caution.**

For the comparison with bevacizumab + FOLFIRI, the EGP based these best estimates on a model submitted by Sanofi-Aventis Canada Inc. that presented four different scenarios and was informed by a network meta-analysis conducted by the Submitter, plus reanalyses conducted by the EGP. The reanalysis conducted by the EGP was based on changes to the original model's time horizon and the calibration factor for the number of treatment cycles (similar to the analysis comparing aflibercept + FOLFIRI with placebo + FOLFIRI). The reanalysis (see Table 8, section 2) showed that:

- when the time horizon is decreased from 16 years to 5 years, the average cost of treatment with aflibercept + FOLFIRI and with bevacizumab + FOLFIRI decreases in each of the four scenarios.
- When a calibration factor on the number of treatment cycles is removed, the average cost of treatment with aflibercept + FOLIFIRI and with bevacizumab + FOLFIRI increases in each of the four scenarios
- The decrease in time horizon and removal of the calibration factor have no impact on incremental QALYs in the two analyses that make assumptions of unequal safety between comparators.
- In all scenarios, the cost savings associated with aflibercept + FOLFIRI that were estimated by the EGP are $914.74 more than the cost savings the submitter would have estimated.
- The relative efficacy of aflibercept + FOLFIRI and bevacizumab + FOLFIRI was assumed to be similar by both the EGP and submitter in all of the scenarios. However, because of the serious limitations of the NMA and in the absence of a head-to-head comparison, the relative clinical effect is unknown and the EGP did not conduct further reanalyses due to the vast uncertainty in the true value of this parameter.

All EGP reanalyses assumed that the recommended dosing of aflibercept (4 mg/kg daily) and bevacizumab (5 mg/kg) was followed and that efficacy is similar between bevacizumab and aflibercept. All other parameters were in the model were assumed similar between aflibercept+FOLFIRI and bevacizumab+FOLFIRI. The EGP's best estimates assumed a 5-year time horizon and removed the calibration factor from the model (cost savings of $3518.24). In addition:

- Administration costs may be less for bevacizumab than aflibercept due to a potentially shorter infusion time (30 mins vs. 60 mins) – cost savings of $3205.78 in favour of aflibercept.
- Some differences in safety based on the primary analyses of the NMA – cost savings of $3462.70 and incremental QALYs 0.00006
- Some differences in safety based on the secondary analyses of the NMA – cost savings of $3021.11 and incremental QALYs -0.00467

Although the NMA suggested the possibility of differences in safety between bevacizumab and aflibercept, these results were not statistically significant in the NMA and there are serious limitations to this NMA. Therefore, these should only be considered rough estimates to be used with extreme caution.

The EGPs estimates differed from the submitted estimates. The main reasons for the difference in estimates were due to changes to the original model's time horizon and removing the calibration factor for the number of treatment cycles, both of which increased the costs associated with bevacizumab+FOLFIRI.

According to the supplemental models based on an NMA that were submitted by Sanofi-Aventis Canada Inc., when aflibercept + FOLFIRI is compared with bevacizumab + FOLFIRI

- aflibercept + FOLFIRI is less costly by $2,106 to $2,604, depending on the model assumptions and the data that are used. Costs considered in the models include drug and drug administration and adverse events. Other drug costs and disease management costs are the same in both groups.
- the extra clinical effect of aflibercept was 0 or when assuming unequal safety and was based on the primary NMA was 0.00006 QALYs (approx. 30 minutes extra benefit) or -0.00467 QALYs (approx. 2 days less benefit).

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?

The manufacturer's model assumed a lifetime horizon of 16 years, however, based on the opinion of the Clinical Guidance Panel the expected time horizon for the patient population in which this treatment is indicated is more likely to be four to five years. In addition, the manufacturer applied a calibration factor to drug treatment costs, on the basis that the model overestimated the number of treatment cycles, compared to what was observed in the VELOUR trial, however it was unclear why this adjustment should be made to only this variable. The calibration factor was not applied to other variables in the model that might also be affected by an overestimation of cycles (e.g. other costs, utility

values.) Utility values were obtained from the literature and, in other published analyses (see section 2.3 for more details), these values have been considered too high.

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

Yes. Based on patient advocacy group input, patients considered survival and quality of life to be important, and while side-effects were important, the majority of patients would not refuse a therapy based on a severe toxicity profile. These three factors were considered in the model.

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

The EGP found the submitted model for the aflibercept+FOLFIRI versus the placebo+FOLFIRI comparison to be adequate. Given the lack of direct evidence for the bevacizumab+placebo comparison, the related models relied on an NMA whose validity was brought into question though critical appraisal (see pCODR Clinical Guidance Report, section 7). In addition, a large number of parameters in the model were assumed to be equal, which may have contributed to very unusual results. For example, consistent incremental values were observed regardless of what parameters the EGP modified, across the four scenarios provided by the submitter.

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?

Key variables that had an important impact on the model include the time horizon, the calibration factor on the number of treatment cycles, the utility values used, and drug wastage. The time horizon used by the manufacturer is optimistic in comparison with the prognosis for this patient population. The calibration factor was considered only for drug costs and not for other factors in the model. Utility values were not obtained from the VELOUR trial but from a trial of another treatment, and preliminary utility values from a program that includes patients taking aflibercept, as well as utility values found in the literature, suggest that the values used by the manufacturer may be high. There was no account of drug wastage in the base case analysis. Finally, the manufacturer's model assumed that the benefit of aflibercept + FOLFIRI continued into the post-trial period, which was not supported by the pCODR 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?

For the placebo + FOLFIRI comparison, the EGP would have used similar clinical data, however it would have used utility values obtained from patients who had been treated with aflibercept. The EGP would have used a shorter time horizon that is consistent with the prognosis for this patient population. An accounting for drug wastage would also have been made.

For the bevacizumab + FOLFIRI comparison, the EGP would use the NMA data only with extreme caution and an explicit statement of its limitations. The NMA is of questionable validity given the substantive differences across the included the studies (see pCODR Clinical Guidance Report, section 7). Even when considering these analyses, the estimated impact of aflibercept on quality of life based on observed safety differences is questionable as these were not statistically significant in the NMA. Analysis of safety data

showed no statistically significant difference between treatments in both the primary (HR: 0.8511, 95%CI: 0.505-1.4301) and secondary analyses (HR: 1.044, 95%CI: 0.873-1.25). However, the submitted analyses included an extra benefit of 0.00006 QALYs (approximately 30 minutes of extra benefit) reported in analysis 3, and 0.00467 fewer QALYs (about 2 days) reported in analysis 4 based on these data.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The budget impact analysis estimated the number of patients with metastatic colorectal cancer in Ontario who had previously been treated with an oxaliplatin-based therapy and were eligible to be treated with aflibercept + FOLFIRI over a three year period, under the assumptions of aflibercept reimbursement and no aflibercept reimbursement. Key variables in this analysis included the estimated number of new cases of CRC in Canada by province, population growth in the 50+ age group, the distribution of new cases of disease by stage and by province, expected survival, market share, and drug costs. Sensitivity analyses considered the number of incident cases per year, projected population growth rates, the percentage of patients treated with first-line chemotherapy, patients eligible to receive second-line chemotherapy, aflibercept market share, 2nd-line FOLFIRI market share, number of treatment cycles, relative dose intensity (RDI), wastage, and an alternative bevacizumab scenario where this treatment would be reimbursed beyond progression.

The submitter's results were most sensitive to assumptions regarding market share and wastage.

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

There is regional variability in Canada with regard to practice patterns and the use of either FOLFIRI first line, or FOLFIRI or FOLFOX with bevacizumab first line. Patients receiving FOLFIRI first line would not be eligible for the aflibercept + FOLFIRI combination second line. If aflibercept were funded in second line, there is a possibility that some patients would opt to use FOLFOX + bevacizumab first line, knowing that this would give them the option to use aflibercept + FOLFIRI second line. This scenario was not addressed in the budget impact analysis, and is an important consideration when assessing the regional budget impacts of approving aflibercept + FOLFIRI.

1.5 Future Research

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

- Long-term clinical data to validate the projections and assumptions regarding post-trial survival;
- Health state utilities for patients taking aflibercept.
- Direct evidence for a comparison with bevacizumab

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

Canadian data on the availability, utilization, and administration of aflibercept, to better understand patterns of use and drug wastage.

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 Gastrointestinal 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 aflibercept (Zaltrap) for metastatic colorectal cancer. A full assessment of the clinical evidence of aflibercept (Zaltrap) for metastatic colorectal cancer 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*. 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.

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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