PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Final Economic Guidance Report

Ruxolitinib (Jakavi) for Myelofibrosis

January 14, 2013

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Novartis Pharmaceuticals Canada Inc.,** compared ruxolitinib to best available therapy (BAT) for patients with myelofibrosis (MF). This patient population reflects patients from the COMFORT-II trial (Harrison et al. 2012). Ruxolitinib is administered orally. Best available treatment was defined as a treatment or combination of treatments in accordance with the protocol of the COMFORT-II trial.

According to the pCODR Clinical Guidance Panel (CGP), this comparison was appropriate.

Patient advocacy groups considered the following factors important in the review of ruxolitinib, which are relevant to the economic analysis: improvement in a patient's quality of life and survival, and an accessible treatment that will enable them to continue to work and maintain a normal life. A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

- The submitted economic analysis explicitly considered improvements in quality of life by applying utility scores and measuring outcomes in quality-adjusted life years. The quality of life information was collected from the COMFORT-II trial.
- The model has not considered whether ruxolitinib will enable patients to spend more time working or with family – the model adopts the perspective of the publicly funded health care system which is appropriate for pCODR because drug funding recommendations must be considered from a health system perspective.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for ruxolitinib, and which are relevant to the economic analysis: oral dosing and administration of ruxolitinib, patient monitoring, and implementation costs. A full summary of Provincial Advisory Group input is provided in the pCODR Clinical Guidance Report.

- Oral administration of ruxolitinib was not explicitly considered in the submitted model as ruxolitinib was compared with oral (predominantly) and injectable treatments.
- Patient monitoring costs for drug interactions were not explicitly considered in the submitted model.
- Implementation costs - workload at chemotherapy clinics to allow for appropriate monitoring of ruxolitinib for dose adjustments, adverse effects and drug interactions - were not explicitly considered in the submitted model.

At the list price, ruxolitinib costs $82.19 per 5 mg, 15 mg, or 20 mg tablets. At the recommended dose of 15 mg twice daily, the average cost per day in a 28-day course of ruxolitinib is $164.38 and the average cost per 28-day course is $4602.64

1.2 Summary of Results

The Economic Guidance Panel's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $276,191/QALY and $383,686/QALY when ruxolitinib is compared to best available therapy. This estimate is based on reanalyses conducted by the Economic Guidance Panel and using the model submitted by Novartis Pharmaceuticals Canada Inc.

The incremental cost-effectiveness ratio (ICER) 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 (ΔC) of ruxolitinib is between $20,360 and $21,620. Costs included drug costs and healthcare costs associated with routine follow-up for patients receiving active treatment, adverse events, leukemic transformation, and palliative care.
- the extra clinical effect (ΔQALY) of ruxolitinib is between 0.06 QALYs (3.12 weeks) and 0.07 QALYs (3.64 weeks). Key clinical effects included quality of life data from COMFORT-II trial (Harrison et al, 2012) and survival benefit from an observational study (Vestovsek et al. 2010).

This range is based on Economic Guidance Panel reanalyses that assumed the model's time horizon to be shorter than the proposed lifetime time horizon ([redacted]) modelled by the manufacturer and assuming that the treatment did not provide a survival advantage. (*Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).* Given the model's limitation and the heavy reliance on extrapolation of clinical benefit, it was felt appropriate to consider more conservative options related to shorter time horizons. The assumptions that the time horizon should be reduced and there should be no survival advantage were suggested by the pCODR Clinical Guidance Panel.

- The upper estimate of the range (ICER of $383,686) assumed that ruxolitinib did not reduce risk of mortality and that the time horizon of the model was reduced to 96 weeks versus the lifetime time horizon modelled by the manufacturer. The extra costs associated with ruxolitinib were $21,620 and the extra QALYs associated with ruxolitinib were 0.06.
- The lower estimate of the range (ICER of $276,191) assumed that ruxolitinib did not reduce the risk of mortality and that the time horizon of the model was reduced to 144 weeks versus the manufacturer's lifetime time horizon. The extra costs associated with ruxolitinib were $20,360 and the extra QALYs associated with ruxolitinib were 0.07.
- The estimates above represent the EGP's best estimates in light of the model's inherent structural limitation that does not permit the EGP to adjust the time horizon input parameter beyond what was originally programmed by the manufacturer. The EGP attempted to conduct reanalyses to explore the impact of time horizons between 144 weeks and lifetime ([redacted]). (*Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).* However, the submitted model did not permit modifications to this parameter other than what was originally provided (24, 48, 96, 144 weeks, and lifetime) and thus it was difficult to assess any possible impact on the Submitter's cost and effect estimates.

- The EGP's original estimates (ICER between $199,118/QALY and $259,698/QALY with upper and lower estimates of the extra cost (ΔC) for ruxolitinib being between $14,634 and $14,679) were revised in this final report based on the discovery of an error in the model's technical file. This error would cause the model to report lower incremental costs associated with patients with intermediate-2 risk levels when time horizons are shortened from the lifetime horizon. The submitted model assumed more patients would be intermediate-2 rather than high risk, therefore underestimated incremental costs in the intermediate-2 risk patient population, when measured over a time horizon shorter than lifetime, would produce a lower overall ICER.

The Economic Guidance Panel's estimates differed from the submitted estimates. This is primarily because in the submitted model, there is an assumption that ruxolitinib provides a survival benefit by reducing the risk of mortality compared to patients on best available therapy, and that treatment effects of ruxolitinib have been extrapolated using short term data (median follow-up time of 12 months) (Harrison et al. 2012). Therefore, in the Economic Guidance Panel reanalyses, when the time horizon was shortened to align with clinical data as suggested by the CGP, extra QALY gains for ruxolitinib are lower and lead to a decrease in the extra healthcare-associated costs for ruxolitinib.

According to the economic analysis that was submitted by the manufacturer, when ruxolitinib was compared to best available therapy:

- The extra cost (ΔC) of ruxolitinib is $83,246.
- The extra clinical effect (ΔE) of ruxolitinib is 0.82 QALYs. This was largely driven by the implicit model assumption that ruxolitinib provides a survival benefit. This survival benefit is conferred to the ruxolitinib arm by assuming that a 50% or greater reduction in palpable spleen length improved OS.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC/ΔE) was $101,207 per QALY.

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 key reasons for differences between the submitter's and Economic Guidance Panel's estimates relate to assumptions around survival benefit and extrapolation of treatment effects of ruxolitinib beyond the duration of the clinical trial. The manufacturer submitted a model where a survival benefit can be obtained if a 50% or greater reduction in palpable spleen length is achieved. This confers a survival benefit to the ruxolitinib arm. The COMFORT-II study did not show any statistically significant differences in survival between patients receiving ruxolitinib or best available therapy; however, the model's assumption of survival benefit was based on the results of an open-label, single-arm observational study (Verstovsek et al., 2011a). Also, the model assumed that treatment effects of ruxolitinib will extend beyond the COMFORT-II trial duration of 48 weeks despite the lack of evidence to support this assumption. The Clinical Guidance Panel determined that there may not be sufficient evidence to assume a survival benefit with ruxolitinib and that it is unclear whether treatment benefits with ruxolitinib would be anticipated beyond clinical trial duration. The Economic Guidance Panel estimate is based on a reanalysis which assumed no survival benefit associated with ruxolitinib and that the time horizon of the model was reduced to align with a more clinically realistic time frame for benefit.

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

Yes. Based on patient advocacy group input, patients considered the following factors important in the review of ruxolitinib and which were relevant to the economic analysis: improvement in a patient's quality of life and an accessible treatment that will enable them to continue to work and maintain a normal life. These factors were addressed in the economic analysis when possible and appropriate.

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 had an important effect on the results?

In the submitted economic model, the manufacturer assumed that ruxolitinib had a survival benefit based on an observational study that compared ruxolitinib patients to a historical cohort. The comparative trial, COMFORT-II, did not detect a survival benefit with ruxolitinib compared to BAT. The submitter also assumes that the treatment effects of ruxolitinib, reducing splenomegaly and improving quality of life, are extended over a lifetime time horizon. The time horizon of the data from the clinical trial, COMFORT-II study is short (48 weeks) in comparison with the lifetime time horizon of the model. Based on the clinical data currently available and expected estimates of biological plausibility, the Clinical Guidance Panel suggested that it was unlikely there would be any survival benefit accrued with ruxolitinib or that treatment benefits would extend beyond trial duration. Therefore, assumptions around survival benefit and extrapolation using short term data could have a pronounced effect on clinical effect estimates. Overall, this has an impact on the cost-effectiveness estimates and the Economic Guidance Panel conducted reanalyses to address these limitations, which led to higher estimates of the ICUR.

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?

The utility data used was adequate and the EGP would have used similar data. However, estimates of resource costs associated with non-responders was based on a chart review. It was unclear how these costs were estimated from the chart review or how many patient charts were reviewed. As the resource costs associated with non-responders are generally expected to be higher than the resource costs associated with responders, the resource cost can partially offset the cost of ruxolitinib in those who respond to ruxolitinib. Therefore, it is important to have a reliable estimate of the difference in resource cost between non-responders and responders to avoid biasing the result of the ICER. The remainder cost information was adequate. Also, estimates of long term treatment gains and survival benefit were uncertain due to lack of available long-term data and the Economic Guidance Panel would not have applied a survival benefit.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The manufacturer submitted a budget impact analysis that provides estimates of the increased costs for the three years subsequent to the listing of ruxolitinib for MF. The key

variables included in the manufacturer's budget impact analysis are: total population of Canada, prevalence of MF, and proportion of population covered by a provincial public drug plan. As the manufacturer did not disclose the results of the analysis to pCODR (results were presented to the public drug plans separately), the EGP predicts that the factors which most heavily influenced the budget impact analysis is the proportion of MF patients eligible for public coverage.

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

The model structure of the budget impact analysis was appropriate. The key limitation of the submitted budget impact analysis relates to the limited data to support the assumption relating to the proportion of eligible patients who would be covered by a drug plan.

1.5 Future Research

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

The economic evaluation of ruxolitinib could have been improved by including efficacy and survival data from clinical trials that included long term data to evaluate these assumptions are needed as foci of further research.

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

If ruxolitinib becomes a standard treatment option for patients with MF, further assessment of effectiveness and cost-effectiveness of ruxolitinib compared BAT in the treatment of MF would provide a more accurate reflection of real-world cost-effectiveness.

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 Myelofibrosis 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 ruxolitinib for myelofibrosis. A full assessment of the clinical evidence of ruxolitinib for myelofibrosis 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 has been 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.

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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