pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Ruxolitinib (Jakavi) for Polycythemia Vera

March 3, 2016

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The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Novartis Pharmaceuticals Canada Inc.** compared ruxolitinib to best available therapy (BAT) for patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea.

Table 1. Summary of submitted economic model

Submitted Economic Model	
Funding Request/Patient Population Modelled	*For the treatment of adult patients with PV that are resistant or intolerant to hydroxyurea*
Type of Analysis	*CUA*
Type of Model	*Markov state transition*
Comparator	*Best available therapy (BAT)*
Year of costs	*2014*
Time Horizon	*15 years, 3 month cycle length*
Perspective	*Canadian healthcare payer*
Cost of Ruxolitinib	• $82.1918 per 10 mg tablet • Daily cost of $164.38 *(two 10 mg tablets per day)* • $4,602.7408 per 28-day course
Cost of Hydroxyurea	• $1.020 per 500 mg tablet • Daily cost of $2.041 *(two 500 mg tablets per day)* • $57.137 per 28-day course
Cost of Anagrelide	• $3.3491 per 0.5 mg tablet • Daily cost between $8.373 - $26.793 *(2.0 mg per day for 1 week, then 1 - 4 mg per day for maintenance)* • $234.437 - $750.198 per 28-day course
Cost of peginterferon	• $399.40 per 180 mcg / 0.5 mL vial • Daily cost $57.057 *(90 mcg weekly for 2 weeks, then 180 mcg weekly)* • $1,597.60 per 28-day course
Model Structure	The model was comprised of 4 health states: on primary treatment, first subsequent therapy, second subsequent therapy and death. All patients start on either ruxolitinib or BAT. Patients are then distributed to 'WBC control' group based on their achieved WBC counts from the RESPONSE trial. Remaining patients in each arm were assigned to 'No WBC control' group. Patients that discontinued ruxolitinib were assumed to receive BAT as first subsequent therapy, then interferon (IFN) as the second subsequent therapy until death.
Key Data Sources	*Phase III trial data (RESPONSE)*
Other	Cross-over was allowed in the RESPONSE trial. The majority of patients (85.7%) in the standard

Submitted Economic Model	
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	therapy group crossed over to ruxolitinib at or after week 32. Median exposure to therapy was 81 weeks for ruxolitinib and 34 weeks for standard therapy. Survival is not an end-point in the trial; surrogacy for survival was calculated using external data sources (*Alvarez-Larran[1], Tefferi[2]*).

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate, as it reflects standard treatments used in clinical practice.

- Relevant issues identified included:
  - The CGP concluded that there is a net overall clinical benefit with ruxolitinib in patients with PV in the second line setting.
  - Symptoms score related to PV were significantly reduced.
  - Grade 3/4 adverse events were uncommon, manageable and similar across treatment arms.
  - Ruxolitinib may be used up to 32 weeks in the absence of a response, at which point treatment should be discontinued. Should a response be present, the duration of therapy is indefinite (given the level of evidence at this time). Regular monitoring for the duration of therapy is essential.
  - Three retrospective cohort studies suggest that elevated WBC count is associated with worse overall survival in PV, however, it has not been demonstrated that modifying the WBC count changes overall survival. Thus, the CGP felt that based on the current level of evidence, a more appropriate end-point for the submitted cost-effectiveness analysis was complete hematological response (CHR).

Summary of Patient Advocacy Group input relevant to the economic analysis
Patients considered the following to be advantages to ruxolitinib: decreased frequency of phlebotomies, delayed progression of the disease, increased quality of life and better management of symptoms. The economic model took into consideration all of these factors. Patient respondents indicated that some had experienced side effects on ruxolitinib, including nausea or abdominal effects (diarrhea and pain); none experienced serious side effects or problems with the drug.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for ruxolitinib, which are relevant to the economic analysis:

- Fills a gap in therapy for patients resistant or intolerant to hydroxyurea;
- Potential for indication creep (evidence not available in first line);
- High number of patients deemed intolerant to hydroxyurea;
- Duration of treatment in responding patients not clear;
- Potential wastage of drug if dose adjustments are needed; and
- High cost of drug, including the use of flat pricing (same price for 10 mg tablet as 20 mg tablet). The economic analysis considers the use of 10mg tablets, twice a day.

Relevant factors were considered in the economic analysis.

1.3 Submitted and EGP Reanalysis Estimates

Estimates	Submitted	EGP Reanalysis
ICER estimate ($/QALY), range/point	$156,250	$282,785 - $284,555
ΔE (QALY), range/point	1.35	0.5997 - 0.5984
ΔE (LY), range/point	0.80	0.43
ΔC ($), range/point	$211,240	$169,575 - $170,274

The main assumptions and limitations, in no order of importance with the submitted economic evaluation were:

- The use of surrogate outcomes to determine the end-point (*Alvarez-Larran[1], Tefferi[2]*). In brief, the submitter made two adjustments to the data in order to determine overall survival (OS). The first adjustment to OS was required to generate a single background OS curve that was representative of the patient population of interest, including both hydroxyurea (HU) resistant and HU intolerant patients. The second adjustment was to generate separate survival curves for patients with WBC Control versus those with No WBC Control in order to model the effects of WBC control on OS. Both of these adjustments were required in order to generate appropriate transition probabilities of death for HU resistant/intolerant patients according to whether they had WBC Control or no WBC Control. These adjustments have been done through a model that has not been validated.
- Post-progression survival gains are greater in the best available therapy arm than in the ruxolitinib arm. These gains in the post-progression state, occurring when therapy has been discontinued, cannot be explained clinically, nor can these gains be adjusted for in the economic model. The CGP supported these concerns.
- Transformations to Post-Polycythemia Vera Myelofibrosis (PPV-MF) or acute myeloid leukemia (AML) were not included in the model. Though this is not a major limitation, the CGP did indicate that cause of death is often not due to PV but to transformation to MF.
- There was an incremental difference between the two treatment arms for utilities gained. The CGP did not support a difference of this magnitude between those on ruxolitinib and those on best available therapy.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the economic model:

- The end point to determine efficacy in the model was modified to complete hematologic response and not white blood cell control. The strategy used to model overall survival was based on white blood cell control. A model was used to correlate this to survival. This model has not yet been validated and the CGP identified it as speculative. Further, there is no evidence to support that the data from Tefferi is valid in a HU-resistant/intolerant population. Finally, clinical practice is often tailored to hematocrit response and not white blood cell count control. Based on this, the CGP & EGP concurred that CHR is best to use for the end point for efficacy.
- The cost of a thrombotic event at baseline was based on the mean not median estimate of the difference in costs of those with a thrombotic event and those without. Costs are often skewed; a large magnitude in difference between the mean and the median is an indication of skewedness (observed here). The median is more appropriate to accurately represent costs in these instances.
- The submitter used a rate of thrombotic events (TEs) from the RESPONSE trial. The CGP identified that in their clinical experience the rate for TEs for the two treatment arms should be similar. Given that the rate of TEs is a cost driver in the model, an equal rate for TEs, was explored using the rate for the BAT arm and the ruxolitinib arm to provide a range of estimates.
- Utilities used to inform the model were derived from the RESPONSE trial. The CGP did not support the large magnitude of difference seen between the utilities for those on ruxolitinib compared to those on best available therapy. In order to address this uncertainty, also given the small number of patients available to determine utility values and uncertainty about the clinically significant difference, the utility for the total intention-to-treat population was used (i.e. same utility value for both treatment arms) for the upper bound. Differing utilities for subsequent therapies was not modified.

Table 2. EGP Reanalysis for Best Case Estimates

Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICER (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	**$211,240**	**1.35**	**0.80**	**$156,250**	--
Lower bound					
End point for efficacy: (complete hematologic response)	$157,168	0.8790	0.43	$178,804	$22,554
Cost of thrombotic events - median ($18,585)	$220,657	1.35	0.80	$163,216	$6,966
Utility for on treatment - different for treatment arms	$211,240	1.35	0.80	$156,250	---------
Rate of thrombotic events - same for both treatments (0.0037)	$227,500	1.34	0.80	$169,765	$13,515
Best case estimate of the above four parameters	**$169,575**	**0.87**	**0.43**	**$194,954**	**$38,704**

Upper bound					
End point for efficacy: (complete hematologic response)	$157,168	0.8790	0.43	$178,804	$22,554
Cost of thrombotic events - median ($18,585)	$220,657	1.35	0.80	$163,216	$6,966
Utility for on treatment - same for treatment arms (0.775)	$211,240	1.00	0.80	$211,047	$54,797
Rate of thrombotic events - same for both treatments (0.0255)	$227,500	1.34	0.80	$169,765	$13,515
Best case estimate of the above four parameters	**$170,274**	**0.5984**	**0.43**	**$284,555**	**$128,305**

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include cost of ruxolitinib, and percent eligible for provincial coverage. Increasing the cost of ruxolitinib and the percent eligible for provincial coverage increase the budget impact.

Key limitations of the BIA model include an assumption that not all patients would be eligible for provincial coverage and are covered in the analysis. This parameter was able to be modified and explored by the EGP and had a significant impact on the BIA.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for ruxolitinib when compared to best available therapy is:

- Between $194,954/QALY and $284,555/QALY
- The extra cost of ruxolitinib is between $169,575 and $170,274 (ΔC). The factors that most influence cost are: the cost of ruxolitinib, the time horizon and the composition of patients (resistant vs intolerant).
- The extra clinical effect of ruxolitinib is between 0.60 and 0.87 (ΔE). The factors that most influence effectiveness are: the time horizon, the end point for efficacy and utilities.
- As the reanalysis by the EGP was completed with the model provided by the submitter, the narrow range of the EGP's best estimate does not indicate precision.

Overall conclusions of the submitted model:

- The above best estimate is valid based on the assumption that complete haematological response is a reasonable surrogate for survival.
- This economic model, however, is based on the current best evidence available.
- Future research should focus on incorporating measures of survival into the clinical trials to better inform economic models.

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 Hematology 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 (Jakavi) for polycythemia vera. A full assessment of the clinical evidence of ruxolitinib (Jakavi) for polycythemia vera 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.cadth.ca/pcodr).

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. 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.cadth.ca/pcodr). 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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