PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Axitinib (Inlyta) for metastatic Renal Cell Carcinoma

March 7, 2013

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TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Pfizer Canada Inc.** compared axitinib to everolimus for patients with metastatic renal cell carcinoma (mRCC) after failure to prior systemic therapy. A cost minimization analysis was submitted. This form of analysis compares the costs of axitinib and everolimus while assuming similar efficacy and safety profiles. Cost minimization analysis is only justifiable in situations when the evidence shows that the important patient outcomes of the intervention and comparators are essentially equivalent[1].

According to the pCODR Clinical Guidance Panel (CGP) everolimus is an appropriate comparator since is the current standard of care (SOC) for patients with mRCC after failure to prior systemic therapy in Canada.

Patient advocacy groups considered the following factors important in the review of axitinib, which are relevant to the economic analysis: comparison of efficacy and side effects with everolimus.

- The safety profiles as well as the costs associated with the management of adverse events were assumed to be comparable between axitinib and everolimus and therefore were not included in the submitted model.
- The efficacy of everolimus and axitinib was considered to be equivalent in the cost minimization analysis submitted, and therefore only comparison of drug cost was considered.

A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for axitinib and which are relevant to the economic analysis: clinical and cost-effectiveness comparison to everolimus, potential for use of axitinib as a first or third line agent, cost impact of dose titration, availability as an oral dosage form, drug interaction monitoring and potential for sequential use after or before everolimus.

- The efficacy of everolimus and axitinib was considered to be equivalent in the cost minimization analysis submitted. In this analysis only the comparison of drug costs of axitinib and everolimus was considered.
- PAG identified "Indication creep", i.e. potential for axitinib being used as first line or third line, as the most common barrier that could affect implementation. This was not explored in the submitted economic evaluation.
- Axitinib dose titrations were not explicitly considered in the model. However, the Economics Guidance Panel noted that in a presence of dose increase, axitinib is no longer cost- neutral.
- Because axitinib and everolimus are both oral tablets no effect of dosage form was reflected in the economic evaluation.
- PAG identified that drug interaction monitoring could act as a barrier to implementation with respect to ensuring adequate health care professional resources

and time to support optimal therapy. This was not considered in the submitted economic evaluation.

- PAG noted that there is a potential for sequential use for axitinib and everolimus (or vice versa) and this poses a barrier to implementation in the absence of evidence to support this possible practice. This was not considered in the submitted economic evaluation.

At the list price, axitinib costs $18.60 per 1 mg tablet and $93 per 5 mg tablet. At the recommended dose of 5 mg twice daily, the average cost per day is $186 and the average cost per 30-day course is $5,580. At a list price everolimus costs $186 per 5 mg and 10 mg tablets; and at the recommended dose of 10 mg daily, the average cost per day in is $186 and the average cost per 30-day course is $5,580.

1.2 Summary of Results

The EGP's best estimate of the added cost is between $0 and $334.80 per month per patient when axitinib is compared with everolimus. This estimate is based on reanalyses conducted by the Economic Guidance Panel and using the analysis submitted by Pfizer Canada Inc.

The results were based on cost minimization analysis, assuming equivalent clinical effect and the cost included drug cost only.

This range is based on Economic Guidance Panel reanalyses that considered **dose titration** of axitinib.

- The upper estimate of the range (ΔC of $334.8) was based on the average daily dose of 10.6 mg observed in the AXIS trial.
- The lower estimate of the range (ΔC of $0) assumed that average dose of axitinib will remain to be 5mg twice daily.

Based on the currently available data, the EGPs estimates were slightly different than the submitted estimate. However EGP noted a high level of uncertainty around the results. This is primarily because the majority of axitinib-treated patients in AXIS required dosage adjustments and it would appear that the correct dosing for axitinib has yet to be defined. Also, there is uncertainty around the assumption of similar efficacy and safety among axitinib and everolimus which need to be considered when interpreting the results. Namely if the assumption around equal efficacy and safety among axitinib and everolimus is proven to be incorrect, then cost-minimization analysis is no longer valid approach. Standard cost effectiveness/utility analysis would then need to be considered based on the incremental difference efficacy and safety between axitinib and everolimus.

According to the economic analysis that was submitted by Pfizer Canada Inc., axitinib is cost neutral when compared with everolimus:

- The cost difference ΔC is $0. Costs considered in the analysis included drug costs only.
- The clinical effects of axitinib and everolimus were considered to be equal, based on indirect treatment comparisons.

So, the Submitter estimated that there is no added cost for axitinib.

1.3 Summary of Economic Guidance Panel Evaluation

Is a cost-minimization analysis adequate for summarizing the evidence and answering the relevant question?

Yes. In the absence of head to head data, in order to support equivalent efficacy of axitinib and everolimus, the manufacturer conducted three different approaches for indirect treatment comparisons: a side by side comparison, the Bucher fixed effect model, a Bayesian fixed-effect model, and a simulated treatment comparison. Based on the pCODR Clinical Guidance Report, conclusions drawn from such indirect comparisons are not as robust as conclusions based on direct, head-to-head trial data and there are some serious limitations which need to be considered when interpreting the results of indirect treatment comparisons. However, the pCODR Clinical Guidance Panel concluded that the clinical effects of axitinib and everolimus appear similar and it is on this clinical basis that a cost minimization analysis was considered justifiable.

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

The submitter did not take into account the possibility of dose titration with axitinib, which could lead to increased costs and put at risk the cost-neutrality of axitinib versus everolimus.

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

Yes. Patient advocacy groups considered the comparison of safety profiles of axitinib and everolimus, as well as the overall comparison among these two agents important and relevant to the economic analysis in the review of axitinib. Safety and efficacy of axitinib and everolimus were considered equivalent in the presented cost minimization analysis.

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?

The submitted cost-minimization analysis is based on indirect treatment comparison, assuming equal efficacy for axitinib and everolimus. There are some serious limitations with the indirect treatment comparison which need to be considered when interpreting the results. If this assumption is proven to be incorrect with time, then a cost minimization approach would be inappropriate and therefore, the cost-effectiveness of axitinib versus everolimus would be unknown.

The only variable included in the analysis is the drug costs. As noted before, the possibility of dose titration with axitinib was not taken into account. Also, additional differences in cost, such as in monitoring cost were not included.

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?

Yes, although EGP felt that more extensive sensitivity analysis to account for the possibility of dose titration or difference in monitoring cost would have been helpful.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The manufacturer submitted an Ontario-specific budget impact analysis providing estimates of the costs for the three years subsequent to the listing of axitinib as 2nd line treatment for mRCC. The key variables included in the manufacturer's budget impact analysis are: prevalence of disease, proportion of patients progressing to second line treatment, proportion of population covered by a provincial public drug plan and the market share for those who are covered.

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

Due to the price parity at recommended doses with the most relevant comparator, everolimus, none of the parameters varied in the sensitivity analysis have impact to the results. If axitinib and everolimus are assumed to be the same price then changes in disease prevalence, proportion progress and market share make no difference to the overall budget impact. An important limitation of the submitted model was that it did not considerthe variation in the dosing of axitinib and the potential for dose increases which would result in higher costs. PAG also noted the potential of sequential use of everolimus and axitinib that is not addressed in the submitted budget impact analysis.

1.5 Future Research

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

Cost minimization is the simplest of economic models. The current analysis considers only the acquisition costs of the drugs. The model may have been improved by including more cost inputs. The safety profiles of axitinib and everolimus are not identical, and therefore the costs of managing these side effects are likely to be different. Full costing of the impact of adverse events would have improved the analysis. Also differences in monitoring costs are expected and their inclusion would have improved the analysis as well. In general, all current and future costs that are a consequence of the interventions should be included in economic evaluation.

Inclusion of more extensive sensitivity analysis would have also improved the analysis and addressed the questions around uncertainty of results.

Is there economic research that could be conducted in the future that would provide valuable information related to axitinib for treatment of metastatic renal cell carcinoma (mRCC) after failure to prior systemic therapy?

Assessment of cost-effectiveness of axitinib versus everolimus, ideally based on head to head comparison in the future would provide valuable information to decision makers.

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 Genitourinary 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 Axitinib (Inlyta) for mRCC. A full assessment of the clinical evidence of Axitinib (Inlyta) for mRCC 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. 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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