pan-Canadian Oncology Drug Review Final Economic Guidance Report

Enzalutamide (Xtandi) for Metastatic Castration-Resistant Prostate Cancer

July 23, 2013

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TABLE OF CONTENTS

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

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analyses submitted to PCODR by Astellas Pharma Canada compares enzalutamide with best supportive care (BSC), and to abiraterone in metastatic castrate resistant prostate cancer (mCRPC) patients previously treated with docetaxel-based chemotherapy. Other comparative strategies included in the economic report were cabazitaxel and mitoxantrone.

Enzalutamide is administered orally as a tablet.
BSC was defined as consisting of analgesics, bisphosphonates, antihistamines, anti-emetics and corticosteroids.
Abiraterone 1,000mg orally daily (+prednisone+ BSC)
Cabazitaxel 25mg/m2 intravenously every three weeks (+prednisone + BSC)
Mitoxantrone 12mg/m2 intravenously every three weeks (+ prednisone + BSC)

According to the pCODR Clinical Guidance Panel (CGP), these comparisons were appropriate. However, the CGP noted that while both abiraterone and cabazitaxel have demonstrated a survival benefit, mitoxantrone does not have a survival benefit, but has some palliative benefit.

Patient advocacy group input considered the following factors important in the review of enzalutamide which are relevant to the economic analysis: access to additional therapies with minimal side effects, seek a therapy that will increase their quality of life and allow them to minimize pain and dysfunction, and value ease of use. The model somewhat addresses the concerns of patients through including QALYs as the endpoint. 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 enzalutamide (enzalutamide), and which are relevant to the economic analysis: factors related to comparators (the pivotal trial for enzalutamide compared enzalutamide to placebo and not to abiraterone which the PAG identified as the main comparator), enzalutamide doesn't require concomitant steroids, factor related to the patient population (PAG identified the potential for indication creep as a potential barrier if enzalutamide is used in earlier lines of therapy prior to evidence), factors related to accessibility given that it is an oral drug and may be more easily accessed by patients, factors related to dosing (4 tablets per day which is similar to abiraterone), factors related to implementation (use of enzalutamide will be minimize wastage as only one capsule strength, and screening for seizure potential in patients could add costs). Most of these items were not addressed by the manufacturer's model. A full summary of Provincial Advisory Group input is provided in the pCODR Clinical Guidance Report.

At the list price enzalutamide costs $28 per 40 mg tablet. At the recommended dose of 160mg capsules daily, the average cost per day in a 28-day course of enzalutamide is $113 and the average cost per 28-day course is $3175.

At the list price abiraterone costs $28 per 250mg tablet. At the recommended dose of 1000mg capsules daily, the average cost per day in a 28-day course of abiraterone is $113 and the average cost per 28-day course is $3173.

At the list price cabazitaxel costs 40mg/ml. At the recommended dose of 25mg/m^2 intravenously on day 1 and 21, the average cost per 28-day course of cabazitaxel is $207 and the average cost per 28-day course is $5800.

1.2 Summary of Results

For the results, the EGP focused on the two main comparators (BSC and abiraterone).

<u>Economic evaluation of enzalutamide compared to BSC</u>
The EGP's best estimate of the incremental cost-effectiveness ratio was $115,345 per additional QALY gained versus BSC. The extra clinical effect of enzalutamide is 0.291 QALYs and the additional costs are $33,608. The EGP based these estimates on the model submitted by Astellas Pharma Canada and re-analyses conducted by the EGP. The clinical effects were based on patient-level data obtained from the AFFIRM trial, which compared enzalutamide with placebo, where BSC represents that placebo arm of the trial. Any re-analysis done by the EGP only resulted in minor increases in the ICER as compared to the manufacturer's estimates.

According to the economic analysis that was submitted by **Astellas Pharma Canada**, when enzalutamide is compared with BSC:

- The incremental cost of the enzalutamide strategy is $33,608
- The incremental QALY benefit of enzalutamide is 0.306.

As such the manufacturer's model estimated that the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) was $109,667 per additional QALY gained for enzalutamide vs BSC

<u>Economic evaluation of enzalutamide compared to abiraterone:</u>
For the analysis comparing to abiraterone, there were numerous assumptions that, when examined, were not based on substantive evidence and favoured enzalutamide. These included use of overall survival data for abiraterone that violated key statistical assumptions, utility estimates for abiraterone that were unsubstantiated and a flawed indirect comparison for which limited details were available. Therefore, there was vast uncertainty in many of the model's parameters, which resulted in an unstable ICER estimate. The manufacturer's ICER estimates are likely at the low end of the range of possible ICER estimates and the EGP's estimates are the middle of the range, with much higher ICERs being possible.

The EGP's best estimate of the incremental cost-effectiveness ratio was $117,913 per additional QALY gained versus abiraterone. The extra cost of enzalutamide is $5424 and the extra clinical effect of enzalutamide is 0.046. Clinical effects were based on an unpublished indirect comparison conducted by Astellas Pharma Canada, which is outlined in the pCODR Clinical Guidance Report. However, based on the uncertainty in many of the model inputs, this estimate is unstable and could likely be much higher than $117,913 per QALY.

The EGP based these estimates on the model submitted by Astellas Pharma Canada and reanalysis conducted by the EGP. The reanalysis conducted by the EGP using the manufacturer's submitted model indicates that when:

- o If the hazard ratio for overall survival (OS) in the abiraterone arm changes from 0.74 to 0.65, the incremental cost of enzalutamide is $3771 and the incremental QALY benefit of enzalutamide is 0.061 which increases the estimated ICER of enzalutamide vs abiraterone to $61,332 per QALY. The hazard ratio of 0.74, which was used in the base case, appears to be based on an analysis where the proportional hazards assumption is violated (1) while the estimate of 0.65 appears more valid (2) and the follow-up time was more comparable to the enzalutamide estimate for overall survival.

- o If the same utility gain (0.04) is assumed for enzalutamide and abiraterone,(in the base case, the manufacturer used 0.06 for enzalutamide and 0.04 for abiraterone) the incremental cost of enzalutamide is $5420 and the QALY benefit of enzalutamide is 0.113 which increases the estimated ICER of enzalutamide vs abiraterone to $48,020 per QALY.

- o When the cost of laboratory tests needed for monitoring the abiraterone arm (blood count and liver function tests, which are currently estimated to be weekly in the base model) is assumed to be same as other arms (monthly), the incremental cost of enzalutamide is $5739 and the incremental QALY benefit of enzalutamide is 0.128 which increases the estimated ICER of enzalutamide vs abiraterone to $44,820 per QALY.

- o Assuming active treatment after progression costs for abiraterone and enzalutamide are the same, the incremental cost of enzalutamide is $6754 and the incremental QALY benefit of enzalutamide is 0.128 which increases the estimated ICER of enzalutamide vs abiraterone to $52,745 per additional QALY.

- o If the abiraterone costs are assumed to be $113.33 per day (as reported by the manufacturer) then the incremental cost of enzalutamide is $5424 and the incremental QALY benefit of enzalutamide is 0.046, the recalculated ICER for the model (which includes all other parameter changes described above) is $117, 913

The EGPs estimates for the ICER for abiraterone differed from the manufacturer's submitted estimates.

According to the economic analysis that was submitted by **Astellas Pharma Canada**, when enzalutamide is compared with abiraterone:

- ▪ The incremental cost of the enzalutamide strategy is $5,419
- ▪ The incremental QALY benefit of enzalutamide is 0.128

As such the manufacturer's model estimated that the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) was $42,325 per additional QALY gained for enzalutamide vs abiraterone.

<u>Economic evaluation of enzalutamide compared to cabazitaxel</u>
Although the EGP did not do a full reanalysis of the cabazitaxel estimates, these estimates have more validity than the abiraterone estimates given fewer assumptions were made in the model regarding cabazitaxel then were made with abiraterone (e.g. proportional hazards assumptions were not violated, utility estimates were valid). However, the cabazitaxel estimates are still based on an indirect comparison for which a number of limitations were identified as outlined in the pCODR Clinical Guidance Report. In addition, the indirect comparison provided limited detail on the comparison between enzalutamide and cabazitaxel, focusing primarily on the comparison with abiraterone.

According to the economic analysis that was submitted by **Astellas Pharma Canada**, when enzalutamide is compared with cabazitaxel:

- The incremental cost of the enzalutamide strategy is $6,782

- The incremental QALY benefit of enzalutamide is 0.157.

As such the manufacturer's model estimated that the incremental cost-effectiveness ratio ($\Delta C / \Delta E$) was $43,105 per additional QALY gained for enzalutamide vs cabazitaxel.

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?

There are some assumptions regarding the key variables in the model, which have been mentioned earlier in this report. These variables mostly affect the model's outcome when enzalutamide is compared to abiraterone and, in most cases; these assumptions are not based on substantive evidence. Specifically, changes to the HR for OS, the QALY gained and the price of abiraterone resulted in most of the changes in the ICER when enzalutamide was compared to abiraterone.

The other comparisons (specifically, enzalutamide vs. cabazitaxel and mitoxantrone) appear to be more valid. However, these other comparisons depend heavily on the validity of the underlying indirect comparison for which there was limited information available and flaws were identified as outlined in the pCODR Clinical Guidance Report.

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

From the Patient Advocacy group input, patients would like "access to additional therapies that will stop progression of their disease with minimal side effects and are convenient to use are important aspects when consideration is given to treatment. Patients seek a therapy that will help improve their quality of life and enable them to partake in normal daily activities while extending their life. In addition, controlling pain, fatigue, urinary incontinence and erectile dysfunction are important priorities to advanced prostate cancer patients, as is the reduction of bone metastasis and PSA levels. The hope of patients is that all of these can be achieved at the same time. Patients with prostate cancer are willing to tolerate side effects of treatment and seek choice in selecting a therapy to manage their disease."

The model somewhat addresses the concerns of patients through including QALYs as the endpoint. The QALY metric incorporates both survival and quality of life which were both identified by patients as important. However, the quality of life measure used in the AFFIRM trial was the EQ-5D which is unlikely to pick-up some of the concerns of patients such as urinary incontinence and erectile dysfunction. The EQ-5D does include both pain and usual activities as domains of health measured. In addition, bone metastasis and PSA levels were not explicitly modeled in the economic evaluation.

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

Overall, the model structure is fairly sophisticated and is generally adequate. There are assumptions in both the model inputs and structure that are not justifiable according to the clinical evidence. The model input assumptions under question in the comparison of enzalutamide and abiraterone are described elsewhere. In addition, the manufacturer submitted a partitioned survival model where survival and progression are modeled independently and it is assumed that a patient's risk of dying is a function of time and is not influenced directly by the increasing proportion of patients in the post-progression state. As a result, the submitted analysis resulted in a sizeable percentage of the total survival gain in post-progression state.

In addition, the model is populated by many parameters and the size of the spreadsheet is somewhat unwieldy. In addition, many macros have been written which were not available to the EGP. As such, when going through the spreadsheet cell by cell, the EGP detected some issues in the model that did not appear to support the face validity of the analysis. For example, changing the hospitalization cost for abiraterone or for cabazitaxel can result in a change in QALYs. In the absence of the macros, the EGP was unable to verify the full impact of these errors, however, in light of other major limitations in the economic analysis, these were considered relatively minor errors.

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 hazard ratio (0.74) for OS that has been applied in the model for the abiraterone strategy appears to be taken from a report with a longer follow-up time (median follow-up of 20.2 months) with an analysis that appeared to violate the proportional hazards assumption (1). However, the manufacturer states the HR comes from an indirect comparison with description of the calculations involved and little else. This input has a large impact on the outcomes of the cost effectiveness model as the HR used for enzalutamide is 0.63 (from the AFFIRM trial with a median follow-up time of 14.4 months) conferring a sizeable survival advantage on enzalutamide. A HR for OS taken from a shorter follow up time from the abiraterone trial is very much in line with that achieved by enzalutamide in the AFFIRM trial (a HR for OS of 0.65 with a median follow-up time of 12.8 months). (2)

The manufacturer's model assumes that the cost of routine visits for abiraterone is more than other comparators - this difference comes from weekly complete blood counts and liver function tests for abiraterone while, for other treatments, is reported to be monthly monitoring. After verification with the pCODR Clinical Guidance Panel, a schedule of monthly is most appropriately applied to each comparator arm.

The manufacturer's model assumes that utility treatment gain of enzalutamide is 0.06 and for abiraterone is 0.04. The enzalutamide estimate comes from a mapping of EQ5D measured in the AFFIRM trial compared to the abiraterone estimate which is referenced from a Dutch health technology assessment report (without mention of the source). With the lack of evidence to suggest otherwise, it is likely reasonable to assume equal utility gain.

The manufacturer's model assumes that the active treatment cost after progression for the enzalutamide arm is $12,109 and for abiraterone arm is $16,488. The higher cost for abiraterone comes from different, and more expensive treatments after progression. With the lack of evidence to suggest otherwise, it is likely reasonable to assume equal costs of progression.

The manufacturer's model is based on a 10-year time horizon. The EGP was concerned that the 10-year time horizon might result in some aberrations resulted from the applied survival functions that would further benefit enzalutamide due to its modelled higher OS. We examined outcomes using a 5-year time horizon and the results of the manufacturer's model were robust to changes in the time horizon (see below):

Table1- The result of manufacturer's model based on 10-year and 5-year time horizon

Comparator to enzalutamide	5 year ICER (per additional QALY)	10 year ICER (per additional QALY)
BSC	$109,198	$ 109,667
abiraterone	$41,586	$ 42,325
Cabazitaxel	$42,564	$43,105
Mitoxantrone	$106,233	$106,706

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?

Specific issues with the model have already been described. In summary, many parameter estimates were not based on substantive evidence and favoured enzalutamide. The most influential parameter was OS and this was based on an indirect comparison completed by the manufacturer. As noted in the Clinical Review Panel's report, "The comparative efficacy of enzalutamide and abiraterone acetate treatment for OS was indirectly assessed in men with mCRPC using Bucher's method. No statistically significant differences were found between these treatments. In addition, differences between enzalutamide and cabazitaxel or mitoxantrone could not be assessed as the results of this portion of the indirect comparison were not provided. Limitations surrounding the indirect comparison were also a cause for concern regarding the robustness of any provided results and, therefore, any conclusions drawn from this indirect comparison should be interpreted with caution." Finally, even with the EGP's best estimated ICER, the uncertainty in many of the model parameters is too large to make a definitive conclusion and a wide range of ICER estimates is possible.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The manufacturer's budget impact analysis (BIA) forecasts absolute costs following the listing of enzalutamide. The BIA model forecasts patient usage and reimbursement costs for 3 years beginning in January 2014. The key variables in the BIA model are the estimated cost per claim, forecasted market size and anticipated market share.

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

The key limitations in the submitted budget impact analysis are as follows:

1. No source or method mentioned for anticipated market share of abiraterone that has been used as a base of the analysis. It is stated in the economic report that 10-20% of prostate cancer cases will evolve to mCRPC within approximately 5 years of follow-up. The estimated numbers of patients eligible in the BIA model to receive abiraterone or enzalutamide (enzalutamide) therapy are less than 5% of incident cases in 2012. This represents either an underestimation in the BIA or an overestimation in the cost-effectiveness model. It is assumed that introducing enzalutamide will not change the total market size for both drugs (60% of mCRPC). However, it is likely people may switch to the newer drugs (like enzalutamide) due to inability to tolerate listed drugs.

2. The BIA also assumes that the payer costs would not change with enzalutamide entering onto the market because of the unchanged market size and similar price for daily use of enzalutamide and abiraterone. However, due to higher overall survival rate of patients who use enzalutamide (as claimed by the manufacturer), we would expect an increase in cost to the payer reflecting this increased survival.

1.5 Future Research

Is there economic research that could be conducted in the future that would provide valuable information related to enzalutamide for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have received docetaxel therapy?

Directly comparable evidence generated with enzalutamide and its competitors would provide value both from a clinical and economic perspective. In addition, information that addresses current sources of parameter uncertainty (ie such as the utility gain from abiraterone, comparative HR for OS, etc) would benefit the current model.

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 enzalutamide for mCRPC. A full assessment of the clinical evidence of enzalutamide for mCRPC 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 on in this publicly posted 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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