pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Enzalutamide for First-Line Metastatic Castration-Resistant Prostate Cancer

June 22, 2015

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TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analyses submitted to pCODR by Astellas Pharma Canada compares enzalutamide with watchful waiting, WW (best supportive care) followed by docetaxel, and to abiraterone (plus prednisone) in metastatic castrate resistant prostate cancer (mCRPC) patients after failure of androgen deprivation therapy (ADT), prior to cytotoxic chemotherapy (chemo-naïve).

Enzalutamide 160 mg is administered orally daily as a tablet.

Abiraterone 1,000 mg orally daily (+prednisone).

The CGP noted that abiraterone was the most appropriate comparator and that there is no direct comparison between enzalutamide and abiraterone. An indirect comparison was provided by the manufacturer and results were used in the pharmacoeconomic analysis.

Patient advocacy group input

From the patient perspective, respondents to both the Canadian Cancer Survivor Network (CCSN) and Prostate Cancer Canada (PCC) surveys are looking for a cure for their cancer and want to live longer. While a large number of respondents agreed or strongly agreed that their current therapy/therapies could manage their prostate cancer symptoms, respondents reported that there are needs in their current therapies that are not being met. Respondents who underwent the drug treatment reported significant adverse effects, but were generally willing to tolerate the side effects. According to the CCSN survey respondents, half of the respondents reported that enzalutamide halted disease progression and the same percentage also found it easier to use than previous therapies. The PCC survey respondents also reported improved quality of life compared to therapies they have used in the past.

Provincial Advisory Group (PAG)

The **Provincial Advisory Group (PAG)** stated that the key enablers include familiarity with enzalutamide and the fact that it is an oral therapy. Key barriers to implementation are the high cost of enzalutamide, the potentially substantial budget impact associated with the large patient population and concerns with inappropriate use as a number of these patients are seen by urologists outside the cancer programs. Moreover, PAG noted the lack of direct comparative data with abiraterone/prednisone and the unknown sequencing of therapy with existing treatments. The submitted model does not consider possible inappropriate use and there are major limitations in the indirect comparison with abiraterone. Additionally, only one treatment pattern is considered on three treatment lines.

At the list price, enzalutamide costs $28.34 per 40mg tablet. At the recommended dose of 160mg daily, the average cost per day in a 28-day course of enzalutamide is $113.38 and the average cost per 28-day course is $3,174.64.

At the list price, abiraterone costs $28.33 per 250mg tablet. At the recommended dose of 1,000mg daily, the average cost per day in a 28-day course of abiraterone is $113.33 and the average cost per 28-day course is $3,173.33.

1.2 Summary of Results

For the results, the EGP focused on the two main comparators, WW followed by docetaxel (based on results of the PREVAIL study: enzalutamide compared to BSC+placebo) and also abiraterone plus prednisone.

Economic evaluation of enzalutamide compared to BSC followed by docetaxel

The EGP's best estimates of the incremental cost-effective ratio (ΔC/ΔE), based on the submitted confidential price, ranged from $125,424/QALY to $224,266/QALY and $166,517/LY to $267,402/LY when varying some important assumptions on OS extrapolations, utility values and time horizon.

- The extra cost of enzalutamide is between $60,433 and $65,108.
- The extra clinical effect of enzalutamide is between 0.269 to 0.519 QALYs and 0.226 to 0.391 LYs. The factors that most influence the effectiveness of enzalutamide are OS extrapolation, time horizon and utility values.

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

- The incremental cost of the enzalutamide strategy is $72,807
- The incremental QALY benefit of enzalutamide is 0.666

As such, the manufacturer's model estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $109,397 per additional QALY gained for enzalutamide vs. BSC followed by docetaxel.

The EGP based these estimates on the model submitted by **Astellas Pharma Canada** and reanalyses conducted by the Panel showed that when:

1. The time horizon is reduced to 5 years, based on input from the Clinical Guidance Panel, the incremental cost of enzalutamide is $65,108, and the incremental benefit of enzalutamide is 0.519 QALY. These changes increased the estimated incremental cost-effectiveness ratio to $125,424/QALY gained (*EGP's best estimate, lower limit*).
2. OS, PFS and TTC, are extrapolated with a Weibull distribution and when using the January 2014 cutoff (instead of the September 2013 cutoff), the incremental cost of enzalutamide is $60,796, and the incremental benefit of enzalutamide is 0.402 QALY based on a mean 2.3 months gain in OS, which is similar to the median OS gain with enzalutamide in the PREVAIL study. These changes increased the estimated incremental cost-effectiveness ratio to $151,167/QALY gained.
3. The stable disease utility value is reduced by 10%, the post-progression 1 and 2 (PP1 and PP2) utility values are adjusted, and without considering on-treatment utility gain to avoid double-counting in QALY estimates (utility gain as well as PFS gain with a higher utility value), the incremental cost of enzalutamide is $72,807, and the incremental benefit of enzalutamide is between 0.551 QALY and 0.619 QALY. These changes increased the estimated incremental cost-effectiveness ratio between $110,226 and $132,213/QALY gained.
4. OS curves, time horizon and utility values are varied simultaneously (as presented in the univariate sensitivity analyzes above), the incremental cost of enzalutamide is $60,433, and the incremental benefit of enzalutamide is 0.269 QALY. These changes increased the estimated incremental cost-effectiveness ratio to $224,266/QALY gained (*EGP's best estimate, higher limit*).

In the EGP's best estimates, effect of treatment durations in the first three lines of treatment and of different sequencing patterns were not quantified but were considered as a source of uncertainty. Also, uncertainty remains surrounding the WW population ineligible for docetaxel.

Economic evaluation of enzalutamide compared to abiraterone:

As reported in the Clinical Guidance Report, "The comparative efficacy of enzalutamide and abiraterone acetate treatment for OS in mCRPC patients who were chemotherapy-naïve was assessed in an indirect comparison analysis. However, only findings from individual studies were presented. Results from the pooled analysis were not available in this ITC. Limitations surrounding the indirect comparison were a cause for concern regarding the robustness of any provided results, such as the substantial heterogeneities existing in the included studies of this analysis, the use of mixed population instead of chemo-naïve mCRPC patients only, the limited clinical relevance of comparisons between enzalutamide and the other treatments, and the lack of common comparator between study drugs. Therefore, any conclusions drawn from this indirect comparison regarding the comparative clinical effectiveness between enzalutamide and abiraterone should be interpreted with caution."

Consequently, for the economic analysis comparing enzalutamide to abiraterone, there were numerous assumptions that, when examined, were not sufficiently robust to support the model and the cost-effectiveness estimate is unstable. Based on available data, there were major uncertainties regarding the cost-effectiveness estimates and the EGP preferred to base the review on a cost-consequences approach. Treatment costs between the two drugs are similar. With regards to clinical effects, it was the opinion of the CGP that both pivotal studies (COU-AA 302 and PREVAIL) demonstrated a similar magnitude of clinical benefit for enzalutamide and abiraterone, however, these results were observed in different study settings. Any comparison of both studies results should be done with caution taking into consideration the limitations of such a comparison.

As an example, the pharmacoeconomic model simulated a median OS gain of 2.6 months and a median PFS gain of 7.9 months when enzalutamide is compared to abiraterone. Both drugs demonstrated the following clinical benefits in their respective pivotal clinical studies:

- For abiraterone (+prednisone) as compared to placebo (+prednisone):
  - a median OS gain of 5.2 months (HR: 0.79 [95% CI, 0.66-0.95]; p=0.0151) but did not reach the prespecified statistical efficacy boundary (α-level: 0.0035) (Rathkopf)
  - a median PFS gain of 8.2 months (COU-AA-302),
- For enzalutamide as compared to WW followed by docetaxel:
  - a median OS gain of 2.2 months (HR: 0.71 [95% CI, 0.60-0.84]; p<0.001);
  - a median PFS gain of 14.3 months (PREVAIL)

According to the CGP, the therapeutic choice between these two drugs should be based on patient's characteristics and should consider respective adverse events profiles, drug interactions and contra-indications. As abiraterone is available in most of the provinces in this indication, any pricing agreement concluded for this drug should be considered when evaluating the cost-effectiveness of enzalutamide compared to this comparator.

The EGP's appreciation of the enzalutamide cost-effectiveness compared to 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, based on the indirect comparison:

- The incremental cost of the enzalutamide strategy is $21,342
- The incremental QALY benefit of enzalutamide is 0.303. This is based on a mean 2.9 months OS gain and a mean 10.5 months PFS gain.

As such, the manufacturer's model estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $70,410 per additional QALY gained for enzalutamide vs. abiraterone.

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 many 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.

Regarding the first comparison with WW followed by docetaxel, generally, the assumptions were considered to be adequate. However, uncertainty remains in that changes to the OS extrapolation, utility values and time horizon resulted in most of the changes to the ICER. Also treatment duration and sequencing patterns are a source of uncertainty.

The pharmacoeconomic evaluation of enzalutamide and abiraterone depends heavily on the validity of the underlying indirect comparison for which there was limited available information and flaws were identified earlier in this report and were outlined in the pCODR Clinical Guidance Report.

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

Factors that are important to patients were generally addressed in the economic analysis. Progression free survival, overall survival, adverse effects, ease of use and quality of life were all considered in the model. However, assumptions and corresponding pharmacoeconomic results, particularly in the comparison with abiraterone, must be interpreted with caution because of the absence of a direct treatment comparison.

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

The model structure is generally adequate. However, 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 with WW and with abiraterone are described elsewhere.

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?

Regarding the comparison with WW followed by docetaxel, most assumptions made in this pharmacoeconomic model were based on the PREVAIL trial data and are considered to be appropriate in presence of uncertainty. OS and PFS were the key clinical inputs for the economic submission and the estimation of the cost-effectiveness of enzalutamide for this patient population. The incremental benefits of enzalutamide were generated from the PREVAIL trial data. OS extrapolation led to pharmacoeconomic uncertainty that needs to be quantified. Furthermore, treatment duration depends on PFS and has an impact on total costs. This is crucial to the estimation of the cost-effectiveness of enzalutamide in this population. Utility values considered also represent an important assumption affecting results as they directly impact utility gain estimation. The time horizon of the model also affects results as the lower this is, the higher the ICER. A time horizon shortened from 10 to 5 years was considered by EGP. Moreover, toxicities associated with enzalutamide and their costs are important variables in the model. Finally, uncertainty relating to treatment patterns has to be quantified (as well as the proportion of patients receiving third line treatment).

With regards to the comparison with abiraterone, the incremental benefits of enzalutamide (0.303 QALYs) were generated from the indirect comparison based on the PREVAIL and COU-AA 302 trials data. OS extrapolation led to pharmacoeconomic uncertainty that needs to be quantified. In fact, the assumptions that the control arms are similar in both studies and that the patient populations are similar are questionable. Consequently, the effectiveness of enzalutamide could be higher than, less than, or the same as the effectiveness of abiraterone. Based on that, the indirect comparison's study results are uncertain and this does not allow for an adequate and valid estimate of the incremental cost-effectiveness ratio.

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 questions?

Specific issues with the model have already been described. In summary, the EGP was of the opinion that many parameter estimates were not based on substantive evidence and their inclusion had the effect of favouring enzalutamide in the economic evaluation. The most influential parameter was OS for both comparisons.

Specifically, the comparison with abiraterone, the most appropriate comparator, was based on an indirect comparison conducted by the manufacturer. Any conclusions drawn from this indirect comparison should be interpreted with caution. Consequently, the uncertainty in many of the model parameters is too high to draw a definitive conclusion and a wide range of ICER estimates are possible. Based on available clinical data, the ICER could be in any quadrant of the incremental cost-effectiveness plane.

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 the impact of the introduction of enzalutamide following listing for the targeted population. The BIA model forecasts patient usage and reimbursement costs over a three-year time horizon. The key variables in the BIA model are treatment duration, number of eligible patients and market share.

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

Limitations of the budget impact analysis include the uncertainty surrounding the impact of sequencing patterns and of a new entry for treating mCRPC as currently there is abiraterone used in the same treatment indication as well as BSC. Several sensitivity analyses were conducted. As enzalutamide daily treatment costs is slightly lower than abiraterone cost, most of the scenarios lead to small savings. However, it was assumed in the reference case (without enzalutamide), that 10% of the targeted population would receive BSC and 90% abiraterone. If enzalutamide listing would lead to a decrease in the proportion of patients receiving BSC, total increased costs could be observed. Also, scenarios where treatment duration is higher with enzalutamide than with abiraterone, (as it is the case in the pharmacoeconomic model) are resulting in increased total costs. Finally, inappropriate use might also potentially increase the budget impact.

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 comparator, abiraterone, would provide valuable information both from a clinical and economic perspective. In addition, information that addresses current sources of parameter uncertainty 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.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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