PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Abiraterone Acetate (Zytiga) for Metastatic Castration-Resistant Prostate Cancer

October 22, 2013

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Janssen Inc.** compared abiraterone acetate + prednisone (abiraterone hereafter) to prednisone alone (prednisone hereafter) for patients with asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer (mCRPC) after failure of androgen deprivation therapy (ADT). Both abiraterone and prednisone are administered orally.

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

Patients considered the following factors important in the review of abiraterone, which are relevant to the economic analysis: stopping disease progression and/or extending life, improving quality of life, and affordable price.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for abiraterone, and which are relevant to the economic analysis: budget impact associated with the large patient population, treatment algorithm for mCRPC (possibility of retreatment with abiraterone after docetaxel), and coverage for oral medications.

At the submitted list price, abiraterone acetate costs $28.33 per 250mg tablet. At the recommended dose of 1000 mg per day, the average cost per day in a 28-day course of abiraterone acetate is $113 and the average cost per 28-day course is $3,173.

1.2 Summary of Results

The Economic Guidance Panel (EGP)'s best estimate of the incremental cost-effectiveness ratio is $128,197 per QALY (ΔC $44,844 and ΔE 0.3498 QALY) when abiraterone + prednisone is compared to prednisone alone. However, given the inherent uncertainty in the true benefit in overall survival, there is limited confidence in this 'best' estimate, and the plausible range of the incremental cost-effectiveness ratio may be as high as $258,428 per QALY (ΔC $44,642 and ΔE 0.1727 QALY). The EGP based these estimates on the model submitted by Janssen Inc. and reanalyses conducted by the Panel.

The EGP's estimates ranged from $104,198/QALY (lower 95% CI) to $258,428/QALY using the lower and upper 95% CI on the overall survival and PFS, during and beyond trial periods. Depending on the true effectiveness of abiraterone on overall survival and PFS, cost-effectiveness estimates may lie somewhere within this range. However, the EGP's best estimates have focused on the more plausible upper end of the range ($128, 197/QALY to 258, 428/QALY).

The manufacturer's base case assumed a difference in overall survival using point estimates from the trial that did not reach pre-specified level of statistical significance. While this estimate is the 'best' estimate, it is highly uncertain. The EGP considered that the pCODR CGP accepted that there is a net overall clinical benefit of abiraterone based on the results of Study COU-AA-302 (despite overall survival not reaching the pre-specified level of statistical significance), the true magnitude of this difference from available data is uncertain. As such, while the submitted reference case using point estimate from the trial (ICUR = $128,197 per QALY (ΔC $44,844 and ΔE 0.3498 QALY) is not unreasonable and reflects the net benefit observed in the study, it does not capture the inherent uncertainty in both short-term and long-term incremental survival. If this survival benefit is less than assumed in the manufacturer's base case, or survival benefit attenuates over time, ICUR will be >$175K per QALY.

According to the economic analysis that was submitted by Janssen Inc. when abiraterone + prednisone is compared with prednisone alone:

- the extra cost of abiraterone + prednisone is $44,844 (ΔC). Costs considered in the analysis included drug cost, scheduled disease-related follow up cost, adverse event cost and subsequent treatment cost.
- the extra clinical effect of abiraterone + prednisone is 0.3405 life years (LY) gained or 0.3498 quality-adjusted life years (QALY) gained (ΔE). The clinical effect considered in the analysis was based on overall survival and progression-free survival.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $131,688 per LY gained or $128,197 per QALY gained.

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?

While the reference case provided by the submitter uses trial point estimates, which is appropriate, the originally provided exploration of uncertainty was sub-optimal. As OS did not meet the pre-specified level of significance, the magnitude of difference in OS is uncertain. The manufacturer has resubmitted a series of one-way sensitivity analysis to explore the inherent uncertainty in incremental survival between the two treatment arms. The results are most sensitive to overall survival for abiraterone during the trial period - when using the upper 95% CI, the ICUR increases to more than $200K/QALY. In addition to the uncertainty around the true magnitude of OS in the short term, there is uncertainty around the benefits on OS and PFS beyond the trial period as they were extrapolated in the model. However, the sensitivity analyses showed that the results were less sensitive to benefits on OS and PFS beyond the trial period.

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

Based on the pCODR patient advocacy group input, patients are seeking treatments that have a positive impact on reducing/stopping disease progression, lowering PSA, extending life, and improving quality of life at an affordable price. Patient groups also noted the impact on caregivers, such as the emotional stress and the sexual relations with their partners.

Quality of life, progression-free survival and life expectancy have been captured in the manufacturer's economic submission in their cost utility analysis. The costs on adverse events were also included in the submitter's model.

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

While the original submission did not allow full exploration of uncertainty, the design and structure of the re-submitted economic model was adequate.

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?

Most assumptions made in this submission were based on the COU-AA-302 trial data (1) and considered to be appropriate. The submitter also consulted clinical opinion in order to ensure the model on subsequent treatments reflects Canadian practices. The model assumed 58% of prednisone patients would receive abiraterone after chemotherapy, and thus significantly increase the subsequent treatment costs in this group ($[redacted]K for prednisone alone vs. $[redacted]K for abiraterone), as well as disutility from adverse events. (*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). In addition, the model did not consider retreatment in the post-abiraterone group after chemotherapy, as there is currently no data on the benefits/harms of retreatment.

OS and progression-free survival (PFS) were the key clinical inputs for the economic submission. The incremental benefits of abiraterone were generated from the third interim COU-AA-302 trial data. The survival benefit might be attenuated due to unblinding and crossover after the second interim of the trial. The ICUR decreased to $96,896 per QALY when the second interim data was used. Also, no data are available to infer treatment costs and outcomes beyond the trial period when a 10-year time horizon was adopted in the base case, although it was appropriate for the less severe mCRPC patients.

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?

While the projected survival benefits in the reference case were reasonable, inherent uncertainty in OS could now be assessed in the re-submitted model; all other clinical and cost inputs appeared reasonable.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

A budget impact analysis (BIA) was submitted to determine the impact of the introduction of abiraterone over a three-year time horizon. Assumptions were made on the number of patients treated and market shares through market research, published literature and expert opinion. Budget impact would be greater if higher proportion of patients treated longer duration of therapy, higher number of eligible patients and higher abiraterone market share. Inappropriate use outside the cancer programs (e.g. urologists) might also potentially increase the budget impact.

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

Limitations of the budget impact analysis include the uncertainty surrounding the impact of a new entry for treating mCRPC as currently there is no standard treatment. Several sensitivity analyses were conducted to explore the impact of the assumptions of market share and did not significantly change the results.

1.5 Future Research

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

Flexibility was given in the re-submitted model to explore inherent uncertainty when modelling the survival curves during and beyond the trial period in one way sensitivity analysis.

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

There are no other economic evaluations in the indicated patient population as there is no standard of care established. A complete validation through independent research would be valuable in this patient group.

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 Final 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 abiraterone acetate (Zytiga). A full assessment of the clinical evidence of abiraterone acetate (Zytiga) 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*. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was 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. 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.

REFERENCES

1. Janssen Research & Development. Report of Updated Data from Study COU-AA-302 - 22 May 2012 Data Cut Off. 2012. 1-72 p.

2. Wilkinson AN, Brundage MD, Siemens R. Approach to primary care follow-up of patients with prostate cancer. Can Fam Physician. 2008 Feb;54(2):204-10.

3. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, Staffurth JN, North S, Vogelzang NJ, Saad F, Mainwaring P, Harland S, Goodman OB,Jr, Sternberg CN, Li JH, Kheoh T, Haqq CM, de Bono JS, COU-AA-301 Investigators. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: Final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012 Oct;13(10):983-92.

4. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Theodore C, James ND, Turesson I, Rosenthal MA, Eisenberger MA, TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004 Oct 7;351(15):1502-1.

5. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, Gravis G, Bodrogi I, Mackenzie MJ, Shen L, Roessner M, Gupta S, Sartor AO, TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. Lancet. 2010 Oct 2;376(9747):1147-54.

6. Diels J, Spencer M, Hamberg P, Wheatley Price P, Dass RN. PCN116 mapping FACT-P to EQ-5D in a large cross-sectional study of metastatic castrate-resistant prostate cancer patients. Value in Health. 2012;15(7):A430.

7. National Institute for Health and Care Excellence. Abiraterone for castrationresistant metastatic prostate cancer previously treated with a docetaxel-containing regimen. London: National Institute for Health and Care Excellence; Jun 2012. Report No.: 259.

8. Zhong L, Pon V, Srinivas S, Nguyen N, Frear M, Kwon S, Gong C, Malmstrom R, Wilson L. Therapeutic options in docetaxel-refractory metastatic castration-resistant prostate cancer: A cost-effectiveness analysis. PLoS One. 2013 May 22;8(5):e64275.