pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

Providing Feedback on this Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pERC will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug:
Enzalutamide (Xtandi)

Submitter's Funding Request:
For the treatment of patients with metastatic castration-resistant prostate cancer, who have previously received docetaxel therapy.

Submitted By:
Astellas Pharma Canada Inc.

Manufactured By:
Astellas Pharma Canada Inc.

NOC Date:
May 29, 2013

Submission Date:
March 4, 2013

Initial Recommendation Issued:

July 5, 2013

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) recommends funding enzalutamide (Xtandi) for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have progressed on docetaxel-based chemotherapy. Funding should be for patients who have an ECOG performance status ≤2 and no risk factors for seizures. pERC made this recommendation because it was satisfied enzalutamide has a net clinical benefit compared with placebo and is marginally cost effective compared with best supportive care. pERC was also satisfied that enzalutamide is a reasonable therapeutic alternative to abiraterone, despite the limitations of the indirect comparison, and is marginally cost effective compared with abiraterone, based on the Economic Guidance Panels best estimates of cost-effectiveness and assuming similar pricing of the two therapies.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Confirming Cost-Effectiveness of Enzalutamide** Provinces should be aware that the cost-effectiveness estimates of enzalutamide compared with abiraterone assumed similar pricing of the two therapies. Therefore, any changes in these drug prices could considerably change the cost-effectiveness of enzalutamide compared with abiraterone.

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SUMMARY OF pERC DELIBERATIONS

pERC noted that prostate cancer is the most common malignancy in Canadian men but that the proportion of patients with metastatic castration-resistant prostate cancer is relatively small and the proportion of these patients who would be treated post-docetaxel therapy would be even smaller. Standard treatment for patients with metastatic castration-resistant prostate cancer who have progressed on docetaxel-based chemotherapy is currently abiraterone. The pCODR systematic review included one randomized controlled trial, AFFIRM (Scehr 2012) comparing enzalutamide with placebo. pERC considered that the most relevant comparator in this setting would be abiraterone, which must be used in combination with prednisone. pERC considered that given the availability of abiraterone there is a limited therapeutic need for enzalutamide but that enzalutamide would offer another option for patients with metastatic castration-resistant prostate cancer and would decrease the need for co-administration of prednisone, which may be associated with intolerable side effects for some patients.

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of the AFFIRM study and considered that there was a net clinical benefit of enzalutamide compared with placebo. pERC noted that compared with placebo there was a clinically and statistically significant improvement for enzalutamide in overall survival, radiographic progression-free survival and other key secondary outcomes.

pERC discussed the safety of enzalutamide based on the results of the AFFIRM study. It was noted that a greater proportion of patients in the enzalutamide group compared with the placebo group reported spinal cord compressions, pathological fractures and seizures. In general, pERC considered that enzalutamide was well-tolerated and, because it is not administered with prednisone, patients would be spared potential side effects associated with steroids. However, pERC noted that patients with a seizure disorder or at a higher risk of seizures were excluded from the AFFIRM study and that these patients should not receive enzalutamide.

pERC discussed the alignment of enzalutamide with patient values. pERC noted that results from the AFFIRM study indicated that compared with placebo, enzalutamide extends survival and improves quality of life compared with placebo, which would align with these patient values. In addition, pERC considered that patients were seeking additional options to allow for a choice of therapy and that providing enzalutamide would align with this patient value. In addition, patients indicated a preference for treatments with minimal side effects and providing an option that does not require concomitant use of prednisone would spare patients the side effects associated with steroid treatments.

pERC deliberated upon the cost-effectiveness of enzalutamide. It was noted that enzalutamide was marginally cost-effective compared with best supportive care, based on clinical effects from the AFFIRM study. However, pERC discussed that the most relevant comparator in this population was abiraterone and that, despite the limitations of relying on evidence from an indirect comparison, it was important to consider the cost-effectiveness of enzalutamide compared with abiraterone. pERC accepted the pCODR Economic Guidance Panel's interpretations and estimates of cost-effectiveness of enzalutamide compared with abiraterone. However, pERC also noted that the price of abiraterone and enzalutamide is identical and that both drugs have demonstrated an improvement in overall survival, suggesting that the two treatments may have similar costs and effects. pERC noted that the estimated incremental benefit of enzalutamide versus abiraterone was very small (EGP estimate of 0.046 QALY) and as a result the incremental cost effectiveness ratio (ICER) was extremely sensitive to small changes in the incremental effect. pERC noted that because the ICER was driven by estimates of overall survival, small differences in the survival estimates for enzalutamide and abiraterone, which may not be considered meaningful in clinical practice, could lead to large incremental changes in the cost-effectiveness ratio. Therefore, based on the available information and recognizing the limitations of the indirect comparison, pERC considered that enzalutamide was only marginally cost-effective compared with abiraterone. pERC also

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considered that the cost-effectiveness estimates of enzalutamide compared with abiraterone were heavily dependent on the submitted price of enzalutamide and the list price of abiraterone. Therefore, any changes in these drug prices could be expected to considerably change the cost-effectiveness of enzalutamide compared with abiraterone.

pERC discussed the place in therapy of enzalutamide and how this might impact its feasibility of adoption. pERC considered that enzalutamide would be an alternative to abiraterone for some patients in the post-docetaxel setting rather than being an add-on to abiraterone treatment. pERC also discussed the potential for sequencing of enzalutamide and other therapies in the post-docetaxel treatment setting for patients with metastatic castration-resistant prostate cancer. pERC considered that the optimal sequencing of these treatments is still unknown and currently, there are no studies evaluating this question.

EVIDENCE IN BRIEF

pERC deliberated upon a pCODR systematic review, other literature in the Clinical Guidance Report providing clinical context, an evaluation of the manufacturer's economic model and budget impact analysis, guidance from pCODR clinical and economic review panels, input from two patient advocacy groups
(Prostate Cancer Canada and Canadian Cancer Survivor Network) and input from pCODR's Provincial Advisory Group.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the efficacy and safety of enzalutamide (Xtandi) on patient outcomes compared to standard therapies or placebo in patients with metastatic castration-resistant prostate cancer (mCRPC) who have received docetaxel-based chemotherapy.

Studies included: one randomized placebo-controlled trial

The pCODR systematic review included one double-blind, placebo-controlled randomized trial (N=1199), the AFFIRM study (Scher 2012), which evaluated the efficacy and safety of enzalutamide (160 mg once-daily) compared to placebo. After a pre-specified interim analysis demonstrating a statistically significant improvement in overall survival for enzalutamide compared with placebo, the AFFIRM study was unblinded and stopped early.

The pCODR review also provided contextual information on relevant comparators including a critical appraisal of an indirect comparison of enzalutamide with abiraterone, cabazitaxel and mitoxantrone which was conducted by the Submitter. In addition, contextual information was provided on the validity of skeletal-related events as an outcome in prostate cancer. However, no studies have formally evaluated the validity and reliability of skeletal-related events as an endpoint in advanced prostate cancer trials.

Patient populations: patients at risk of seizure excluded

The AFFIRM study included patients with an ECOG performance status ≤ 2, although the majority of patients had an ECOG performance status of 0 or 1. pERC also noted that patients with a history of seizure or any condition that may predispose to seizure were excluded from the AFFIRM study and that it would not be appropriate for these patients to receive enzalutamide.

Key efficacy results: improvement in overall survival compared with placebo

Key outcomes deliberated on by pERC included overall survival, the primary endpoint of AFFIRM, and radiographic progression-free survival (rPFS). pERC noted that a statistically significant improvement in median overall survival was observed for enzalutamide compared with placebo at the pre-specified interim analysis (18.4 versus 13.6 months, respectively, HR=0.63, 95% CI: 0.53 to 0.75, P<0.0001).

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A statistically significant improvement in radiographic progression-free survival favouring enzalutamide over placebo was also observed (8.3 versus 2.9 months, respectively, HR=0.40, 95% CI 0.35 to 0.47, P<0.001). Statistically significant improvements favouring enzalutmide over placebo were also observed for other secondary outcomes including time to first skeletal-related event, time to PSA progression and PSA response rate.

Quality of life: meaningful improvement compared with placebo

pERC discussed quality of life data from the AFFIRM study. More patients in the enzalutamide group compared with the placebo group had an improvement in quality of life (43% versus 18%, respectively, P<0.001), which was defined as a 10-point improvement in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) global score compared to baseline.

Safety: well-tolerated, no adverse events due to concomitant prednisone use

pERC discussed the toxicity profile of enzalutamide as demonstrated in the AFFIRM study and considered that it was well-tolerated. Overall, serious adverse events were more common in the placebo group compared to the enzalutamide group. Serious adverse events that occurred more commonly in the enzalutamide group compared to the placebo group included spinal cord compression, hematuria, bone pain, pathological fracture, metastatic pain, general physical health deterioration, and pneumonia. In addition, pERC considered that because enzalutamide is not administered concomitantly with prednisone, patients would be spared potential side effects that can be associated with steroids.

pERC also noted that in the AFFIRM study, seven patients in the enzalutamide group experienced a seizure while no patients in the placebo group did. In addition, patients with a history of seizure, taking medications known to decrease the seizure threshold, or with other risk factors for seizures were excluded from the AFFIRM study. Therefore, pERC noted that the safety of enzalutamide in patients at risk of seizure is unknown and these patients should not receive enzalutamide

Comparator information: uncertainty in results of indirect comparison with abiraterone

pERC noted that although the AFFIRM study compared enzalutamide with placebo, abiraterone is a more relevant comparator. Therefore, pERC discussed the results and critical appraisal of an indirect comparison of enzalutamide with abiraterone, which had been conducted by the manufacturer. pERC noted the limitations of the analysis and noted that there was substantial uncertainty in the conclusions drawn from the indirect comparison. However, pERC noted that both enzalutamide and abiraterone had demonstrated a similar survival benefit versus placebo in their respective pivotal trials (Scher 2012 and de Bono 2010, respectively). Despite the limitations of relying on indirect and cross-trial comparisons, pERC considered the difference between the two trials with respect to the magnitude of the overall survival benefit achieved would not be considered meaningful in clinical practice or lead an oncologist to choose one treatment over the other. In addition, the difference was not statistically significant based on the results of the indirect comparison.

Need: therapeutic options that are both effective and well tolerated

pERC noted that prostate cancer is the most common malignancy in Canadian men but that the number of patients with metastatic castration-resistant prostate cancer is relatively small and the proportion of these patients who would be treated post-docetaxel therapy would be even smaller. Standard treatment for patients with metastatic castration-resistant prostate cancer who have progressed on docetaxel-based chemotherapy is currently abiraterone. Cabazitaxel has also demonstrated a survival benefit in this setting. Patients progressing on docetaxel based chemotherapy have few treatment options and a short life expectancy, underscoring the need for novel therapeutic strategies that are both effective and well tolerated. pERC considered that given the availability of abiraterone there is a limited therapeutic need for enzalutamide. However, enzalutamide would offer another option for patients with metastatic castration-resistant prostate cancer and would decrease the need for the concomitant use of prednisone, which is usually administered with abiraterone and which may be associated with intolerable side effects in some patients.

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PATIENT-BASED VALUES

Values of patients with metastatic castrate resistant prostate cancer: delay progression and control symptoms

Input from two patient advocacy groups indicated that patients with metastatic castrate-resistant prostate cancer value access to additional therapies that will stop progression of their disease and control symptoms. Controlling pain, fatigue, urinary incontinence and erectile dysfunction are important priorities to advanced prostate cancer patients, as is the reduction of bone metastases and prostate-specific antigen (PSA) levels. pERC also noted some of the patient concerns related to symptoms of prostate cancer, and others related to the side effects of first-line treatments. pERC noted that treatment with enzalutamide in the post-docetaxel setting would not be able to address all of these adverse effects. However, based on the results of the AFFIRM study, enzalutamide will provide another treatment option for patients that would delay disease progression and control symptoms, which aligns with patient values.

Patient values on treatment: alternative treatment options with manageable side effects and improved quality of life

pERC noted that metastatic castration resistant prostate cancer patients are looking for treatments that will control symptoms with minimal side effects and which are convenient to use. In addition, patients are seeking therapies that will help improve their quality of life and enable them to partake in normal daily activities while extending their life. pERC noted that results from the AFFIRM study indicated that enzalutamide extends survival and improves quality of life compared with placebo. Patient advocacy group input indicated that patients with prostate cancer are willing to tolerate side effects of treatment but are seeking choice in selecting a therapy to manage their disease. In addition, patients indicated a preference for treatments with minimal side effects. Providing enzalutamide as a treatment option that does not require concomitant use of prednisone would spare patients the side effects associated with steroid treatments. In addition, pERC considered that patients were seeking additional options to allow for a choice of therapy and that providing enzalutamide would align with this patient value.

ECONOMIC EVALUATION

Economic model submitted: cost-utility

The pCODR Economic Guidance Panel assessed a cost effectiveness analysis comparing enzalutamide to best supportive care (BSC) in patients with metastatic castrate resistant prostate cancer based on the results of the AFFIRM study. A cost-effectiveness analysis comparing enzalutamide with, abiraterone acetate, cabazitaxel and mitoxantrone, based on an indirect comparison, was also assessed.

Basis of the economic model: clinical and economic inputs

Costs included in the model were medication treatment costs, medical resource utilization (outpatient visits, procedures, laboratory tests, hospitalizations and terminal care costs), costs for treatment of adverse events and the cost of skeletal-related events.

Key clinical effects included progression-free and overall survival data. In the analysis versus best-supportive care, these were based on the AFFIRM study, and, in the analysis versus abiraterone, these were based on an indirect comparison. Effects also incorporated literature-based utility values.

Drug costs: similar list price of enzalutamide and abiraterone

At the list price enzalutamide costs $28 per 40 mg tablet. At the recommended daily dose of 160 mg, 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 daily dose of 1000 mg, the average cost per day in a 28-day course of abiraterone is $113 and the average cost per 28-day course is $3175.

pERC discussed the current list prices of abiraterone and enzalutamide and noted they are identical. pERC discussed potential uncertainty associated with actual pricing arrangements in different provinces and

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considered that changes in either of these drug prices could considerably change the cost-effectiveness of enzalutamide compared with abiraterone.

Cost-effectiveness estimates: marginally cost-effective compared with abiraterone or with best supportive care

pERC deliberated upon the cost-effectiveness of enzalutamide and discussed the pCODR Economic Guidance Panel's critique of the manufacturer's economic analysis. It was noted that when data from the AFFIRM trial were used, enzalutamide was marginally cost-effective compared with best supportive care considering both the manufacturer's estimates and the Economic Guidance Panel's best estimates. The EGP's best estimate of the incremental cost-effectiveness ratio was $115,345 per additional QALY while the manufacturer's model estimated $109,667 per additional QALY gained. However, pERC discussed that the most relevant comparator in this population was abiraterone and that, despite the limitations of relying on evidence from an indirect comparison, it was important to consider the cost-effectiveness of enzalutamide compared with abiraterone. pERC accepted the pCODR Economic Guidance Panel's interpretations and estimates of cost-effectiveness of enzalutamide compared with abiraterone, although they were substantially higher than the manufacturer's estimates. However, pERC also noted that the price of abiraterone and enzalutamide was identical and that both drugs have demonstrated an improvement in overall survival, suggesting that the two treatments may have similar costs and effects. pERC noted that the difference in the incremental effect between enzalutamide and abiraterone was very small (EGP estimate of 0.046) and as a result the incremental cost effectiveness ratio (ICER) was extremely sensitive to small changes in the incremental effect. pERC noted that because the ICER was driven by estimates of overall survival, small differences in the survival estimates for enzalutamide and abiraterone, which may not be considered meaningful in clinical practice, could lead to a large incremental changes in the cost-effectiveness ratio. Therefore, based on the available information and recognizing the limitations of the indirect comparison, pERC considered that enzalutamide was marginally cost-effective compared with abiraterone. pERC also considered that the cost-effectiveness estimates of enzalutamide compared with abiraterone were heavily dependent on the submitted price of enzalutamide and the list price of abiraterone and that any changes in these drug prices could considerably change the cost-effectiveness of enzalutamide compared with abiraterone.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: indirect comparison to abiraterone, indication creep, screening for seizures

pERC considered the feasibility of implementing a funding recommendation for enzalutamide. pERC discussed the place in therapy of enzalutamide and how this might impact its feasibility of adoption. pERC considered that enzalutamide would be an alternative to abiraterone in the post-docetaxel setting for some patients rather than being an add-on to abiraterone treatment. pERC also discussed the potential for sequencing of enzalutamide and other therapies in the post-docetaxel treatment setting. pERC considered that the optimal sequencing of these treatments remains unknown and currently, there are no studies evaluating this question. pERC also noted that enzalutamide's not requiring concomitant use of prednisone, could be facilitate its implementation.

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DRUG AND CONDITION INFORMATION

Drug Information	• Hormonal therapy, androgen receptor inhibitor • Enzalutamide is available as 40 mg capsules • The recommended dose is 160 mg once daily
Cancer Treated	• Metastatic castration-resistant prostate cancer (mCRPC)
Burden of Illness	• Prostate cancer is the second most commonly diagnosed cancer in Canadian men and accounts for 10% of all cancer deaths in Canada. • Approximately 10-20% of prostate cancer cases will evolve to mCRPC within approximately five years of follow-up.
Current Standard Treatment	• Cabazitaxel and abiraterone have demonstrated survival benefits in the post docetaxel setting
Limitations of Current Therapy	• Patients progressing on docetaxel-based chemotherapy have limited treatment options and a short life expectancy

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Lister, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Dr. Maureen Trudeau and Dr. Peter Venner who were excluded from voting due to a conflict of interest
- Dr. Bill Evans, Dr. Scott Berry and Dr. Sunil Desai who were not present
- Carole McMahon who was excluded from voting due her role as a patient member alternate

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of enzalutamide (Xtandi) for metastatic castrate resistant prostate cancer, through their declarations, three members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, two of these members were excluded from voting.

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Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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