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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Enzalutamide (Xtandi) for non-Metastatic Castration-Resistant Prostate Cancer

March 26, 2019

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Astellas Pharma Inc. compared enzalutamide plus Androgen Deprivation Therapy (ADT) with the comparator placebo (ADT alone) for patients with high risk, non-metastatic castration-resistant prostate cancer (nmCRPC). In addition, enzalutamide plus ADT was compared to apalutamide plus ADT.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	The patient population in the economic evaluation was consistent with the funding request and the PROSPER trial patient population of high risk, non-metastatic castration-resistant prostate cancer (nmCRPC) in adults.
Type of Analysis	Cost Utility Analysis (Cost/QALY), and Cost Effectiveness Analysis (Cost/LY)
Type of Model	Markov model
Treatment	Enzalutamide with ADT
Comparator 1	Placebo (ADT alone)
Comparator 2	Apalutamide plus ADT
Comparator 3	Bicalutamide plus ADT Bicalutamide plus ADT was not considered to be relevant comparator at the time of this pCODR review as the pCODR Clinical Guidance Panel noted that there is insufficient evidence to show a clinically meaningful benefit of adding bicalutamide to ADT in the targeted patient population. Furthermore, bicalutamide currently does not have regulatory approval in this setting.
Year of costs	2018
Time Horizon	10 years
Perspective	Health-care payer perspective
Cost of enzalutamide* Source: ODB formulary	Cost per capsule: Oral, 40mg caps $29.1954 each Daily dosage= 4 caps per day= $116.78 28-day cost: $3,269.88
Cost of apalutamide* Source: pCODR recommendation (August 2018)	Cost per tablet: $28.34 per 60mg tablet. Daily dosage = 4 caps per day= $113.36 28-day cost: $3,174.08
Cost of bicalutamide*	Cost per tablet: $1.27 per 50 mg tablet Daily dosage = 50 mg tablet= $1.27 28-day cost: $35.56
Cost of leuprolide*	Cost per mg: $39.60 One 22.5 mg subcutaneous depot injection once every three months: Daily cost: $10.60 28-day cost: $297.00. OR:

	One 7.5 mg subcutaneous depot injection every month: Daily cost: $13.85 28-day cycle: $387.97.
Model Structure	The model was based on 3 health states: nmCRPC, progressed metastatic castration-resistant prostate cancer (mCRPC), and death. mCRPC was further split into first-line progressive disease (PD)1, second-line PD2, and third line PD3. Figure available in section 2.1
Key Data Sources	PROSPER trial: enzalutamide versus placebo SPARTAN trial: apalutamide versus placebo Network meta-analysis (NMA) to derive progression free survival (PFS) and overall survival (OS) associated with the comparator apalutamide.
**Drug costs in this table are based on costing information provided by the submitter, Astellas Pharma Canada, Inc., and used in the submitted economic model.*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison enzalutamide versus placebo is appropriate, where placebo (ADT alone) is the current standard of care. In addition, the CGP considered that apalutamide should also be investigated as a comparator, because it has received a positive pCODR recommendation in 2018. The Submitter did include the comparator apalutamide as a scenario analysis.

Relevant issues identified included:

- The CGP concluded that there is a net overall clinical benefit to enzalutamide plus ADT for high-risk nmCRPC patients compared with ADT alone.
- The CGP identified the transition of non-metastatic CRPC to metastatic CRPC as a clinically relevant event which correlates with developments of symptoms (pain, fatigue, and a decline in quality of life) and additional interventions. For metastases-free survival (MFS) to be a reasonable endpoint, a significant clinical benefit will need to be realized with a favorable benefit–risk ratio for toxicity and cost evaluation.
  - *The economic evaluation is built on the disease progression of non-metastatic CRPC to metastatic CRPC with the outcome MFS, based on direct clinical evidence from the PROSPER trial.*
- While an OS improvement could not be ascertained in the PROSPER trial, an exploratory analysis from SPARTAN trial suggests MFS can be a surrogate marker for overall survival (OS).
  - *The economic evaluation incorporated MFS from the PROSPER trial as well as modelling OS in 2 stages: 1) prior to metastatic disease based on OS in the PROSPER trial, and 2) post progression based on OS from the SPARTAN trial. The impact of choosing different OS models was addressed in sensitivity analyses and in reanalysis.*
- The grade 3 and 4 adverse events were low and clinically acceptable.
  - *The economic evaluation incorporated differences between enzalutamide and placebo for serious adverse events, skeletal related adverse events, time to discontinuation, and overall quality of life.*
- Currently, there are no accepted standard active treatment options for patients with nmCRPC. The optimal management of nmCRPC remains an unmet need for a large number of patients.

- The CGP considered that apalutamide should also be investigated as a comparator, because it has received a conditional final pCODR recommendation in 2018. A submitter-provided network meta-analysis (NMA) and a published indirect treatment comparison (ITC) reported no differences between enzalutamide and apalutamide in MFS, OS (NMA and ITC) and toxicities (ITC).
    - *A comparison of enzalutamide versus apalutamide was made as a scenario analysis by the submitter.*

Summary of registered clinician input relevant to the economic analysis

While treatment options and available clinical evidence are both limited for patients with nm-CRPC, available treatment options include watchful waiting, chemotherapy, bicalutamide, and apalutamide. Use of enzalutamide was suggested to be restricted to patients at high risk of developing metastases. Registered clinicians noted that there will be both high incident and prevalent cases due to prostate cancer being a very common form of cancer, and extrapolations made using clinical trial data. Enzalutamide may cause potentially serious side effects in patients, including severe fatigue and drug-drug interactions; however, the benefits were expected to outweigh the potential toxicity risks to patients. Clinician input suggested that enzalutamide would be an appreciated option for patients and clinicians to consider, however, it may be a 'nice to have' therapy and not a necessity.

Summary of patient input relevant to the economic analysis

Overall the following factors were important for patients when assessing the value of a new drug for nm-CRPC: maintaining quality of life, access to a new treatment option, delaying the need for chemotherapy or palliative care, and delaying onset of symptoms. Patients reported a willingness to tolerate side effects of treatment (in particular fatigue [86%], loss of appetite [57%], rash [29%], and dizziness [14%]) if it could delay metastasis of their prostate cancer.

Patients where surveyed about what symptoms or problems they experienced with prostate cancer that affected their day-to- day living and quality of life, and to rate their top three symptoms that are the most important to control. Fatigue was the most important 84% and the most important to control (79%). Clearly, prostate cancer patients are both physically and psychologically impacted by living with prostate cancer. More than half are dealing with sexual dysfunction. One third is living with uncertainty and/or pain, and many are affected by not sleeping at night. All of these problems and issues affect their quality-of- life and the ability to enjoy life.

Patients who have experience with enzalutamide reported experiencing fatigue, however, expressed uncertainty about whether the fatigue experienced was due to treatment with enzalutamide or concurrent ADT.

- *The economic evaluation addressed the quality of life based on stage of disease (nmCRPC versus mCRPC), as well as incorporating impairment of quality of life for adverse events and for skeletal related side effects. The economic evaluation captured the rates and impact on quality of life for 37 side effects including fatigue and dizziness.*

SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for enzalutamide which are relevant to the economic analysis:

- PAG noted that the current treatment for nmCRPC is androgen deprivation therapy (ADT).
    - *The economic evaluation includes placebo (ADT alone) as a comparator to enzalutamide plus ADT. In addition, a scenario analysis of comparison of enzalutamide plus ADT to the recently approved apalutamide plus ADT.*

- Enzalutamide is an add-on therapy to ADT.
    - *The economic evaluation compared enzalutamide plus ADT versus ADT alone. Thus, the cost of ADT was included in both treatment arms.*

- PAG identified that there may be more frequent clinic visits for monitoring of blood work and side effects (e.g., fatigue, risk of fractures) and treatment time compared to ADT alone
    - *In the PROSPER trial patients were seen at week 1 and 5 and then every 16 weeks. The CGP noted that in clinical practice they are expecting the number of visits will be more with enzalutamide initially (at least once a month for the first 3 months) and then as per the current practice every 3-4 months. The current economic model did not examine variations in resource utilization.*

- PAG noted that enzalutamide is an oral treatment that can be administered at the patient's home and chemotherapy chair time is not required.

- Enzalutamide is available in one capsule strength and the dose is four capsules daily. Dose adjustments are made by adjusting the number of capsules and there would be minimal drug wastage.
    - *Wastage was not addressed in the economic model.*

- PAG is also seeking guidance on treatment options (e.g., abiraterone or chemotherapy) in the metastatic setting following enzalutamide in the non-metastatic setting.
    - The *economic evaluation included treatments in the metastatic stage according to Canadian expert opinion for both comparators. Scenario analysis included investigated the effect of not using Docetaxel (90%) and Radium 223 (10%), and instead using abiraterone (100%). It was noted by CGP that there were provincial variations in availability of treatments for metastatic disease.*
- PAG noted that treatment with enzalutamide in the PROSPER trial was continued until radiographic progression. Discontinuation solely because of an increase in the PSA level was discouraged, however, discontinuation on basis of clinical progression or toxic effects was allowed. If enzalutamide is recommended for reimbursement, PAG is seeking guidance on the appropriate criteria for discontinuation of enzalutamide (i.e., definition of progression).
    - *The economic evaluation did not address the consequences of different criteria for discontinuation. CGP believed discontinuation based on radiological progression or toxic effects would be appropriate, which is consistent with the PROSPER trial.*
- PAG noted that apalutamide for nm-CRPC was recently reviewed at pCODR. PAG is seeking guidance on what clinical scenarios apalutamide or enzalutamide would be the preferred treatment for patients with nmCRPC in this setting. PAG is also seeking guidance on whether there are specific clinical situations where apalutamide or enzalutamide would be the preferred treatment.
    - *The economic evaluation did not address the conditions under which a patient should receive enzalutamide versus apalutamide. The economic evaluation only compared enzalutamide versus apalutamide for patients similar to those in the PROSPER trial. However, CGP felt that there is currently insufficient evidence to suggest the superiority of either apalutamide or enzalutamide over the other. The CGP suggested that, drug price, patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection in clinical practice. CGP discussed that some physicians may have*

more experience with enzalutamide versus apalutamide and therefore may be more aware of the potential adverse events, and may be slightly more inclined to prefer enzalutamide. This was addressed in the budget impact reanalysis.

1.3 Submitted and EGP Reanalysis Estimates

The largest cost drivers for the economic evaluation were the cost of the drugs in the nmCRPC stage, which was estimated to be $154,866 for enzalutamide and $8,932 for placebo. There were cost savings for enzalutamide in the mCRPC stage, as patients who progressed from nmCRPC were treated with enzalutamide as first line PD1 therapy instead of in the nmCRPC stage (-$55,260). The largest clinical benefit for enzalutamide occurred with the large increase in time spent in nmCRPC stage with enzalutamide (40.4 months) versus placebo (19.3 months), for a gain of 21.1 months. This resulted in 1.42 additional QALYs in the nmCRPC stage. This QALY gain in the nmCRPC stage was partially offset by a shorter period in PD1 for enzalutamide resulting in loss of 0.92 QALYs in the PD1 stage. (Table 2).

While most sensitivity analyses had little impact on the results, the results were sensitive to the choice of the regression model used to project clinical progression and overall survival beyond the trial period up to the 10-year time horizon. Specifically, if less optimistic regression models were chosen for metastatic-free survival and overall survival, the ICUR for enzalutamide versus placebo increased from $145,748/QALY to $231,705/QALY.

Table 2. Submitted and EGP Estimates

Enzalutamide versus placebo		
Estimates (range/point)	Submitted (deterministic)	EGP Reanalysis (deterministic)
ΔE (LY)	0.88	0.47
ΔE (QALY)	0.74	0.44
nmCRPC	1.419	1.233
PD1	-0.921	-0.929
PD2	0.158	0.129
PD3	0.108	0.006
End of life disutility	0.006	0.004
ΔC ($)	$ 108,385	$ 100,868
nmCRPC	$154,866	$153,013
PD1	-$55,260	-$55,776
PD2	$9,654	$7,307
PD3	$348	-$3,317
Terminal care	-$574	-$440
ICUR estimate ($/QALY)	$145,748	$231,705

The main assumptions and limitations with the submitted economic evaluation were:

The economic model was built on direct trial evidence from the PROSPER trial comparing enzalutamide versus placebo. The model was sufficiently complex to capture the main inputs of the model: underlying disease progression and relative efficacy; the costs of drugs, types and costs of adverse events; costs of treatment upon disease progression; and utility values for disease state and adverse events. The main limitation was that the economic model was built on regression models making predictions beyond the trial period. This was apparent when the time horizon was varied to indicate that a large amount of economic benefit occurred in the 6 to 10-year time horizon.

While most of the patients had progressed to the clinical endpoint of metastatic free survival (MFS) which made variation in MFS modelling less uncertain, overall survival (OS) data was immature and projecting OS was subject to more variation. If you believe that MFS is a surrogate for OS and the large clinical benefit of increased MFS will project to a large OS benefit, then the ICUR is $145,748/QALY. If the projected OS benefit would be more

conservative and decreasing over time, which is similar to results seen in the trial, then the upper end of this estimate is $231,705/QALY.

In addition, a comparison of enzalutamide versus apalutamide was estimated by EGP using a submitter provided network-meta analysis (NMA). The economic model comparing enzalutamide versus apalutamide indicated little differences in cost and effects, and thus generated a small ICUR $24,405/QALY for enzalutamide versus apalutamide.

1.4 Detailed Highlights of the EGP Reanalysis

Overall the ICUR is higher than what the submitter reported by +$85,957/QALY, because of the choice of projected survival models.

The EGP made the following changes to the economic model:

[1] The long term projected MFS for placebo was underestimated, which was adjusted to create a more reasonable long term difference in MFS for enzalutamide versus placebo. The gamma parameter of MFS-ADT curve was adjusted. This increased the ICUR from $145,748/QALY to $166,406/QALY (+$20,658/QALY), driven by a small decrease in QALY benefit and a small increase in incremental cost.

[2] The long term projected OS for placebo was underestimated, which was adjusted to create a more reasonable long term difference in OS for enzalutamide versus placebo. The parameters of the Weibull function for ADT were adjusted. This increased the ICUR from $145,748/QALY to $192,701 (+$46,953/QALY), driven by a decrease in QALY benefit.

For the EGP's best case estimate when both changes are made, there is a smaller benefit in QALYs and a small difference in incremental cost to change the ICUR from $145,748/QALY to $231,705/QALY (+$85,957/QALY). Overall, the increased ICUR from the EGP reanalysis is based on a 0.30 decrease in QALY benefits, occurring in the nmCRPC stage (-0.186) and in PD2 (-0.102). The difference in costs of -$7,517 occurs in later stages PD2 and PD3 due to decreased projected long term benefit.

For the comparison between enzalutamide and apalutamide, the manufacturer-submitted NMA reported no statistically significant difference between the two treatments for the following endpoints (enzalutamide versus apalutamide): MFS (HR: 1.04 [95% CrI, 0.76 to 1.43]) and overall survival (HR: 1.14 [95% CrI, 0.68 to 1.89). The published indirect comparison reported identical mean estimates for differences between enzalutamide and apalutamide in MFS (HR: 1.04 [95% CI, 0.78 to 1.37]), and overall survival (HR: 1.14 [95% CI, 0.69 to1.90]). The reanalysis of the economic evaluation relied on the submitter-provided NMA to compare enzalutamide versus apalutamide.

Table 3: Detailed Description of EGP Reanalysis

EGP's Reanalysis for the Best Case Estimate, enzalutamide versus placebo (probabilistic)					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs (not discounted)	ICUR (QALY)	Δ from baseline submitted ICUR
Base case analysis	$108,385	0.74	0.88	$145,748	--
[1] MFS placebo projection	$113,957	0.68	0.83	$166,406	+$20,658/QALY
[2] OS placebo projection	$95,227	0.49	0.53	$192,701	+$46,953/QALY
Best case estimate of above [1],[2] parameters, **enzalutamide versus placebo**					
Best case estimate	$100,868	0.44	0.47	$231,705	+$85,957/QALY
EGP's Best Case Estimate, enzalutamide versus apalutamide (no modifications) (probabilistic)					
Best Case Estimate	-$5,855	-0.24	-0.28	$24,405*	

* This ICUR is the inverse of the normal representation of cost effectiveness, where the positive incremental cost is typically compared to the positive incremental benefit. The ICUR of $24,405/QALY indicates that switching from apalutamide to enzalutamide will reduce costs (-$5,855) and will also reduce QALYs (-0.28). Switching from enzalutamide to apalutamide will cost an incremental $5,855 per patient, and yield 0.28 incremental QALYs, with the incremental cost per 1 QALY being $24,405.

1.5 Evaluation of Submitted Budget Impact Analysis

The key factor influencing the incremental budget impact was the assumed market share (i.e., enzalutamide versus the recently approved apalutamide). Other factors included the size of the eligible patient population, the drug cost and the duration of enzalutamide therapy.

The key limitation of the BIA model is the unknown effect of the recent addition of apalutamide. However, any variation in the market share between apalutamide and enzalutamide creates small differences in the budget impact, due to similar prices.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for enzalutamide when compared to placebo is:

- Between $145,748/QALY to $231,705/QALY.
- Within this range, the best estimate would likely be: $231,705/QALY.
- The extra cost of enzalutamide from the submitted base case is between $100,868 and $108,385. The difference in cost is driven by the upfront cost of the drug and the cost of the drug in the metastatic stage.
- The extra clinical effect of enzalutamide from the submitted base case is between 0.44 and 0.74. The size of the effect is driven by projection of benefit in the metastatic stage.

The EGP's best estimate of ΔC and ΔE for enzalutamide when compared to apalutamide is:

- likely to be: $24,405/QALY.
- The extra cost of enzalutamide from the submitted base case is -$5,855. The main cost driver is the cost of the drug.
- The extra clinical effect of enzalutamide from the submitted base case is -0.24 QALYs, which is observed with prolonged nmCRPC stage.

Overall conclusions of the submitted model

The economic model comparing enzalutamide versus placebo was consistent with the clinical pathway and an appropriate model structure was used; costs of health states, adverse events costs, and utility values were reasonably applied. When the submitter performed one-way deterministic sensitivity analyses on some parameters, or in a few selected scenario analyses such as compliance (which was not a clinical issue), the ICUR did not change significantly. However, there is a high degree of uncertainty from choosing among many long term survival models. If you believe that the large clinical benefit of increased MFS will project to an even larger OS benefit, then the ICUR is $145,748/QALY. If the projected OS benefit would be more conservative, then the upper end of this estimate is $231,705/QALY.

The economic model comparing enzalutamide versus apalutamide indicated little differences in cost and effects, and thus generated a small ICUR $24,405/QALY.

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 nmCRPC. A full assessment of the clinical evidence of enzalutamide for nmCRPC 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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