Canada's Drug and
Health Technology Agency

DRAFT Reimbursement Recommendation

Enzalutamide

Reimbursement request: For the treatment of patients with non-metastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk of metastasis (high-risk BCR)

Draft Recommendation: Reimburse with conditions

Summary of Recommendation

- The Formulary Management Expert Committee (FMEC) recommends that enzalutamide, with or without androgen deprivation therapy (ADT), be reimbursed for the treatment of patients with nonmetastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence (BCR), provided certain clinical conditions are met.
- FMEC reviewed the EMBARK trial, a phase III, randomized trial which enrolled patients with nmCSPC with BCR at high-risk for metastases. FMEC concluded that the findings suggest enzalutamide, with or without ADT, delays the development of metastasis and suppresses PSA more effectively than ADT alone. Both outcomes are deemed important by patients. Enzalutamide (with or without ADT) was also associated with higher incidences of adverse events.
- The expected cost of enzalutamide (with or without ADT) is higher than that of comparators based on publicly available list prices.

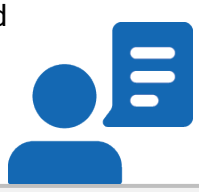
Therapeutic Landscape

What Is Non-metastatic Castration-sensitive Prostate Cancer?

Non-metastatic castration-sensitive prostate cancer (nmCSPC) describes the early stage of prostate cancer wherein the disease remains localized and androgen deprivation therapy (ADT) is still an effective treatment. When prostate specific antigen (PSA) levels rise rapidly over a short period of time (i.e. biochemical recurrence), patients may be at a higher risk of disease progression.

Why Did We Conduct This Review?

There are limited treatment options for patients with nmCSPC who have biochemical disease recurrence after surgery or radiotherapy. Based on the evidence from the EMBARK trial, publicly funded drug plans requested this nonsponsored reimbursement review.



Person With Lived Experience

A 69-year-old shared his prostate cancer journey, after a diagnosis in 2007. He began with radiation therapy, but by 2010 his PSA levels rose, leading to treatment with ADT. It worked initially, but by 2011 his cancer became more aggressive. His oncologist advised him to get his affairs in order with a 1-year prognosis. He outlined the profound impact this diagnosis has had on him and his family, and the related challenges around employment, friends, and associated stigma. He explained that during treatment, his most desired outcomes were cancer control and reduced side effects. In 2012, he turned to abiraterone acetate and prednisone, which worked but caused skin issues, leading him to switch to enzalutamide. Although the side effects subsided quickly, he experienced physical, cognitive, and speech issues. He shared that enzalutamide significantly extended his lifespan and quality of life for multiple years.

Input from Community Partners

What Did We Hear From Patients?

One patient group provided input, and highlighted their concerns about treatment choices, rising PSA levels post-treatment, recurrence, issues concerning hormone therapy, metastases, psychosocial impact and quality of life. The patient group emphasized that, since individual responses to treatments vary, it is important for patients and prescribers to have access to all available options.

What Did We Hear From Clinicians?

One clinician group provided input and shared that there is currently no defined treatment for patients with BCR nmCSPC at high-risk of metastasis. For patients in this setting, the goals of therapy are to reduce the risk of metastasis, improve overall survival, and maintain quality of life.

What Did We Hear From the Pharmaceutical Industry?

One pharmaceutical company provided input, agreeing with the scope of the review. They provided comments on the appropriate comparators and outcomes.

What Did We Hear From Public Drug Programs?

Public drug plans inquired about criteria for initiating therapy, considerations for treatment duration, and discontinuation of therapy. Questions were asked regarding interchangeability of different ADT options and questions related to retreatment of enzalutamide in advanced stages.

Refer to Input section of the report.

Deliberation

With an 8 to 0 vote, the FMEC concluded that enzalutamide with or without ADT may delay metastasis and suppress PSA levels more effectively compared to ADT alone in patients with nmCSPC with high-risk BCR. FMEC heard from patients who expressed that they value the benefits of treatments that suppress PSA levels and delay the onset of metastatic disease. However, there remains uncertainty in the sequencing of treatment options when progression occurs to nmCRPC or to metastatic settings, and the clinical unmet need remains unclear. FMEC also noted that enzalutamide (with or without ADT) was associated with higher incidences of adverse events. Although enzalutamide (with or without ADT) will be associated with increased drug program spending at public list prices, the cost-effectiveness of this drug is unknown.

FMEC deliberated using the following 5 domains of value:

- **Unmet Clinical Need:** Unmet clinical need refers to morbidity and/or mortality arising from a condition or symptom that is not addressed effectively by available treatments.
- **Clinical Value:** Clinical value is the value that patients derive from a health technology in terms of its effect on their health and health-related quality of life. The determination of the clinical value of a health technology requires the measurement of its clinical benefits and harms and an assessment of the impact of these effects on patients. Clinical benefits and harms are assessed against relevant comparators.
- **Economic Considerations:** Economic considerations refer to economic evidence to inform the financial, human or other resource implications associated with the technology under review, and whether it is reasonable to allocate resources to the technology under review given its expected clinical benefits. Considerations may include the potential resource or cost impacts of the technology under review versus relevant comparator(s) and/or the potential economic value of the technology under review versus relevant comparator(s). For this review, only the relative cost impacts were considered.
- **Impacts to Health Systems:** This domain considers 2 distinct but interrelated components: organizational feasibility of adoption is the ease with which the health technology can be implemented in the health system while realizing its clinical value, while economic feasibility of adoption (affordability) considers how the adoption of a health technology will financially impact the payer or budget holder. For this review, only the first component (i.e., organizational feasibility) was considered.
- **Distinct Social and Ethical Considerations:** This domain considers the distinct social and ethical implications of health technologies (including in their design, evaluation, and implementation) not already assessed in the other domains and how they affect patients, caregivers, populations, and the organization of health systems.

Decision Summary

Table 1: Summary of Deliberation

Overarching question(s)	Discussion point(s)
Unmet Clinical Need	
Is there significant clinical need arising from the condition despite available treatments?	• FMEC discussed that the unmet need is unclear with the use of enzalutamide with or without ADT in nmCSPC. However, it has been noted that patients and clinicians want access to enzalutamide with or without ADT as a treatment option for biochemical recurrent prostate cancer to delay metastases and reduce PSA level. • FMEC noted that there is uncertainty around the standard of care for nmCSPC based on input from the clinical experts. There is also considerable heterogeneity in when ADT-based treatment is initiated. • FMEC also highlighted that additional clarity is needed around the need for early treatment with enzalutamide in combination with ADT regimen to delay disease progression and how this translates to improving long term outcomes such as survival. • The clinical expert has noted that biochemically recurrent nmCSPC patients who have radical prostatectomy (RP) should be evaluated for salvage radiation therapy (with or without ADT) with curative intent. For these patients who are not candidates for salvage radiation therapy, they may be offered ADT-based therapy.
Clinical Value	
Does the drug under review demonstrate acceptable clinical value versus relevant comparators in the Canadian setting?	• FMEC discussed that the EMBARK trial was a well conducted trial with clinically meaningful endpoints with improvement in MFS for both enzalutamide plus ADT (5 yr MFS 87.3% versus 71.4%; HR = 0.42, p < 0.001) and enzalutamide alone versus ADT therapy (5 years MFS 80% versus 71.4%, HR = 0.63, p = 0.005). However, FMEC highlighted that the OS data was immature. • FMEC discussed that there were numerically more adverse events in the enzalutamide arms of the trial leading to greater discontinuation (20.7% and 17.8% versus 10.2%) than in the ADT arm. Fatigue and seizures were numerically more common in the enzalutamide arms. • FMEC noted that populations with higher morbidity and mortality (e.g., Black, Indigenous) were not well represented in the study. • FMEC noted that patients value delaying metastasis and reducing PSA level which is seen as a marker of the disease. Both of which can be a source of psychological stress for patients. Patients advocated for more treatment choices, including those that are effective in delaying metastasis,

Overarching question(s)	Discussion point(s)
	maintaining their QoL and avoiding or delaying the need for additional treatment options. • FMEC also noted that there is potentially inequity of access to this oral treatment, especially in younger patient population where their eligibility for public drug program coverage may be variable across different jurisdictions. • There were some opposing discussion on what patient populations would benefit from treatment with enzalutamide, with or without ADT, but FMEC agreed that access to therapy should be based on the inclusion criteria of the study. • FMEC also discussed that while ADT have undesirable adverse effects, most patients who initiate on ADT will remain on treatment to manage the disease. The 10.2% discontinuation rate observed in the EMBARK trial for this treatment arm is comparable to what is typically observed in clinical practice.
Economic Considerations	
Are there economic considerations that are relevant to address when implementing reimbursement of the drug under review?	• FMEC discussed that the acquisition costs per patient per 28-day cycle are higher for enzalutamide (with or without ADT) compared to other options at public list prices. • FMEC discussed that generic versions of enzalutamide are currently under review at Health Canada, however, it is unknown when or if these will become available. FMEC discussed that treatment acquisition costs associated with enzalutamide are likely to decrease once generics become available. However, enzalutamide plus ADT will still be associated with incremental costs given it is typically an add-on therapy.
Impacts to Health Systems	
Are there expected organizational impacts of implementing the drug under review?	• FMEC discussed that this oral treatment regimen should be easy to implement. However, there may be uncertainty in the subsequent treatment options. The clinical specialists have clarified that, in general, patients who progress onto metastatic settings while on enzalutamide would not usually be treated immediately after with other ARPI. Possible treatment options include chemotherapy or other radiopharmaceutical options. • FMEC also discussed that most toxicities related to enzalutamide are managed in an out-patient basis with strategies such as dose reduction, supportive therapy or discontinuation of treatment. • FMEC noted that while the long-term benefit remains uncertain, there is additional monitoring requirement associated with this treatment (e.g., checking PSA level more frequently or addressing adverse events).
Distinct Social and Ethical Considerations	
Is there significant non-clinical need arising from the	• FMEC noted that because enzalutamide is only available as a capsule formulation where gelatin (pork) may be an included ingredient, this could

Overarching question(s)	Discussion point(s)
condition, despite available treatments, that would potentially be addressed by the technology under review? Are there any important measures that should be implemented to ensure that the use of the technology addresses relevant social and ethical implications?	pose as a concern for individuals with dietary restrictions or ethical preferences to avoid animal products.

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; BCR = biochemical recurrence; CRPC = castrate resistance prostate cancer; FMEC = Formulary Management Expert Committee; nmCSPC = non-metastatic castrate sensitive prostate cancer; OS = overall survival; PSA = prostate specific antigen; PSADT = prostate specific agent doubling time; QoL = quality of life; RP = radical prostatectomy; RT = radiation

Full Recommendation

With a 6 to 2 vote, the FMEC recommends that enzalutamide with or without ADT for the treatment of non-metastatic castration-sensitive prostate cancer with biochemical recurrence at high risk for metastasis be reimbursed if the conditions presented in Table 2 are met.

Table 2: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
Enzalutamide with or without ADT should be reimbursed in patients who meet the criteria for high-risk prostate cancer with biochemical recurrence after radical prostatectomy (RP) or radiation (RT) who have all of the following characteristics: 1. High risk is defined as a. PSA doubling time of 9 months or less b. Screening PSA level	Initiation criteria reflect the enrolment criteria in the EMBARK trial.	Salvage radiation therapy remains a curative treatment for this population after RP and would typically be considered first before offering enzalutamide with or without ADT unless they are not a candidate for this treatment. Enzalutamide plus ADT may improve survival by delaying the development of metastatic CRPC.

Reimbursement condition	Reason	Implementation guidance
i. 1ng/mL or higher in prior RP (with or without post-operative RT) patients ii. at least 2ng/mL above nadir in prior RT 2. Testosterone 150ng/dL or higher 3. No evidence of metastases on conventional imaging 4. Good performance status 5. Not a candidate for salvage radiation therapy		Enzalutamide monotherapy may offer a treatment option for individuals unable to take or tolerate ADT adverse effects. Conventional imaging could include CT/PET scans depending on local practices. PSMA PET imaging may be available in some jurisdictions, but it is not considered a standard of care for detecting metastasis at this time.
Discontinuation and Renewal		
1. Enzalutamide should be held after 36 weeks and if PSA is well suppressed to 0.2ng/mL or less and may be restarted based on appropriate PSA level. 2. Enzalutamide should be discontinued if there is disease progression or intolerable adverse effects.	The majority of patients discontinue therapy once PSA is sufficiently suppressed.	Restarting enzalutamide with or without ADT should be based on PSA level as per the EMBARK trial. For patients with no prior RP, the PSA level threshold to restart treatment is at least 5 ng/mL. For patients with prior RP, the PSA level threshold to restart treatment is at least 2ng/mL.
Prescribing		
1. This therapy should be initiated by clinicians with expertise in the treatment of prostate cancer, including medical oncology, radiation oncology and urologic oncologist.	This is a specialized population who would be under the care of a treatment team experienced in their care.	
Cost		
1. A price reduction may be required.	Based on publicly available prices, enzalutamide (with or without ADT) is more expensive than relevant comparators. A price reduction may therefore be required. A cost-effectiveness analysis would be needed to determine the extent of price reduction.	

ADT = androgen deprivation therapy; CRPC = castrate resistance prostate cancer; PSA = prostate specific antigen; RP = radical prostatectomy; RT = radiation therapy; TBD = to be determined

Feedback on Draft Recommendation

<to be updated after the feedback period>

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr Zaina Albalawi, Dr. Hardit Khuman, Ms. Valerie McDonald, Dr Bill Semchuk, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, as well as two medical oncologists from Ontario and Nova Scotia.

Meeting date: September 19, 2024

Conflicts of interest: None

Special thanks: CDA-AMC extends our special thanks to the individuals who presented directly to FMEC on behalf of patients with lived experience and to patient organizations representing the community of those living with prostate cancer, notably the Prostate Cancer Foundation Canada which includes Leah Lariviere and Frank J. Altin.

Note: CDA-AMC makes every attempt to engage with people with lived experience as closely to the indication and treatments under review as possible, however at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys or use with comparators under review to ensure lived experience perspectives are included and considered in reimbursement reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journey with the FMEC committee.

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