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Reimbursement Recommendation

Talazoparib (Talzenna)

Indication: Talazoparib in combination with enzalutamide for the treatment of adult patients with homologous recombination repair gene-mutated metastatic castration-resistant prostate cancer

Sponsor: Pfizer Canada ULC

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Talzenna?

Canada's Drug Agency (CDA-AMC) recommends that Talzenna in combination with enzalutamide should be reimbursed by public drug plans for the first-line treatment of adult patients with homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Talzenna plus enzalutamide should only be covered to treat adult patients with mCRPC who have an HRR mutation, have not been treated with an androgen receptor pathway inhibitor (ARPI) for earlier stages of prostate cancer, and have not received treatments for mCRPC or a poly(ADP-ribose) polymerase inhibitor (PARPI) for mCRPC. Moreover, patients should be in relatively good health.

What Are the Conditions for Reimbursement?

Talzenna plus enzalutamide should only be reimbursed if it is prescribed by a clinician with expertise in treating prostate cancer and should not be reimbursed when used in combination with other anticancer drugs.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Talzenna plus enzalutamide delays disease progression (as indicated by medical imaging) or death in patients with HRR gene-mutated mCRPC compared with placebo plus enzalutamide.
- Talzenna meets patient's needs for a treatment that delays disease progression or death; avoids the need for continuous corticosteroid exposure, which is required for other PARPI and ARPI combination therapies; and covers a broader range of gene mutations than available combination therapies.
- Based on the assessment by CDA-AMC of the health economic evidence, Talzenna plus enzalutamide does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Talzenna plus enzalutamide is estimated to cost the public drug plans approximately $21.8 million over the next 3 years.

Summary

Additional Information

What Is mCRPC?

mCRPC is prostate cancer that has spread to other parts of the body and does not respond to hormone treatments that lower testosterone. In Canada, approximately 1 of 2 of every 100 patients with prostate cancer have mCRPC. Approximately 25% to 30% of patients with mCRPC have HRR gene mutations.

Unmet Needs In mCRPC

There is no cure for mCRPC with available treatments. There is a need for treatments with fewer side effects that can extend survival while improving or maintaining the quality of life of patients.

How Much Does Talzenna Cost?

Treatment with Talzenna is expected to cost $5,564 per patient per 28 days. When Talzenna is used in combination with enzalutamide, the expected cost is $8,833 per patient per 28 days.

Recommendation

The pan-Canadian Oncology Drug Review Expert Committee (pERC) recommends that talazoparib with enzalutamide be reimbursed for the first-line treatment of adult patients with HRR gene-mutated mCRPC, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, double-blind, randomized controlled trial (RCT) (TALAPRO-2; N = 399) demonstrated that treatment with talazoparib-enzalutamide resulted in added benefit in radiographic progression-free survival (rPFS) and overall survival (OS) compared with placebo-enzalutamide in adults with HRR gene-mutated mCRPC who have not received prior systemic therapy in the mCRPC setting. At the second data cut-off date of September 3, 2024, the median rPFS was 30.7 months (95% confidence interval [CI], 24.3 months to 38.5 months) in the talazoparib-enzalutamide group and 12.3 months (95% CI, 11.0 months to 16.5 months) in the placebo-enzalutamide group, with a between-group hazard ratio (HR) of 0.47 (95% CI, 0.36 to 0.61). The Kaplan-Meier (KM)–estimated between-group difference in the probability of rPFS at 12 months (data cut-off date of October 3, 2022) and 48 months (data cut-off date of September 3, 2024) was [redacted] and [redacted], respectively. At the same data cut-off date, the median OS was 45.1 months (95% CI, 35.4 months to not reached) in the talazoparib-enzalutamide group and 31.1 months (95% CI, 27.3 months to 35.4 months) in the placebo-enzalutamide group, with a between-group HR of 0.62 (95% CI, 0.48 to 0.81). The KM-estimated between-group difference in the probability of being alive at 48 months was [redacted]. No comparative evidence for talazoparib-enzalutamide in the second-line or later-line mCRPC setting was submitted.

Patients identified a need for treatments that delay disease progression, prolong life, improve quality of life, and have fewer treatment side effects. pERC concluded that talazoparib-enzalutamide met some important needs identified by patients, such as prolonged rPFS and OS, compared to placebo-enzalutamide. Additionally, talazoparib-enzalutamide may meet an unmet need for first-line combination therapy with poly(ADP-ribose) polymerase inhibitors (PARPIs) and ARPIs in patients with HRR gene alterations beyond *BRCA*. Talazoparib-enzalutamide also avoids the need for continuous corticosteroid exposure, which is required for other PARPI and ARPI combination therapies. However, its comparative efficacy and safety versus other PARPI and ARPI combinations in patients with *BRCA* mutation are uncertain due to methodological limitations in the submitted indirect treatment comparison.

Using the sponsor-submitted price for talazoparib-enzalutamide and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for talazoparib-enzalutamide was $242,571 per quality-adjusted life-year (QALY) gained compared with enzalutamide. At this ICER, talazoparib-enzalutamide is not cost-effective at a $50,000 per QALY gained willingness to pay threshold for adults with HRR gene-mutated mCRPC. A price reduction is required for talazoparib-enzalutamide to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adults (18 years or older) with all of the following: 1.1. mCRPC 1.2. positive for a HRR gene alteration 1.3. have not received prior treatment with ARPI for mCSPC or nmCRPC 1.4. have not received prior systemic therapy for mCRPC 1.5. have not received prior treatment with a PARPI for mCRPC.	Evidence from the TALAPRO-2 trial demonstrated a clinical benefit in adults with mCRPC with HRR gene mutations who had not received prior systemic therapy in the mCRPC setting, except for androgen deprivation therapy and first-generation antiandrogen drugs. Patients were ineligible to participate if they had received any prior treatment with second-generation androgen receptor inhibitors (enzalutamide, apalutamide, and darolutamide), a PARPI, cyclophosphamide, or mitoxantrone for prostate cancer. Although patients who had received abiraterone acetate for mCSPC were eligible to participate in the TALAPRO-2 trial, the evidence supporting the use of talazoparib-enzalutamide in this subgroup is limited since they represented a small proportion (8%) of the population who were enrolled with HRR gene mutations.	Patients must have confirmation of an HRR gene-mutation before treatment is initiated. HRR testing must be available in jurisdictions and accessible to patients. No prior use of ARPIs was allowed for mCRPC in the TALAPRO-2 trial; however, pERC agreed that patients with mCRPC treated with either enzalutamide or abiraterone for a maximum of 4 months may be eligible for treatment with talazoparib-enzalutamide, to align with the recommendations for niraparib-abiraterone acetate plus prednisone and olaparib plus abiraterone acetate plus prednisone.
2. Patients should have good performance status.	Patients with an ECOG PS score of 0 or 1 were included in the TALAPRO-2 trial.	Treating patients with an ECOG PS score of greater than 1 may be at the discretion of the treating clinician.
Discontinuation		
3. Reimbursement of talazoparib-enzalutamide should continue until disease progression or unacceptable toxicity.	Patients from the TALAPRO-2 trial discontinued treatment upon disease progression or unacceptable toxicity.	—
Prescribing		
4. Talazoparib-enzalutamide should be initiated by a clinician with expertise in treating mCRPC in an outpatient oncology clinic.	To ensure that talazoparib-enzalutamide is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
5. Talazoparib-enzalutamide should not be reimbursed when administered in combination with other anticancer drugs.	There are no data supporting the efficacy and safety of talazoparib-enzalutamide when used in combination with additional anticancer drugs.	—
Pricing		
6. A reduction in price.	The ICER for talazoparib-enzalutamide is $242,571 per QALY gained when compared with enzalutamide. A price reduction of greater than 90% would be required for talazoparib-enzalutamide to achieve an ICER of $50,000 per QALY gained	—

Reimbursement condition	Reason	Implementation guidance
	compared to enzalutamide. Price reductions for different thresholds are available in the Pharmacoeconomic Review report.	

ARPI = androgen receptor pathway inhibitor; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HRR = homologous recombination repair; ICER = incremental cost-effectiveness ratio; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; PARPI = poly(ADP-ribose) polymerase inhibitor; pERC = pan-Canadian Oncology Drug Review Expert Committee; QALY = quality-adjusted life-year.

Discussion Points

- **Unmet need**: pERC acknowledged input from patients and clinicians that there is an unmet need for effective and safe therapies for mCRPC which is an aggressive disease with poor prognosis. pERC discussed that current first-line treatment options for patients with HRR gene-mutated mCRPC include ARPIs (enzalutamide, abiraterone acetate plus prednisone) as monotherapy or in combination with PARPIs (niraparib-abiraterone acetate plus prednisone, olaparib plus abiraterone acetate plus prednisone), and chemotherapy. Notably, niraparib-abiraterone acetate plus prednisone and olaparib plus abiraterone acetate plus prednisone are therapies for *BRCA1 and BRCA2* mutations only in the first-line setting. Based on the submitted evidence, pERC concluded that talazoparib-enzalutamide may meet an unmet need as a first-line PARPI and ARPI combination therapy that is effective for a wider panel of HRR gene alternations beyond *BRCA*. pERC also noted that in the TALAPRO-2 trial, the prespecified subgroup analysis by *BRCA* mutation status (with or without) suggested results consistent with the primary rPFS analysis, in favour of talazoparib-enzalutamide. Additionally, pERC discussed that talazoparib-enzalutamide is a steroid-sparing option; it does not require the use of steroids (prednisone), which is a part of existing PARPI and ARPI combination regimens (niraparib-abiraterone acetate plus prednisone, olaparib plus abiraterone acetate plus prednisone).
- **Place in therapy**: pERC noted that the reviewed evidence was limited to the use of talazoparib-enzalutamide who are naive to ARPI in the first-line mCRPC setting. pERC acknowledged that the Health Canada indication is line-agnostic and that the clinical experts consulted by CDA-AMC indicated that clinicians may favour using talazoparib-enzalutamide as a second-line or later-line treatment due to the decreasing number of patients who are naive to ARPI in the first-line mCRPC setting. However, pERC noted that treatment effects of talazoparib-enzalutamide in the second-line or later-line setting is unknown because such evidence was not submitted. Only evidence for the use of talazoparib-enzalutamide in the first-line mCRPC setting was submitted.
- **Health-related quality of life:** pERC noted that patients and clinicians highlighted improvement in health-related quality of life (HRQoL) as an important outcome and treatment goal for patients with mCRPC. However, pERC was unable to draw definitive conclusions on the effects of talazoparib-enzalutamide compared to placebo-enzalutamide on HRQoL due to concerns about imprecision and missing outcome data in the TALAPRO-2 trial.
- **Harms**: pERC highlighted the input from the patient group and clinicians of an unmet need for alternative treatments with fewer side effects. Although a higher proportion of grade 3 or 4 treatment-

emergent adverse events (TEAEs), serious TEAEs, and withdrawals due to TEAEs were reported in patients receiving talazoparib-enzalutamide compared to placebo-enzalutamide, pERC considered the side effects to be manageable, given that treatment is expected to be prescribed and overseen by clinicians who are experienced in treating patients with mCRPC. pERC agreed with the clinical experts that there was no new safety signals identified from the TALAPRO-2 trial, and the safety profile of talazoparib-enzalutamide was consistent with the known safety profiles of both drugs.

- **Indirect evidence:** Direct evidence between talazoparib-enzalutamide and relevant comparators (abiraterone acetate plus prednisone alone, niraparib-abiraterone acetate plus prednisone, olaparib plus abiraterone acetate plus prednisone, or chemotherapy) was not submitted. pERC discussed the indirect evidence from the sponsor-submitted unanchored matching-adjusted indirect comparison (MAIC). [redacted]; however, the CDA-AMC review team noted there is uncertainty in the results due to heterogeneity in the populations and studies that could not be accounted for in the analyses, and lack of HRQoL and harms assessments. pERC also noted that no direct or indirect comparative evidence for talazoparib-enzalutamide versus chemotherapy was submitted, which represents a gap in the available evidence given the potential shared place in therapy for HRR-deficient mCRPC when used as first-line treatments.
- **Testing procedure:** pERC noted that public funding status and clinical practices for somatic or germline mutation testing in patients with mCRPC are not consistent across Canada. Not all jurisdictions have access to testing for all HRR pathway genes. While next-generation sequencing panels for *BRCA1*, *BRCA2*, or *ATM* are generally available and funded across jurisdictions, testing for other HRR genes may not be currently available or accessible to all patients. pERC noted that a small proportion of patients with mCRPC who have mutations in genes other than *BRCA1*, *BRCA2*, or *ATM* may not be identified depending on what testing panels are available in their region.
- **Economic considerations**: The estimate by CDA-AMC of the ICER and the price reduction needed to achieve cost-effectiveness are based on evidence from the TALAPRO-2 trial, which was restricted to patients receiving first-line treatment. The ICER and price reduction required to achieve cost-effectiveness in subsequent lines of therapy are unknown. pERC discussed that talazoparib-enzalutamide is indicated for the HRR-mutated population and noted that olaparib plus abiraterone acetate plus prednisone and niraparib-abiraterone acetate plus prednisone are both indicated to be used in first-line treatment of patients with deleterious or suspected deleterious germline and/or somatic *BRCA*-mutated mCRPC; *BRCA* mutations represented between 30% and 40% of all HRR mutations based on the TALAPRO-2 trial. Although the CDA-AMC noted that the comparative evidence was associated with significant uncertainty, pERC considered talazoparib-enzalutamide likely to have similar efficacy as olaparib plus abiraterone acetate plus prednisone, and niraparib-abiraterone acetate plus prednisone. This should be considered by decision-makers to

inform price negotiations. No analysis was submitted which compared talazoparib-enzalutamide and chemotherapy; thus, the relative cost-effectiveness is unknown.

- **Budget impact**: Based on the submitted evidence, pERC concluded that talazoparib-enzalutamide may meet an unmet need as a first-line PARPI and ARPI combination therapy. pERC noted that in the submitted budget impact analysis, patients were eligible to receive talazoparib-enzalutamide in both first-line and subsequent lines of treatment. If talazoparib-enzalutamide were to be used as first-line treatment only, the budget impact estimated by CDA-AMC might differ.

Background

Castration-resistant prostate cancer (CRPC) is defined by disease progression despite castrate levels of testosterone and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases. A patient may progress to mCRPC from metastatic castration-sensitive prostate cancer (mCSPC) based on biochemical recurrence (characterized by rising PSA levels despite medical or surgical castration) or from nonmetastatic CRPC (nmCRPC) based on presentation of metastases (assessed radiographically). Progressing to mCRPC is characterized by increased symptomatic burden and reduced HRQoL. In Canada, the estimated prevalence of mCRPC is 1.2% to 2.1% of total prostate cancer cases. The expected 5-year survival for patients diagnosed with prostate cancer is 91% for all stages combined, and for metastatic disease, the 5-year survival rate is approximately 28%.

According to the clinical experts consulted by CDA-AMC, the main treatment goals for patients with mCRPC are to prolong survival, delay disease progression, improve symptoms, and maintain HRQoL. Systemic therapies for the treatment of patients with mCRPC, and the sequencing of these treatments, depends on patient and disease factors, prior treatments used in the mCSPC setting, and access, which varies across Canada. Docetaxel, cabazitaxel, abiraterone, enzalutamide, radium-223 (for patients with bone-only metastatic disease), lutetium vipivotide tetraxetan, and olaparib, olaparib plus abiraterone acetate plus prednisone or niraparib-abiraterone acetate plus prednisone for patients with *BRCA1*, *BRCA2*, and/or *ATM* mutations, are all Health Canada-approved, and most are available across the jurisdictions in Canada.

Talazoparib is a potent inhibitor of poly(ADP-ribose) polymerase enzymes, which are involved in the HRR pathway. The approved Health Canada indication for talazoparib is in combination with enzalutamide for the treatment of adult patients with HRR gene-mutated mCRPC. Talazoparib is available as 0.1 mg and 0.25 mg oral capsules and the recommended dose is 0.5 mg orally once daily in combination with enzalutamide 160 mg orally once daily, until disease progression or unacceptable toxicity.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, double-blind, RCT in adults with mCRPC and 1 indirect treatment comparison
- patients' perspectives gathered by 2 patient groups, PROCURE – Cancer Prostate and the Canadian Cancer Society
- input from public drug plans that participate in the CDA-AMC reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with mCRPC
- input from 1 clinician group, Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to our call for input and from clinical experts consulted for the purpose of this review.

Patient Input

CDA-AMC received 2 patient group inputs from PROCURE – Cancer Prostate and the Canadian Cancer Society. According to the inputs, distress and treatment decisions, rising PSA levels after treatment, recurrence, hormone therapy and its side effects, as well as metastases are among the main concerns of patients and mCRPC impacted mostly sexual activity, followed by the ability to work, maintaining a positive mental health, concentration, travel, exercise or conducting household chores. Both patient groups clarified that patients' expectations regarding new treatments included cancer control with less side effects, having longer-lasting effects, delaying the onset or elimination of metastases, decreasing or keeping PSA levels stable over a long period, convenient treatment regimens, prolonging life, and improving quality of life. Patients also expected treatments to be affordable, easier to access, better follow-up over long-term issues, and needing to be heard and taken seriously.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts indicated that since mCRPC is a terminal phase of prostate cancer, the unmet needs of patients would be new treatments that would prolong survival, maintain or improve quality of life, while exposing patients to minimal toxicity. Both clinical experts highlighted that the balance between treatment efficacy and quality of life would be important. The clinical experts noted that it remains unclear whether talazoparib-enzalutamide would lead to a shift in the current treatment paradigm. This uncertainty stems from the increased use of ARPI in patients with mCSPC and nmCRPC in recent years. They noted that many medical oncologists currently favour prescribing chemotherapy as first-line mCRPC treatment in patients who have previously progressed on an ARPI in the mCSPC and nmCRPC settings. They noted that if a treatment

was used in mCSPC, it is not likely for the patient to receive it again for first-line mCRPC (with the occasional exception of docetaxel if given at least 1 year prior). The clinical experts noted that talazoparib-enzalutamide may have a limited role as a first-line treatment in the mCRPC setting due to the decreasing number of patients who are naive to ARPI and the few patients who would be clinically ineligible for docetaxel; however, it may have a role in subsequent lines of therapy. The clinical experts indicated that patients best suited for talazoparib-enzalutamide would be those that match the eligibility criteria of the TALAPRO-2 trial, which included first-line treatment for HRR gene-mutated mCRPC, and no contraindications to talazoparib or enzalutamide. The experts indicated that in clinical practice, a combination of radiographic, biochemical (e.g., PSA), and clinical parameters (i.e., decrease in disease-related symptoms) are used to determine whether a patient with mCRPC is responding or progressing on treatment. They noted that at the very least, assessments should be performed at 3-month intervals. The experts indicated that treatment with talazoparib-enzalutamide should be discontinued if patients experience disease progression (as defined radiologically or clinically), treatment is intolerable, or patient preference. The experts noted that PARPI, such as talazoparib, have the potential to become toxic; therefore, patients receiving talazoparib-enzalutamide should be under the care of a medical oncologist who can manage toxicity associated with the therapy.

Clinician Group Input

CDA-AMC received 1 input from Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee. According to the clinician group input, the treatment goal is prolonging life and improving quality of life. The group noted that there are no cures currently available for metastatic prostate cancer and there is a need for treatments that prolong life. The group noted that talazoparib in combination with enzalutamide should be used in patients who are treatment-naive to mCRPC and that treatment with chemotherapy or ARPI in the mCSPC setting should not preclude eligibility for treatment with talazoparib and enzalutamide, as per the TALAPRO-2 trial. The group noted that PSA and serial radiographic imaging would be used to monitor response to therapy and that significant side effects and progression of disease viewed on imaging are among the factors for considering discontinuation of the treatment. The clinician group noted that medical oncologists, radiation oncologists, and urologists specialized in prostate cancer care are among the specialists or prescribers that would be required for prescribing the treatment. The Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee added that access to this (and other) combinations in this setting would also require ongoing efforts to ensure equitable, timely access to genomic testing of relevant alterations for all eligible patients in Canada with prostate cancer.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for talazoparib-enzalutamide:

- relevant comparators
- considerations for initiation of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy

- generalizability
- funding algorithm
- care provision issues
- system and economic issues.

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs (Table 2).

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
The comparator in the TALAPRO-2 study was enzalutamide and placebo. This is a reasonable comparator, but is there any evidence comparing talazoparib with enzalutamide to other funded PARPIs, either alone (i.e., olaparib) or in combination with an androgen receptor inhibitor (i.e., olaparib with abiraterone and prednisone or niraparib-abiraterone with prednisone)?	The CDA-AMC review team noted that the comparison between talazoparib-enzalutamide and relevant comparators is to be addressed in the Clinical Review report. The clinical experts noted that, to their knowledge, there is no direct comparative efficacy and safety between talazoparib-enzalutamide and other funded PARPIs, either alone or in combination with an androgen receptor inhibitor. pERC agreed with the CDA-AMC review team and the clinical experts.
Considerations for initiation of therapy	
In the trial, mutation status of HRR genes was determined prospectively using solid tumour tissue or circulating tumour DNA-based next-generation sequencing assays. Patients were required to have a mutation in at least 1 of 12 genes involved directly or indirectly in the HRR pathway (*ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2,* or *RAD51C*). Not all jurisdictions have access to testing for all HRR pathway genes.	This is a comment from the drug plans to inform pERC deliberations.
Should consider alignment with other PARPIs or androgen receptor pathway inhibitors where possible.	This is a comment from the drug plans to inform pERC deliberations.
Considerations for discontinuation of therapy	
In the trial, study treatment could continue after radiographic PFS if the investigator determined benefit was still being derived. What parameters should be used to determine when a patient should discontinue treatment?	The clinical experts indicated that in clinical practice, a combination of radiographic, biochemical, and clinical parameters (e.g., progressing radiological disease, worsening symptoms), as well as tolerability are used to determine whether a patient should discontinue treatment. pERC acknowledged input from the clinical experts and noted that reimbursement of talazoparib-enzalutamide should continue until disease progression or unacceptable toxicity.
Should consider alignment with other PARPIs or androgen receptor pathway inhibitors either monotherapy or in combination therapy as several have been evaluated previously by CDA-AMC.	This is a comment from the drug plans to inform pERC deliberations.

Drug program implementation questions	Clinical expert response
Considerations for prescribing of therapy	
Should patients continue with talazoparib monotherapy if enzalutamide requires discontinuation for reasons other than progression? Are there relevant dosing considerations (i.e., dose escalations)?	pERC agreed with the clinical experts that it would be reasonable for patients to continue with talazoparib monotherapy if enzalutamide requires discontinuation for reasons other than disease progression. The experts noted that they would not consider dose escalation, but dose reduction if patients experience toxicities. pERC agreed with the clinical experts.
Generalizability	
Patients with an ECOG PS score > 1 were not eligible for the trial. Should the eligibility criteria be expanded to an ECOG PS score > 1?	The clinical experts indicated that patients with good performance status should be eligible for talazoparib-enzalutamide, if they are able to tolerate the therapy as determined by the treating physician. pERC agreed with the clinical experts.
Should patients currently receiving monotherapy with enzalutamide (or abiraterone) be able to switch to talazoparib-enzalutamide? And if yes, what are the parameters for this?	The clinical experts indicated that there is no data on the impact of switching patients currently receiving monotherapy with enzalutamide (or abiraterone) to talazoparib-enzalutamide; however, they considered the switch to be reasonable within 3 to 6 months of starting enzalutamide or abiraterone without disease progression. pERC agreed that patients with mCRPC treated with either enzalutamide or abiraterone for a maximum of 4 months may be eligible for treatment with talazoparib-enzalutamide, to align with the recommendations for niraparib-abiraterone acetate plus prednisone and olaparib plus abiraterone acetate plus prednisone.
Funding algorithm	
An update to the algorithm to incorporate the recommendation is needed, if the recommendation is positive.	This is a comment from the drug plans to inform pERC deliberations.
Under what clinical circumstances would talazoparib-enzalutamide be preferred over olaparib-abiraterone or niraparib-abiraterone?	The clinical experts noted that there is no clear approach since there is no head-to-head comparative evidence in favour of 1 treatment over another. The clinical experts also noted that talazoparib-enzalutamide could be considered in patients with HRR gene alterations beyond *BRCA*, as it is currently the only combination treatment with an indication covering a broader range of HRR mutations. pERC agreed with the clinical experts and noted that talazoparib and enzalutamide also avoids the need for continuous corticosteroid exposure which is required for niraparib-abiraterone acetate plus prednisone and olaparib plus abiraterone acetate plus prednisone.
Care provision issues	
There is a statement in the product monograph, that talazoparib is maintained in the original bottle to protect from light. Is this applicable only in the pharmacy or does this include when dispensed to the patient? Would the usual light-blocking medication vials be appropriate to use? Otherwise, there will need to be consideration regarding drug wastage, depending on how the drug is packaged (i.e., how many capsules are in the original container).	This is a comment from the drug plans to inform pERC deliberations. The sponsor noted that the label restriction supported by the stability of talazoparib capsules applies for packaged supplies up to and including dispensing the medication to patients. This also applies to the period after the medication is dispensed to the patient. Therefore, talazoparib is to be maintained

Drug program implementation questions	Clinical expert response
Talazoparib is noted in the product monograph to be available in several strengths – 0.1 mg, 0.25 mg, 0.35 mg, 0.5 mg, and 1 mg. The starting dose for mCRPC is 0.5 mg daily with or without food.	in the original bottle by the patient to protect from light. Repackaging of talazoparib capsules under pharmacy settings per repackaging guidelines with standard pharmacy-grade light-resistant vials is not recommended unless stability in these vials can be demonstrated. The CDA-AMC review team noted that the sponsor did not consider drug wastage in the economic analysis, as such its impact on the results is unknown. In Canada, only the 0.1 mg and 0.25 mg capsules of talazoparib will be made available by the sponsor.
The TALAPRO-2 trial shows a higher rate of adverse effects, particularly anemia and neutropenia, and this may result in dose modification.	This is a comment from the drug plans to inform pERC deliberations.
System and economic issues	
Enzalutamide, olaparib, and niraparib and abiraterone have confidential prices. Abiraterone acetate is generic.	This is a comment from the drug plans to inform pERC deliberations.

CDA-AMC = Canada's Drug Agency; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HRR = homologous recombination repair; mCRPC = metastatic castration-resistant prostate cancer; PARPI = poly(ADP-ribose) polymerase inhibitor; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PFS = progression-free survival.

Testing Procedure Considerations

According to the clinical experts consulted by CDA-AMC, public funding status and clinical practices for somatic or germline HRR mutations testing in patients with mCRPC are not consistent across Canada. Next-generation sequencing panels for mutations in *BRCA1*, *BRCA2*, and *ATM* are generally available in jurisdictions. However, there are several other genes that are involved in the HRR pathway, the testing for which are not available or accessible to all patients. Therefore, a small proportion of patients who have mutations in genes other than *BRCA1, BRCA2, or ATM* may not be identified for eligibility for talazoparib depending on what testing panels are available in their region. There are existing implementation concerns related to testing within health systems, patients, and costs; however, minimal additional impact is anticipated if talazoparib were to be reimbursed.

Clinical Evidence

Systematic Review

Description of Studies

The TALAPRO-2 trial (cohort 2, N = 399) met the inclusion criteria for the systematic review conducted by the sponsor. An objective of the trial was to assess the efficacy and safety of talazoparib 0.5 mg plus enzalutamide 160 mg, taken orally once daily or matched placebo-enzalutamide in adult patients with HRR-deficient mCRPC. The trial enrolled adults with asymptomatic or mildly symptomatic mCRPC who

had not started systemic cancer treatment after the diagnosis of CRPC (metastatic or nonmetastatic), with the exception of androgen deprivation therapy and first-generation antiandrogen drugs. Patients were allowed to have previously received abiraterone or docetaxel for castration-sensitive prostate cancer (CSPC) but were ineligible to participate if they had received any prior treatment with second-generation androgen receptor inhibitors (enzalutamide, apalutamide, and darolutamide), a PARPI, cyclophosphamide, or mitoxantrone for prostate cancer. Patients were required to have had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1, and progressive disease at study entry. The approved Health Canada indication and reimbursement request aligned with the trial's population who were HRR-deficient. The outcomes relevant to this review included the primary outcome of rPFS, key secondary outcome of OS, and HRQoL outcomes of time to deterioration of pain symptoms measured via the Brief Pain Inventory – Short Form (BPI-SF) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer (EORTC QLQ-PR25) functional and symptom scales, and safety. The rPFS data were based on the primary analysis data cut-off date of October 3, 2022, and supportive data from the data cut-off date of September 3, 2024. All other outcomes were based on the data cut-off date of September 3, 2024. Overall, key baseline characteristics were generally balanced between treatment groups. The trial population was predominately white (68%), with a median age of 70 years. Most patients had an ECOG PS score of 0 (approximately 62%), indicating good overall performance, normal or mild renal impairment (approximately 90%), and bone and soft tissue disease site metastasis (approximately 84%), a Gleason score of 8 or more (approximately 74%), and had [redacted]. In both groups, the most common detected HRR gene alteration was *BRCA2* (33.8%), followed by *ATM* (21.6%), *CDK12* (18.8%), and *CHEK2* (17.8%). The talazoparib-enzalutamide group had a [redacted]. These imbalances were likely due to chance, as [redacted].

Efficacy Results

Only those efficacy outcomes and analyses of subgroups identified as important to this review are reported. The main findings for the efficacy outcomes for the TALAPRO-2 trial are from the data cut-off dates of October 3, 2022, and September 3, 2024. The boundary for statistical significance for the primary outcome of rPFS was met at the data cut-off date of October 3, 2022; therefore, rPFS data were reported descriptively at the September 3, 2024, data cut-off (i.e., not controlled for type I error). All other outcomes are based on the data cut-off date of September 3, 2024.

Radiographic Progression-Free Survival by Blinded Independent Central Review

In total, 170 events had occurred in both groups by the data cut-off date of October 3, 2022. The median duration of follow-up for rPFS was 17.5 months (range not reported) for the talazoparib-enzalutamide group and 16.8 months (range not reported) for the placebo-enzalutamide group. The median rPFS was not reached (95% CI, 21.9 months to not reached) in the talazoparib-enzalutamide group and 13.8 months

(95% CI, 11.0 months to 16.7 months) for the placebo-enzalutamide group (log-rank test P < 0.0001), with a between-group HR of 0.45 (95% CI, 0.33 to 0.61) in favour of talazoparib-enzalutamide. The KM-estimated probability of rPFS at 12 months was [redacted] in the talazoparib-enzalutamide and placebo-enzalutamide groups, respectively, [redacted]. The results of sensitivity analyses were consistent with the primary analysis. At the second data cut-off date of September 3, 2024, rPFS descriptive results were consistent with the first data cut-off date. The KM-estimated probability of rPFS at 48 months was [redacted] in the talazoparib-enzalutamide and placebo-enzalutamide groups, respectively, [redacted]. The rPFS results were consistent across the subgroup analyses of interest by *BRCA* alteration status (with or without) and prior treatment with novel hormonal therapy (NHT) or taxane therapy in favour of talazoparib-enzalutamide.

Overall Survival

In total, 219 events had occurred in both groups by the data cut-off date of September 3, 2024. The median follow-up for OS was 44.2 months for the talazoparib-enzalutamide group and [redacted] for the placebo-enzalutamide group. The median OS was 45.1 months (95% CI, 35.4 months to not reached) for the talazoparib-enzalutamide group and 31.1 months (95% CI, 27.3 months to 35.4 months) in the placebo-enzalutamide group (log-rank test P < 0.0001), with a between-group HR of 0.62 (95% CI, 0.48 to 0.81) in favour of talazoparib-enzalutamide. The results of sensitivity analyses were consistent with the primary analysis. The KM-estimated probability of OS at 12 months was [redacted]; and OS at 48 months was [redacted] in the talazoparib-enzalutamide and placebo-enzalutamide groups, respectively.

Time to Deterioration of Pain by BPI-SF

At the data cut-off date of September 3, 2024, 58 events had occurred in both groups, and the median time to deterioration of pain was not reached in either group. The stratified between-group HR was 0.55 (95% CI, 0.33 to 0.94) in favour of talazoparib-enzalutamide. The KM-estimated probability of being free of pain progression at 12 months was [redacted], and at 48 months it was [redacted]) in the talazoparib-enzalutamide and placebo-enzalutamide groups, respectively.

HRQoL by EORTC QLQ-PR25

At the data cut-off date of September 3, 2024, [redacted] patients in the talazoparib-enzalutamide group and [redacted] patients in the placebo-enzalutamide group contributed to almost all of the EORTC QLQ-PR25 functional and symptom scale score analyses up to week 109; the incontinence aid

symptoms score was informed by [redacted] patients, respectively. No comparison was made for the sexual functioning score due to limited data. The sexual activity score and the symptom scale scores were generally maintained and similar in both treatment groups up to week 109. Improvements in urinary and bowel symptoms favoured the talazoparib-enzalutamide group, with urinary symptoms reaching the minimal important difference (MID) threshold of 5 points or more. All other scale scores did not reach the clinically important MID threshold.

Harms Results

Harms data reported in this section were from the data cut-off date of September 3, 2024. Almost all patients in both treatment groups reported at least 1 TEAE (99.5% with talazoparib-enzalutamide and 97.5% with placebo-enzalutamide). The most frequently reported TEAEs in the talazoparib-enzalutamide group were anemia (66.7% versus 18.6% with placebo-enzalutamide), fatigue (34.8% versus 28.1% with placebo-enzalutamide), and decreased neutrophil count (34.8% versus 7.0% with placebo-enzalutamide); a higher proportion of patients in the talazoparib-enzalutamide group reported these TEAEs than the placebo-enzalutamide group. The most frequently reported TEAEs in the placebo-enzalutamide group were fatigue (28.1% versus 34.8% with talazoparib-enzalutamide), arthralgia (24.6% versus 16.7% with talazoparib-enzalutamide), and back pain (23.1% versus 24.2% with talazoparib-enzalutamide). A higher proportion of patients in the talazoparib-enzalutamide group experienced at least 1 grade 3 or 4 TEAE [redacted] versus the placebo-enzalutamide group [redacted] The incidence of serious TEAES were higher in the talazoparib-enzalutamide group [redacted] versus the placebo-enzalutamide group [redacted] In both groups, [redacted] were the most frequently reported serious TEAEs. A higher proportion of TEAEs that led to study treatment discontinuation were reported in the talazoparib-enzalutamide group ([redacted] versus placebo-enzalutamide group [redacted]), with anemia being the most common reason [redacted]. Enzalutamide-only treatment discontinuation was reported for [redacted] of patients in the talazoparib-enzalutamide group versus [redacted] in the placebo-enzalutamide group. A lower proportion of deaths were reported in the talazoparib-enzalutamide group (46.5%) versus the placebo-enzalutamide group (63.3%), with [redacted] being the primary reason for death in both groups [redacted] The incidence of notable harms in both treatment groups was comparable and infrequent. Second primary malignancies (other than hematologic) occurred in [redacted] of patients, and embolic and thrombotic events occurred in 5.6% and 1.0% of patients in the talazoparib-enzalutamide and placebo-enzalutamide groups, respectively. There was 1 case of pneumonitis in each group.

Critical Appraisal

TALAPRO-2 was a randomized, double-blind, phase III trial. The patients and investigators were blinded to talazoparib or placebo, but enzalutamide was open-label. This design was appropriate since different dosing and oral tablets across the 2 treatment groups may have made blinding to enzalutamide impractical. Randomization procedures, including stratification by and prior NHT or taxane therapy for CSPC and HRR gene alteration status (deficient versus nondeficient or unknown), were appropriate and conducted by interactive response technology. The talazoparib-enzalutamide group had a [redacted]

[redacted]. These imbalances were likely due to chance, as [redacted] and based on clinical expert feedback, unlikely to have confounded the effect between treatment and outcomes. Sample size and power calculations were based on the primary outcome of rPFS, and the trial was powered to detect significant differences for rPFS, but it was underpowered for the secondary outcome of OS. The analyses were preplanned with adequately justified stopping boundaries and the prespecified analyses of rPFS and OS were appropriately controlled for multiple comparisons. All other analyses were descriptive (i.e., not controlled for type I error). To minimize the risk of bias in the measurement of rPFS, the trial performed tumour assessments using Response Evaluation Criteria in Solid Tumours Version 1.1 criteria and radiographic scans were assessed by BICR. In addition, the findings of the sensitivity analyses for rPFS were consistent with the primary analysis. Patients were permitted to receive posttreatment anticancer medications after study treatment had been discontinued (36.9% in the talazoparib-enzalutamide group versus 56.8% in the placebo-enzalutamide group), which may influence the assessment of OS. Since no sensitivity analyses were performed to test treatment policy strategy for OS (e.g., exclude the effect of subsequent therapies), the estimated effect would be a combination of treatment with talazoparib-enzalutamide versus placebo-enzalutamide, plus subsequent treatments. Therefore, survival results might be partially attributable to treatments administered after disease progression rather than the study treatment itself, although without the necessary analysis the direction and magnitude of bias is unclear. However, this is a relevant comparison as it is reflective of how the intervention and comparator and subsequent therapies would be used in practice in Canada. Based on the Clinical Study Report and statistical analysis plan, the proportional hazards assumption was not assessed or discussed. Despite the absence of these results, visual inspection of the KM curves for rPFS and OS appear to indicate a clear separation (at approximately 3 and 8 months, respectively), after which, they appeared to be sustained proportionality throughout study treatment. HRQoL was assessed by the BPI-SF and EORTC QLQ-PR25 questionnaires, which have been validated in patients with metastatic prostate cancer with evidence of reliability, responsiveness, and MID. The result of these outcomes was subject to potential bias due to [redacted], which could have biased the results in favour of talazoparib-enzalutamide. For the EORTC QLQ-PR25, no models other than mixed models for repeated measures were tested applying alternative imputation methods or sensitivity analyses to assess the impact of missing data.

In general, the population requested for the reimbursement aligns with the approved Health Canada indication, and the dosing and administration of talazoparib-enzalutamide was consistent with the approved product monograph. However, the trial provided talazoparib-enzalutamide as first-line treatment only (i.e., patients had had not received prior systemic therapy for mCRPC) while the approved Health Canada indication is line-agnostic (i.e., first-line or later-line therapy). Therefore, there is no direct comparative evidence for the use of talazoparib-enzalutamide in later-line settings. The clinical experts consulted by CDA-AMC noted that many medical oncologists currently favour prescribing chemotherapy for the first-line treatment of mCRPC in patients who have previously progressed on an ARPI in the mCSPC and nmCRPC settings. Therefore, the clinical experts indicated that most clinicians would likely prescribe talazoparib-

enzalutamide as second line and beyond treatment due to the decreasing number of patients who are naive to ARPI in the first-line mCRPC setting. According to the clinical experts, the eligibility criteria and baseline characteristics of the TALAPRO-2 trial are generalizable to adult patients with mCRPC in Canada, except that the trial did not include patients with an ECOG PS score of greater than 1. The clinical experts indicated that patients with good ECOG PS scores or a score of 0 to 2 should be eligible for talazoparib-enzalutamide, if they are able to tolerate the therapy. The experts noted that although enzalutamide was an appropriate comparator when the TALAPRO-2 trial was designed and executed, the current treatment paradigm has shifted since then toward the use of chemotherapy as the most common first-line treatment for patients with mCRPC. The evidence submitted to CDA-AMC did not include head-to-head comparisons between talazoparib-enzalutamide and chemotherapy, which represents a gap in the available direct evidence given the potential shared place in therapy when used as first-line treatments for mCRPC.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform the expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for rPFS and OS were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review. A threshold could not be determined for time to deterioration of pain by BPI-SF; therefore, the target of certainty appraisal was any effect. The reference point for the certainty of the evidence assessment for EORTC QLQ-PR25 functional and symptom scale scores were set according to the presence or absence of an important effect based on a threshold informed by the literature.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- survival outcomes (rPFS, OS)
- HRQoL outcomes (time to deterioration of pain by BPI-SF, EORTC QLQ-PR25 functional and symptom scale scores).

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for talazoparib-enzalutamide versus placebo-enzalutamide.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

One sponsor-submitted MAIC was submitted to inform the pharmacoeconomic model, and fill gaps in the comparative evidence for other treatments of interest for adults with HRR gene-mutated mCRPC.

Description of Studies

A systematic literature review identified 49 unique RCTs, of which 42 had published results that met the inclusion criteria for first-line treatments in adults with mCRPC. Three trials (TALAPRO-2, PROpel, and MAGNITUDE) reported on survival data for patients who were HRR-deficient and receiving relevant first-line treatment for mCRPC, and were included in a feasibility assessment. The TALAPRO-2 trial compared talazoparib-enzalutamide to enzalutamide, the PROpel trial compared olaparib plus abiraterone acetate plus prednisone to abiraterone acetate plus prednisone, and the MAGNITUDE trial compared niraparib-abiraterone acetate plus prednisone to abiraterone acetate plus prednisone. The feasibility assessment explored potential sources of heterogeneity that included study design, patient eligibility criteria, baseline patient characteristics, outcome characteristics, and efficacy or safety results. The results of the assessment identified some heterogeneity across the trials, but the sponsor assessed them as sufficiently similar to conduct MAICs between the TALAPRO-2, PROpel, and MAGNITUDE trials. There was no common treatment comparator between the TALAPRO-2 trial and comparator trials; therefore, unanchored MAICs were conducted using individual patient data from the TALAPRO-2 trial and summary level data from the comparator trials. Key treatment effect modifiers and prognostic factors for adjustment were identified and ranked in order of importance based on published analyses on prognostic strength in mCRPC and refined based on external clinical input from a practising clinician experienced in treating mCRPC. Individual patient data from the TALAPRO-2 trial population who were HRR-deficient were adjusted to match the marginal distribution (e.g., mean and variance) of clinical factors of patients for each comparison between the PROpel trial (olaparib plus abiraterone acetate plus prednisone versus abiraterone acetate plus prednisone) and the MAGNITUDE trial (niraparib-abiraterone acetate plus prednisone versus abiraterone acetate plus prednisone). Point estimates for rPFS and OS were reported as HRs with 95% CIs.

Table 3: Summary of Findings for Talazoparib-Enzalutamide Vs. Placebo-Enzalutamide for Patients With HRR Gene-Mutated mCRPC

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo-enzalutamide	Talazoparib-enzalutamide	Difference		
rPFS – ITT population							
Probability of rPFS at 12 months **Median follow-up: 17.5 months for talazoparib-enzalutamide and 16.8 months for placebo-enzalutamide; data cut-off date of October 3, 2022**	399 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Moderate[a]	Talazoparib-enzalutamide likely results in a clinically important higher probability of rPFS at 12 months when compared with placebo-enzalutamide.
Probability of rPFS at 48 months **Median follow-up: 38.0 months for talazoparib-enzalutamide and 30.8 months for placebo-enzalutamide; data cut-off date of September 3, 2024**	399 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Moderate[b]	Talazoparib-enzalutamide likely results in a clinically important higher probability of rPFS at 48 months when compared with placebo-enzalutamide.
OS – ITT population, data cut-off date of September 3, 2024							
Probability of survival at 12 months **Median follow-up: 44.2 months for talazoparib-enzalutamide and [redacted] for placebo-enzalutamide**	399 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	High[c]	Talazoparib-enzalutamide results in little to no clinically important difference in the probability of survival at 12 months when compared with placebo-enzalutamide.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo-enzalutamide	Talazoparib-enzalutamide	Difference		
Probability of survival at 48 months **Median follow-up: 44.2 months for talazoparib-enzalutamide and [redacted] for placebo-enzalutamide**	399 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	High[d]	Talazoparib-enzalutamide results in a clinically important higher probability of survival at 48 months when compared with placebo-enzalutamide.
Time to deterioration of pain by BPI-SF – ITT subset population, data cut-off date of September 3, 2024							
Probability of being free of pain progression at 12 months **Median follow-up: NR**	394 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Low[e]	Talazoparib-enzalutamide may result in a higher probability of being free of pain progression at 12 months when compared with placebo-enzalutamide. The clinical importance of the increase is uncertain.
Probability of being free of pain progression at 48 months **Median follow-up: NR**	394 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Low[f]	Talazoparib-enzalutamide may result in a higher probability of being free of pain progression at 48 months when compared with placebo-enzalutamide. The clinical importance of the increase is uncertain.
EORTC QLQ-PR25 functional scale – ITT subset population, data cut-off date of September 3, 2024							
Mean change from baseline in sexual activity score; scores range from 0 to 100, with higher scores indicating better function	[redacted] (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Low[g]	Talazoparib-enzalutamide may result in little to no clinically important difference in sexual activity up to 109 weeks when compared with placebo-enzalutamide.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo-enzalutamide	Talazoparib-enzalutamide	Difference		
Time point: up to 109 weeks							
Mean change from baseline in EORTC QLQ-PR25 sexual functioning score; scores range from 0 to 100, with higher scores indicating better function **Time point: up to 109 weeks**	[redacted] (1 RCT)	NA	[redacted]	[redacted]	[redacted]	NE	NE
EORTC QLQ-PR25 symptom scale – ITT subset population, data cut-off date of September 3, 2024							
Mean change from baseline in urinary symptoms score; scores range from 0 to 100, with higher scores indicating worsened symptoms **Time point: up to 109 weeks**	[redacted] (1 RCT)	NA	[redacted]	[redacted]	−5.0 (−7.6 to −2.4)	Very low[h]	The evidence is very uncertain about the effect of talazoparib-enzalutamide on urinary symptoms up to 109 weeks when compared with placebo-enzalutamide.
Mean change from baseline in bowel symptoms score; scores range from 0 to 100, with higher scores indicating worsened symptoms **Time point: up to 109 weeks**	[redacted] (1 RCT)	NA	[redacted]	[redacted]	−1.8 (−3.3 to −0.4)	Low[g]	Talazoparib-enzalutamide may result in little to no clinically important difference in bowel symptoms up to 109 weeks when compared with placebo-enzalutamide.
Mean change from baseline in hormonal treatment-related symptoms score; scores range from 0 to 100, with	[redacted] (1 RCT)	NA	[redacted]	[redacted]	−0.8 (−2.5 to 1.0)	Low[g]	Talazoparib-enzalutamide may result in little to no clinically important difference in hormonal treatment-related

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo-enzalutamide	Talazoparib-enzalutamide	Difference		
higher scores indicating worsened symptoms **Time point: up to 109 weeks**							symptoms up to 109 weeks when compared with placebo-enzalutamide.
Mean change from baseline in incontinence aid symptoms score; scores range from 0 to 100, with higher scores indicating worsened symptoms **Time point: up to 109 weeks**	[redacted] (1 RCT)	NA	[redacted]	[redacted]	0.2 (−4.8 to 5.3)	Very low[i]	The evidence is very uncertain about the effect of talazoparib-enzalutamide on incontinence aid symptoms up to 109 weeks when compared with placebo-enzalutamide.

BPI-SF = Brief Pain Inventory – Short Form; CI = confidence interval; EORTC QLQ-PR25 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer; HRR = homologous recombination repair; ITT = intention to treat; mCRPC = metastatic castration-resistant prostate cancer; MID = minimal important difference; NA = not applicable; NE = not estimable; NR = not reported; OS = overall survival; RCT = randomized controlled trial; rPFS = radiographic progression-free survival; vs. = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]Rated down 1 level for serious imprecision due to the 95% CI for the between-group difference including the possibility of both important benefit and trivial effect; a between-group absolute risk difference of 20% (200 fewer or more events per 1,000 patients) at 12 months was clinically significant according to the clinical experts.

[b]Rated down 1 level for serious risk of bias due to few patients at risk at 48 months. A between-group absolute risk difference of 5% (50 fewer or more events per 1,000 patients) at 48 months was clinically significant according to the clinical experts. The point estimate and entire CI exceeded the threshold.

[c]A between-group absolute risk difference of 10% (100 fewer or more events per 1,000 patients) at 12 months was clinically significant according to the clinical experts. There is no imprecision in the estimate (the point estimate and entire 95% CI for the between-group difference shows little to no difference).

[d]A between-group absolute risk difference of 5% (50 fewer or more events per 1,000 patients) at 48 months was clinically significant according to the clinical experts. The point estimate and entire CI exceeded the threshold.

[e]Rated down 2 levels for very serious imprecision due to the 95% CI for the between-group absolute risk difference including the possibility of benefit and harm. No known MID so target of certainty appraisal was any effect.

[f]Rated down 2 levels for very serious risk of bias due to missing outcome data. No known MID so target of certainty appraisal was any effect. The point estimate and entire CI exceeded the null.

[g]Rated down 2 levels for very serious risk of bias due to missing outcome data. There is no imprecision in the estimate (the point estimate and entire 95% CI for the between-group difference shows little to no difference); based on literature, a 5-point change from baseline score was considered clinically important.

[h]Rated down 1 level for serious imprecision due to the 95% CI for the between-group difference including the possibility of both important benefit and little to no difference; based on literature, a 5-point change from baseline score was considered clinically important. Rated down 2 levels for very serious risk of bias due to missing outcome data.

[i]Rated down 1 level for serious imprecision due to the 95% CI for the between-group difference including the possibility of both important harm and little to no difference; based on literature, a 5-point change from baseline score was considered clinically important. Rated down 2 levels for very serious risk of bias due to missing outcome data.

Source: The TALAPRO-2 trial HRR-deficient Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence and additional information provided in the submission.

Efficacy Results

The rPFS HR point estimates and 95% CIs [redacted]. The rPFS and OS primary analyses for the PROpel trial and MAGNITUDE trial MAICs adjusted for 5 and 8 treatment effect modifiers and prognostic factors, respectively. However, not all factors could be matched or adjusted; therefore, imbalances remained.

Harms Results

The MAIC did not include harms, and therefore no conclusions could be drawn on the relative safety of talazoparib-enzalutamide versus relevant comparators.

Critical Appraisal

The methods used to conduct the systematic literature review for the MAIC was a priori registered, and used appropriate criteria to search databases, select studies, extract data, and assess risk of bias of the included studies. The MAIC did not include comparisons between talazoparib-enzalutamide and chemotherapy, which represents a gap in the available indirect evidence given the shared place in therapy for mCRPC. The MAIC included relevant outcomes identified by the CDA-AMC team (rPFS and OS); however, clinical and patient relevant outcomes such as pain, HRQoL, and harms were not included in the comparisons. To account for between-study differences in patient baseline characteristics, several potentially relevant treatment effect modifiers and prognostic factors (i.e., clinical factors) were matched in the weighting process for each comparison between the TALAPRO-2 trial and comparator trials. The methods used to identify and rank the clinical factors were considered appropriate. For both the PROpel and MAGNITUDE trials, adjustments were limited by how, and if, these variables were reported in both trials, and the highest ranking factor could not be included in the adjustment for either study. The TALAPRO-2 trial stratified by prior NHT or taxane therapy per interactive web response system (IWRS) as a single variable whereas the PROpel and MAGNITUDE trials reported these variables separately. The PROpel trial used the IWRS value, whereas the MAGNITUDE trial did not specify IWRS or electronic data capture (EDC). Since IWRS values were combined in the TALAPRO-2 trial but EDC values were presented separately, EDC values were used to align with reporting of comparator trials. Further, the TALAPRO-2 trial stratified by prior therapy in the CSPC stage. The PROpel trial reported the proportion of patients who received NHT and taxane-based therapy but did not specify the disease stage. The MAGNITUDE trial reported the proportion of patients who received NHT and taxane-based therapy in the mCSPC or nmCRPC stage into a single variable. There were important differences in the eligibility criteria between the MAGNITUDE and TALAPRO-2 trials. The MAGNITUDE trial allowed the use of abiraterone acetate plus prednisone in the mCRPC setting for 4 months or less whereas all patients were treatment-naive in the mCRPC setting within the TALAPRO-2 trial. Since only summary level data were available for the MAGNITUDE trial, patients who were not truly treatment-naive could not be removed when

performing analyses. It is possible that these patients had different disease characteristics compared to the rest of the trial population. Overall, the magnitude and direction of potential bias due to imbalances of the rPFS and OS estimates cannot be predicted. Since the unanchored nature of the MAIC requires a stronger assumption (than an anchored MAIC) that all effect modifiers and prognostic factors have been included in the analysis, which was not possible, the effects of talazoparib-enzalutamide on rPFS and OS compared with relevant comparators are uncertain and definitive conclusions based on these results are not recommended.

Studies Addressing Gaps in the Evidence From the Systematic Review

No additional studies were submitted by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

- Talazoparib is available as 0.1 mg and 0.25 mg capsules. At the submitted price of $99.35 per capsule, the 28-day cost of talazoparib is expected to be $5,564 per patient, based on the Health Canada–recommended dosage. When used in combination with enzalutamide, the 28-day cost is expected to be $8,833 per patient. Clinical efficacy in the economic analysis for talazoparib-enzalutamide and enzalutamide was derived from the TALAPRO-2 trial. Evidence submitted by the sponsor indicates that talazoparib-enzalutamide is likely to improve rPFS and OS compared with enzalutamide among patients with HRR gene-mutated mCRPC. Clinical efficacy for all other comparators was informed by a sponsor-submitted MAIC. As not all effect modifiers and prognostic factors could be matched or adjusted for, the results of the MAIC are uncertain and conclusions could not be drawn on the relative efficacy of talazoparib-enzalutamide with comparators included in the MAIC (olaparib plus abiraterone acetate plus prednisone, niraparib-abiraterone acetate plus prednisone, and abiraterone acetate plus prednisone).
- The results of the CDA-AMC base case suggest:
  - Talazoparib-enzalutamide will be associated with higher costs to the health care system than enzalutamide (incremental costs = $183,217), primarily driven by increased costs associated with drug acquisition.
  - Talazoparib-enzalutamide may be associated with a gain of 0.87 life-years compared to enzalutamide. When the impact on HRQoL is also considered, talazoparib-enzalutamide may result in a gain of 0.76 QALYs compared to enzalutamide.
  - The ICER of talazoparib-enzalutamide compared to enzalutamide was $242,571 per QALY gained in the CDA-AMC base case. Approximately 49% of the incremental benefit versus talazoparib-enzalutamide was gained in the extrapolated period (median OS follow-up: 44.2 months, maximum follow-up: not reported). CDA-AMC was unable to adequately explore uncertainty due to limitations with the available evidence (the absence of data to support

sustained treatment effect and use of beyond first-line treatment), and issues with the model structure.

- Due to significant uncertainty associated with the sponsor's submitted MAIC, comparative effectiveness between talazoparib-enzalutamide and olaparib plus abiraterone acetate plus prednisone, niraparib-abiraterone acetate plus prednisone, and abiraterone acetate plus prednisone, is too uncertain to determine. Therefore, there is no robust evidence to support a price premium for talazoparib-enzalutamide in relation to other PARPI plus ARPI combinations (i.e., olaparib plus abiraterone acetate plus prednisone and niraparib-abiraterone acetate plus prednisone plus prednisone).
- Clinical expert input sought for this review noted that chemotherapy (e.g., docetaxel) and radium-223 may also be considered relevant comparators for talazoparib-enzalutamide in the indicated population. Neither of these treatments were included in the analysis.
- CDA-AMC estimates that the budget impact of reimbursing talazoparib-enzalutamide for the indicated population will be approximately $21.8 million over the first 3 years of reimbursement compared to the amount currently spent on enzalutamide, abiraterone acetate plus prednisone, olaparib plus abiraterone acetate plus prednisone, and niraparib-abiraterone acetate plus prednisone, with an estimated expenditure of $23.4 million on talazoparib over this period (talazoparib-enzalutamide = $37.2 million). The actual budget impact of reimbursing talazoparib-enzalutamide will depend on the distribution of market shares for patients with HRR gene-mutated mCRPC, the proportion of patients with HRR-BRCA mutations, and the uptake of talazoparib-enzalutamide.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Kelvin Chan (Vice-Chair), Dr. Philip Blanchette, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villneuve, and Danica Wasney

Meeting date: September 10, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.