Canadian Journal of Health Technologies
February 2024 Volume 4 Issue 2

CADTH Reimbursement Recommendation

Niraparib and Abiraterone Acetate (Akeega)

Indication: With prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCA mutated (germline and/or somatic) mCRPC, who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated

Sponsor: Janssen Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Akeega?

CADTH recommends that Akeega be reimbursed by public drug plans for the first-line treatment of metastatic castration-resistant prostate cancer (mCRPC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Akeega should only be covered to treat patients with mCRPC who have *BRCA* mutations, have not been treated with an androgen receptor pathway inhibitor (ARPi) for earlier stages of prostate cancer, and have not received treatments that affect the entire body for mCRPC (except for treatments of less than 4 months with abiraterone acetate and prednisone) or a poly-(ADP-ribose) polymerase inhibitor (PARPi) for mCRPC. Moreover, patients should be in relatively good health.

What Are the Conditions for Reimbursement?

Akeega should only be reimbursed if it is prescribed by a clinician with expertise in treating prostate cancer with systemic anticancer therapy and if the cost of Akeega is reduced. Akeega should not be reimbursed when used in combination with other anticancer drugs.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Akeega delays disease progression (as indicated by medical imaging) or death in patients with mCRPC compared with placebo and abiraterone acetate with prednisone.
- Akeega meets patients' need to delay disease progression or death, and may delay the worsening of disease symptoms and progression of pain.
- Based on CADTH's assessment of the health economic evidence, Akeega 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, Akeega is estimated to cost the public drug plans approximately $9 million over the next 3 years. However, the actual budget impact is uncertain due to potential differences in the definition of chemotherapy ineligibility across stakeholders.

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. It is

Summary

estimated that 24,600 people will be diagnosed with prostate cancer in 2022, 9% of whom will have metastatic disease. Approximately 10% of all patients with mCRPC have *BRCA* 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 Akeega Cost?

Treatment with Akeega is expected to cost approximately $8,283 per 28 days.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that niraparib and abiraterone acetate with prednisone or prednisolone be reimbursed for the first-line treatment of adults with deleterious or suspected deleterious *BRCA*-mutated (germline and/or somatic) mCRPC who are asymptomatic or mildly symptomatic, and in whom chemotherapy is not clinically indicated only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One multicentre, randomized, double-blind, phase III trial (MAGNITUDE) demonstrated that treatment with niraparib and abiraterone acetate with prednisone resulted in added clinical benefit in radiographic progression-free survival (rPFS) compared with placebo and abiraterone acetate with prednisone in adults with mCRPC with *BRCA1* or *BRCA2* gene alterations who have not received prior systemic therapy in the mCRPC setting. The hazard ratio (HR) for rPFS was 0.55 (95% confidence interval [CI], 0.39 to 0.78) favouring niraparib and abiraterone acetate. The rPFS rate at 12 months was [redacted] (95% CI, [redacted] to [redacted]) in the niraparib and abiraterone acetate group versus [redacted] to [redacted] in the placebo and abiraterone acetate group. The rPFS rate at 24 months was [redacted] (95% CI, [redacted] to [redacted]) in the niraparib and abiraterone acetate group compared to [redacted] (95% CI, [redacted] to [redacted]) in the placebo and abiraterone acetate group.

Patients identified the need for treatments that can extend life, maintain their quality of life, delay disease progression, delay their onset of symptoms, and reduce side effects. As previously described, pERC concluded that niraparib and abiraterone acetate meets the need to delay disease progression. pERC also considered that niraparib and abiraterone acetate with prednisone may result in a clinical benefit in time to symptomatic progression (TSP) and time to pain progression (TPP) compared to placebo and abiraterone acetate, although these results are associated with low certainty due to concerns for imprecision and limitations in the trial such as imbalanced baseline characteristics between treatment groups.

Using the sponsor-submitted price for niraparib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for niraparib and abiraterone acetate with prednisone was $271,803 per quality-adjusted life-year (QALY) gained compared with abiraterone acetate. At this incremental cost-effectiveness ratio, niraparib and abiraterone acetate with prednisone is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for the indicated population. A price reduction is required for niraparib and abiraterone acetate with prednisone to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adults (18 years or older) with all of the following:	Evidence from the MAGNITUDE trial demonstrated a clinical benefit in adults with mCRPC with *BRCA1 or BRCA2*	Patients must have confirmation of *BRCA* mutation before treatment is initiated.

Reimbursement condition	Reason	Implementation guidance
1.1. mCRPC 1.2. positive for a germline and/or somatic *BRCA1* or *BRCA2* gene alteration 1.3. have not received prior treatment with an ARPi for mCSPC or nmCRPC 1.4. have not received prior systemic therapy for mCRPC, except for < 4 months of abiraterone acetate with prednisone for mCRPC 1.5. have not received prior treatment with a PARP inhibitor for mCRPC.	mutations who have not received prior systemic therapy in the mCRPC setting, except for androgen deprivation therapy and had a potentially limited exposure (≤ 4 months) to abiraterone acetate with prednisone. Based on the small number of patients who had prior treatment with an ARPi in the mCSPC setting enrolled in the MAGNITUDE trial, pERC could not draw conclusions regarding the efficacy of niraparib and abiraterone acetate in these patients. Furthermore, clinical experts and pERC noted that there is limited evidence to support a clinical benefit with sequencing of ARPis. Patients with prior treatment with a PARP inhibitor for mCRPC were excluded from the MAGNITUDE trial, thus the safety and efficacy of niraparib and abiraterone acetate in these patients is unknown.	
2. Patients should have good performance status.	Patients with an ECOG performance status 0 or 1 were included in the MAGNITUDE trial.	Treating patients with an ECOG performance status of greater than 1 may be at the discretion of the treating clinician.
Discontinuation		
3. Reimbursement of niraparib and abiraterone acetate should continue until disease progression or unacceptable toxicity.	Patients from the MAGNITUDE trial discontinued treatment upon progression or unacceptable toxicity.	—
Prescribing		
4. Niraparib and abiraterone acetate should be prescribed by a clinician with expertise in treating mCRPC in an outpatient oncology clinic with expertise in systemic therapy.	To ensure that niraparib and abiraterone acetate is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
5. Niraparib and abiraterone acetate with prednisone or prednisolone should not be reimbursed when administered in combination with other anticancer drugs.	There are no data supporting the efficacy and safety of niraparib and abiraterone acetate when used in combination with additional anticancer drugs.	—
Pricing		
6. A reduction in price	The ICER for niraparib and abiraterone acetate with prednisone is $271,803 when compared with abiraterone acetate. A price reduction of 61% would be required	CADTH's estimate of the ICER and the price reduction needed to achieve cost-effectiveness are based on evidence from the MAGNITUDE trial, which was restricted to patients receiving first-line treatment.

Reimbursement condition	Reason	Implementation guidance
	for niraparib and abiraterone acetate to achieve an ICER of $50,000 per QALY gained compared to abiraterone acetate.	The ICER and price reduction required to achieve cost-effectiveness in subsequent lines of therapy are unknown.
Feasibility of adoption		
7. The feasibility of adoption of niraparib and abiraterone acetate must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimates.	—

ARPi = androgen receptor pathway inhibitor; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer; PARP = poly-(ADP-ribose) polymerase.

Discussion Points

- pERC noted that patients with mCRPC identified a need for alternative treatment options with fewer side effects. Niraparib and abiraterone acetate with prednisone appeared to be associated with a higher frequency of treatment-emergent adverse events (TEAEs), grade 3 or 4 adverse events (AEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and notable harms compared with placebo and abiraterone acetate with prednisone in the MAGNITUDE trial. In addition, pERC noted that no evidence on the comparative harms of this treatment versus other treatments for mCRPC (e.g., chemotherapy) was submitted; therefore, it is unknown whether niraparib and abiraterone acetate would have fewer side effects compared to other treatments. Although side effects were not reduced compared to placebo and abiraterone, pERC considered that some patients may value the delay of disease progression over a reduction of side effects. pERC noted that the decision to receive treatment and adopt the risks of side effects can be made by patients who are fully informed of those risks.
- pERC considered evidence from a sponsor-submitted indirect treatment comparison (ITC) that compared niraparib and abiraterone acetate with prednisone versus enzalutamide as first-line treatments for mCRPC. The ITC, which used individual patient-level data from the MAGNITUDE trial compared to data from an observational study, [redacted] Furthermore, the findings were considered to be of high uncertainty due to several major methodologic limitations, [redacted]
- pERC discussed the identification of patients with mCRPC who are chemotherapy ineligible. pERC noted that the definition of chemotherapy ineligibility varies across stakeholders, but there is consensus that identification of these patients would be based on the clinical judgment of the treating physician based on multiple factors, including patient preferences regarding treatment choice. CADTH's estimate of the 3-year budget impact was highly sensitive to assumptions about

the proportion of patients who are deemed to be not eligible for chemotherapy. Because this criterion does not have a consistent clinical definition, CADTH chose a conservative definition of eligibility for chemotherapy that reflected patients who had not received abiraterone acetate or enzalutamide during either the castration-sensitive or castration-resistant phase of treatment based on input from clinical experts. If a broader definition is adopted, the budget impact will increase accordingly.

Background

Prostate cancer is the most common cancer among men in Canada, affecting 1 in 8 men during their lifetime. A patient may progress to mCRPC from metastatic castration-sensitive prostate cancer (mCSPC) or from nonmetastatic castration-resistant prostate cancer. When the disease progresses to the mCRPC stage, the 5-year survival rate reduces to approximately 26% to 28%. Approximately 10% of all patients with mCRPC harbour breast cancer gene (*BRCA*) alterations. When the disease progresses to the mCRPC stage, the 5-year survival rate reduces to approximately 26% to 28%. Patients with *BRCA*-mutated mCRPC are more likely to present with advanced disease, nodal involvement, and distant metastases at diagnosis.

The clinical experts consulted by CADTH indicated that there are several systemic therapies that are approved for the treatment of patients with mCRPC, and the sequencing of these treatments depends on patient and disease factors and prior treatments used in the mCSPC setting. They noted that docetaxel, cabazitaxel, abiraterone, enzalutamide, olaparib (for *BRCA1, BRCA2,* and *ATM)*, radium-223 (for patients with bone predominant disease and no visceral metastasis), and lutetium vipivotide tetraxetan are all Health Canada–approved and, with the exception of lutetium, are widely available in all provinces across Canada.

Niraparib and abiraterone acetate has been approved by Health Canada with prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (germline and/or somatic) mCRPC, who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated. Niraparib and abiraterone acetate is a PARPi. It is available as niraparib 200 mg and abiraterone acetate 1,000 mg and the dosage recommended in the product monograph is 200 mg niraparib and 1,000 mg abiraterone acetate (two 100 mg/500 mg tablets) as a single daily dose. For dose reduction to 100 mg niraparib and 1,000 mg abiraterone acetate, a low strength tablet (two 50mg/500 mg tablets) is recommended.

Sources of Information Used by the Committee

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

- a review of 1 phase III randomized controlled trial in patients with mCRPC and 1 sponsor-submitted ITC
- patients' perspectives gathered by 2 patient groups, the Canadian Cancer Society (CCS) and the Canadian Cancer Survivor Network (CCSN)

- input from the public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with mCRPC
- input from 1 clinician group, including the Ontario Health-Cancer Care Ontario (OH-CCO) Genitourinary Cancer Drug Advisory Committee (GU DAC)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

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

Patient Input

Two patient groups, CCS and CCSN, provided input for this review. In total, 24 responses were gathered by CCS (21 patients and 3 caregivers), and 8 responses (8 patients) were gathered by CCSN. Overall, 97% of the respondents in the CCS survey and 6 of the patients in the CCSN survey were from Canada. Patients reported that the following symptoms affected their quality of life and day-to-day living: changes in libido, sexual function, or fertility; hot flushes; fatigue; low energy; difficulties with urination; loss of appetite; bone or skeletal pain; indigestion; bowel problems; peripheral neuropathy; dizziness; and muscle loss. From the patients' perspective, the prospect of cure, avoiding metabolic syndrome and metastases progressing to other body locations, and prevention or mitigation of spread of cancer in the bones are the most important aspects of their disease to control. One patient from the CCSN survey who has taken niraparib reported constipation and decreased appetite as adverse effects. When asked about their experience with niraparib in comparison to other therapies, the respondent noted that there was little or no difference in symptom management, side effects, and ease of use. The patients also noted that the experience regarding disease progression was much better compared to other therapies.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical specialists with expertise in the diagnosis and management of mCRPC reported that because mCRPC is a terminal phase of prostate cancer, the unmet needs of patients would be prolonged overall survival (OS), improved health-related quality of life (HRQoL), and reduced toxicity. Both clinical experts highlighted that the balance between treatment efficacy and HRQoL would be important. They highlighted a need for new treatments because these patients have primary or acquired resistance to the offered treatments in the mCRPC setting. The clinical experts agreed that it remains unclear whether niraparib and abiraterone acetate would lead to a shift in the current treatment paradigm due to the increased use of ARPis in the mCSPC setting. They believe many medical oncologists would favour a change to chemotherapy in patients progressing on an ARPi, although the CADTH review team notes this could vary across clinicians and treatment centres in Canada. In their opinion, niraparib and abiraterone acetate will be positioned as

a second-line treatment for mCRPC due to the decreasing number of patients who have not been treated with an ARPi. The clinical experts agreed that niraparib and abiraterone acetate would be used in the *BRCA*-mutated mCRPC population. It was noted that most patients with mCRPC, especially those who are otherwise well, would be considered for treatment with cytotoxic chemotherapy. However, the clinical experts reported that it is rare for patients to have an absolute contraindication to chemotherapy. According to the clinical experts, clinicians may consider alternatives to chemotherapy in patients whose disease is asymptomatic or minimally symptomatic and palliative to minimize the toxic effects of treatments. Furthermore, the clinical experts noted that some patients may not want to receive chemotherapy due to adverse effects. In terms of assessing the response treatment, they noted that a combination of radiographic, biochemical, and clinical parameters are used to determine whether a patient with mCRPC is responding to treatment. The clinical experts indicated that treatment should be discontinued if it is intolerable, the disease progresses, or it's the patient's preference to stop the treatment. The clinical experts noted that PARPis have the potential to be toxic; therefore, they outlined that patients receiving niraparib and abiraterone acetate must be under the care of a medical oncologist to manage toxicity.

Clinician Group Input

Clinician group input was received from OH-CCO GU DAC. A total of 8 clinicians provided input on behalf of OH-CCO GU DAC, who highlighted the need to have therapies in the first-line mCRPC setting that can prolong life as there is currently no cure and no targeted treatments are currently available at this setting. They also mentioned the need for treatments that can maximize quality of life. The group noted that niraparib and abiraterone acetate with prednisone would become a standard of care in patients with mCRPC patients with an *HRR* mutation who are treatment naive, although the CADTH review team noted that the Health Canada–approved indication is for patients with *BRCA* mutations only. The group indicated that while a prostate-specific antigen will be used to determine the burden of disease and to monitor response to therapy, serial radiographic imaging will also be used to monitor response and to determine progression as per standard of care. They also noted they would discontinue treatment in cases of significant side effects or disease progression.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs. Refer to Table 2 for details.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The MAGNITUDE phase III clinical trial compared niraparib and abiraterone acetate vs. placebo with abiraterone acetate. In both arms of the study patients also received prednisone or prednisolone. First-line treatment of mCRPC in Canada includes ARATs	This is a comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
(i.e., abiraterone [in combination with prednisone] or enzalutamide), taxane-based chemotherapy (i.e., docetaxel), or radium-223 (funded in some provinces, but used minimally and only for patients with bone predominant disease). Olaparib may also be used as a first-line treatment for mCRPC in patients with a *BRCA* or *ATM* mutations if a patient was previously treated with an ARAT in the nmCRPC or mCSPC setting.	
Considerations for initiation of therapy	
In the MAGNITUDE clinical trial, patients had to have metastatic prostate cancer with castrate levels of testosterone of ≤ 50 ng/dL on a GnRHa or bilateral orchiectomy, and evidence of PSA progression or radiographic progression. Is this the same definition of "castration-resistant" that should be used to determine eligibility for niraparib and abiraterone acetate with prednisone?	The clinical experts consulted by CADTH indicated that this definition could be used to determine eligibility for niraparib and abiraterone acetate with prednisone. pERC agreed with the clinical experts.
Is there a specific definition of "mildly symptomatic" to determine eligibility for niraparib and abiraterone acetate with prednisone?	The clinical experts consulted by CADTH reported that there is no specific definition of "mildly symptomatic" to determine eligibility. The clinical experts noted that determining whether a patient is symptomatic vs. mildly symptomatic is subjective and determined by the patient and their treating clinician. They reported that patients who are asymptomatic are easily identified; however, the definition of mildly symptomatic may vary considerably between patients and clinicians. pERC agreed with the clinical experts.
Should patients with previously untreated mCRPC who have a deleterious *BRCA* mutation and who are candidates for chemotherapy or where chemotherapy is clinically indicated, but who decline chemotherapy, be eligible for niraparib and abiraterone acetate with prednisone?	The clinical experts consulted by CADTH replied that patients who are candidates for chemotherapy or where chemotherapy is clinically indicated, but who decline chemotherapy, should be eligible for niraparib and abiraterone acetate with prednisone. However, the clinical experts highlighted that it is challenging to define "in whom chemotherapy is not clinically indicated" because they reported that all patients are eligible for chemotherapy unless they are too unwell to receive it. In addition, the clinical experts noted that if a patient declines chemotherapy, they would consider that as chemotherapy not being indicated for the patient. pERC agreed with the clinical experts.
Should patients who received abiraterone acetate with prednisone in the metastatic castration-sensitive setting be eligible for niraparib and abiraterone acetate with prednisone in the mCRPC setting?	The clinical experts consulted by CADTH responded that if patients have been on abiraterone acetate for more than 4 months, or if they have progressed from mCSPC to mCRPC while on abiraterone acetate, they should not be eligible for niraparib and abiraterone acetate with prednisone in the mCRPC setting. pERC agreed with the clinical experts.
Should patients who received apalutamide, enzalutamide, or darolutamide in the nonmetastatic castration-resistant setting or metastatic castration-sensitive setting be eligible for niraparib and abiraterone acetate with prednisone in the mCRPC setting?	The clinical experts consulted by CADTH indicated that these patients should not be eligible. pERC agreed with the clinical experts.

Implementation issues	Response
Should patients who have more symptomatic disease (greater than mildly symptomatic) who otherwise meet all eligibility criteria but are not candidates for chemotherapy due to comorbidities be eligible for niraparib and abiraterone acetate with prednisone? Would this subgroup benefit as equally from niraparib and abiraterone acetate with prednisone as those who are asymptomatic or mildly symptomatic?	The clinical experts consulted by CADTH replied that these patients should be eligible for niraparib and abiraterone acetate with prednisone. Although they were not studied in the trial, the clinical experts indicated there is no biological reason to believe that they would respond differently to niraparib and abiraterone acetate with prednisone. pERC agreed with the clinical experts.
Considerations for discontinuation of therapy	
The product monograph recommends that treatment should be continued until disease progression, unequivocal clinical progression, or unacceptable toxicity. What are the definitions of disease progression (e.g., radiographic, biochemical) that should be used to discontinue niraparib and abiraterone acetate with prednisone?	The clinical experts consulted by CADTH noted that the definition of disease progression used to discontinue treatment is subjective. The clinical experts reported that clinicians typically use a composite end point of biochemical, symptomatic, and radiologic progression to determine progression, and these 3 parameters can be weighed differently across clinicians. pERC agreed with the clinical experts.
Generalizability	
Patients with an ECOG PS 0 or 1 were eligible for the MAGNITUDE clinical trial. Should patients with an ECOG PS of > 1 be eligible for niraparib and abiraterone acetate with prednisone?	The clinical experts consulted by CADTH highlighted that this should be left to clinical judgment. The clinical experts suggested that patients who are expected to tolerate niraparib and abiraterone acetate should be eligible. pERC agreed with the clinical experts.
Should patients currently receiving alternate first-line treatment for mCRPC who otherwise meet all eligibility criteria be able to switch to niraparib and abiraterone acetate with prednisone?	The clinical experts consulted by CADTH noted that if patients are receiving first-line treatment to which they are responding and find tolerable, they would not switch therapy. pERC agreed with the clinical experts.
Funding algorithm	
The drug plans noted the following items that may require the development of a provisional funding algorithm by CADTH: • drug may change place in therapy of drugs reimbursed in subsequent lines • complex therapeutic space with multiple lines of therapy, subpopulations, or competing products. Olaparib plus abiraterone for the first-line treatment of patients with mCRPC for whom chemotherapy is not clinically indicated is also under CADTH review.	This is a comment from the drug plans to inform pERC deliberations.
Care provision issues	
Additional patients may require access to *BRCA*-mutation testing before initiating first-line therapy in the mCRPC setting. Currently, some jurisdictions may only test for *BRCA* and/or *ATM* mutations after first-line therapy is initiated. How many patients with mCRPC harbour deleterious *BRCA* mutations?	The clinical experts consulted by CADTH estimated that the proportion of patients with an *HRR* mutation is approximately 25% to 30% overall, and approximately 15% for *BRCA* mutations specifically. CADTH identified literature that reports that approximately 10% of all patients with mCRPC harbour *BRCA* alterations.

Implementation issues	Response
Can patients be switched to niraparib and abiraterone acetate with prednisone if there are delays in accessing *BRCA*-mutation results and patients are initiated on abiraterone acetate and prednisone? Is there a time limit for switching in this situation (e.g., 2 to 4 months)?	The clinical experts consulted by CADTH noted that adding niraparib to abiraterone acetate with prednisone within 4 months of starting on abiraterone acetate with prednisone is appropriate. pERC agreed with the clinical experts.
The recommended dosage of niraparib and abiraterone acetate with prednisone is 200 mg niraparib and 1,000 mg abiraterone acetate (two 100 mg/500 mg tablets), as a single daily dose that must be taken on an empty stomach at approximately the same time every day. For dose reduction to 100 mg niraparib and 1,000 mg abiraterone acetate, a low strength tablet (two 50 mg/500 mg tablets) is recommended. If a further dose reduction below 100 mg/day niraparib is required, it is recommended to discontinue niraparib and abiraterone acetate with prednisone. If toxicity is attributable to niraparib only, could single-drug abiraterone acetate (with prednisone) be prescribed and continued on its own?	The clinical experts consulted by CADTH noted that as long as patients are still responding to treatment, abiraterone acetate could continue if niraparib is stopped due to toxicity. pERC agreed with the clinical experts.
System and economic issues	
The manufacturer estimates the increase in net expenditures attributable to Akeega to be $6,671,716 in year 1, $11,987,626 in year 2, and $13,327,095 in year 3, for a total estimated net budget impact over the first 3 years of $31,986,438. PAG members are concerned about the budget impact if CADTH estimates the budget impact to be substantially higher, as well as because of the high volume of patients with mCRPC. Some drug waste may be expected to occur due to the fixed-dose combination and a separate strength to be used in the event of toxicity. In patients who require a dose reduction, the 100 mg niraparib/500 mg abiraterone acetate strength would be wasted if already dispensed.	This is a comment from the drug plans to inform pERC deliberations.
Generic versions of abiraterone acetate and docetaxel are available. Confidential pCPA pricing is available for enzalutamide and olaparib.	This is a comment from the drug plans to inform pERC deliberations.

ARAT = androgen receptor axis-targeted agent; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GnRHa = gonadotropin-releasing hormone agonist; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer; PAG = Provincial Advisory Group; pCPA = pan-Canadian Pharmaceutical Alliance; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PSA = prostate-specific antigen; vs. = versus.

Clinical Evidence

Description of Studies

One phase III, double-blind, placebo-controlled randomized controlled trial (RCT) (MAGNITUDE; N = 423) met the inclusion criteria for the systematic review conducted by the sponsor. A subgroup of the population accounted for patients with *BRCA1* and *BRCA2* gene alterations (N = 225) as per the Health

Canada–approved indication and requested reimbursement population. In the *BRCA* subgroup, 113 patients were randomized to receive niraparib 200 mg and abiraterone acetate 1,000 mg with prednisone 10 mg once daily and 112 patients to placebo and abiraterone acetate 1,000 mg with prednisone 10 mg once daily. The objective of the MAGNITUDE trial was to evaluate the efficacy and safety of niraparib and abiraterone acetate with prednisone versus placebo and abiraterone acetate with prednisone in adults with mCRPC. The study is ongoing, and patients will be followed up every 3 months to 60 months (5 years) or until death, loss to follow-up, withdrawal of consent, or study termination. The primary outcome was rPFS assessed by blinded independent central review using Response Evaluation Criteria in Solid Tumours (RECIST) v.1.1, and secondary outcomes were OS and TSP.

TPP and HRQoL measured by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire were included as exploratory outcomes in the trial. These outcomes from the trial (i.e., OS, rPFS, TSP, TPP, and HRQoL measured with FACT-P) were the focus of this reimbursement review (refer to the GRADE Summary of Findings and Certainty of the Evidence section).

Some baseline patient characteristics in the *BRCA* subgroup, such as body location of metastases, metastasis stage, Gleason score, and Eastern Cooperative Oncology Group Performance Status (ECOG PS) score were not balanced between the treatment groups. The population was predominately white (72%), with an approximate mean age of 68 years. Most patients had a tumour stage of T3 (41.8%), a Gleason score of 8 or higher (69.2%), and an ECOG PS score of 0 (66.2%). An almost similar proportion of patients in both groups had prior prostate cancer therapy.

Efficacy Results

All results are from the second interim analysis of the MAGNITUDE trial, with a data cut-off date of June 17, 2022.

Overall Survival

The median follow-up time was 24.80 months for all patients in the *BRCA* subgroup. The median duration of follow-up in patients was 20.18 months for the niraparib and abiraterone acetate with prednisone group and 19.98 months for the placebo and abiraterone acetate with prednisone group. More patients had died in the placebo and abiraterone acetate group (44%) than in the niraparib and abiraterone acetate group (38%) by the data cut-off date. The median OS was 29.27 months for niraparib and abiraterone acetate with prednisone and 28.55 months for placebo and abiraterone acetate with prednisone, with an adjusted HR of 0.68 (95% CI, 0.445 to 1.046) and a stratified HR of 0.881 (95% CI, 0.58 to 1.33) The probability of OS at 12 months was 84.1% (95% CI, 75.9% to 89.7%) and 83.9% (95% CI, 75.7% to 89.5%), and the probability of OS at 24 months was 65.6% (95% CI, 55.4% to 74.1%) and 56.6% (95% CI, 45.5% to 66.3%) in the niraparib and abiraterone acetate with prednisone group and in the placebo and abiraterone acetate with prednisone group, respectively. The results from the nonstratified sensitivity analysis of OS for the *BRCA* subgroup were consistent with the stratified analysis.

Radiographic Progression-Free Survival

The between treatment group difference in rPFS met the prespecified criteria for declaring the primary analysis successful at first interim analysis; therefore, no formal statistical testing was performed at the second interim analysis. At the second interim analysis, approximately 50% of patients receiving niraparib and abiraterone acetate had progression events compared with nearly 70% of those in the placebo and abiraterone acetate group by the June 17, 2022, data cut-off in the *BRCA* subgroup. The median rPFS was 19.52 months in the niraparib and abiraterone acetate with prednisone group and 10.87 months in the placebo and abiraterone acetate with prednisone group, with a stratified HR of 0.55 (95% CI, 0.39 to 0.78) favouring niraparib and abiraterone acetate. The probability of being event-free at 12 months was [redacted] (95% CI, [redacted] to [redacted]) and [redacted] ([redacted] to [redacted]) and the probability of being event-free at 24 months was [redacted] (95% CI, [redacted] to [redacted]) and [redacted] (95% CI, [redacted] to [redacted]) in the niraparib and abiraterone acetate with prednisone group and in the placebo and abiraterone acetate with prednisone group, respectively.

Time to Symptomatic Progression

More patients who received placebo and abiraterone acetate (46%) than who received niraparib and abiraterone acetate (27%) reported symptom progression in the *BRCA* subgroup. The median TSP in the niraparib and abiraterone acetate with prednisone group was not estimable and was 23.56 months in the placebo and abiraterone acetate with prednisone group. The stratified HR of 0.54 (95% CI, 0.34 to 0.85) favoured niraparib and abiraterone acetate. The probability of TSP at 12 months was 83.4% (75% to 89.2%) and 75.1% (65.7% to 82.2%), and the probability of TSP at 24 months was 68% (95% CI, 57.3% to 76.6%) and 47.8% (95% CI, 36.1% to 58.5%) in the niraparib and abiraterone acetate with prednisone group and in the placebo and abiraterone acetate with prednisone group, respectively.

Time to Pain Progression

The median TPP for niraparib and abiraterone acetate with prednisone was not estimable and was 22.11 months in the placebo and abiraterone acetate with prednisone group, with a stratified HR of 0.70 (95% CI, 0.43 to 1.12). The probability of TPP at 12 months was 72.90% (62.9% to 80.6%) and 69.4% (59.3% to77.5%), and the probability of TPP at 24 months was 66.9% (95% CI, 55.9% to 75.8%) and 49.9% (95% CI, 36.2% to 61.3%), in the niraparib and abiraterone acetate with prednisone group and in the placebo and abiraterone acetate with prednisone group, respectively.

Change From Baseline in FACT-P Total Score

The difference in the least squares means for the change from baseline in FACT-P total score at cycle 25 between the 2 treatment groups was [redacted] points (95% CI, [redacted]). Data were available for only 26 out of 133 patients in the niraparib and abiraterone acetate group and for 13 out of 112 patients in the placebo and abiraterone acetate group at the latest analysis time point (cycle 25).

Harms Results

At least 1 TEAE was reported in almost all patients in both treatment groups (99.1% of patients in the niraparib and abiraterone acetate with prednisone group and 97.3% of patients in the placebo and abiraterone acetate with prednisone group). The most common TEAEs were anemia ([redacted] in the niraparib and

abiraterone acetate with prednisone group versus [redacted] in the placebo and abiraterone acetate with prednisone group), constipation (33.6% versus 19.6%), hypertension (32.7% versus 24.1%), and nausea (32.7% versus 20.5%). A larger proportion of patients in the niraparib and abiraterone acetate with prednisone group experienced at least 1 grade 3 or 4 TEAE compared to the placebo and abiraterone acetate with prednisone group (68.1% versus 50.9%). At least 1 SAE was reported in 40.7% of patients in the niraparib and abiraterone acetate with prednisone group and 25% of patients in the placebo and abiraterone acetate with prednisone group. The most common SAE in both groups was COVID-19 (4.4% and 2.7% in the niraparib and abiraterone acetate with prednisone and placebo and abiraterone acetate with prednisone groups, respectively). Overall, 15% of patients in the niraparib and abiraterone acetate with prednisone group versus 5.4% in the placebo and abiraterone acetate with prednisone group withdrew from study treatment due to TEAEs. During the follow-up time (i.e., death occurs more than 30 days after the last dose of the study drug), deaths were reported in [redacted]% of patients in the niraparib and abiraterone acetate with prednisone group and [redacted] of patients in the placebo and abiraterone acetate with prednisone group. Most deaths were attributed to disease progression in both treatment groups ([redacted] with niraparib and abiraterone acetate with prednisone and [redacted] with placebo and abiraterone acetate with prednisone).

The notable harms identified in the CADTH review included anemia, which occurred in [redacted] of patients treated with niraparib and abiraterone acetate with prednisone and [redacted] of patients treated with placebo and abiraterone acetate with prednisone, followed by hypertension (32.7% versus 24.1%), fatigue ([redacted] versus [redacted]), thrombocytopenia ([redacted] versus 8[redacted]), asthenia ([redacted] versus [redacted]), fluid retention ([redacted] versus [redacted]), neutropenia ([redacted] versus [redacted]), and edema peripheral ([redacted] versus [redacted]).

Critical Appraisal

Although the MAGNITUDE trial was a randomized trial, several key baseline factors were imbalanced between the 2 groups, such as body location of metastases, metastasis stage at diagnosis, and ECOG PS score, which confounds the results and makes it difficult to determine the true effects of the treatments. The relatively small sample sizes in the trial and in the prespecified *BRCA* subgroup may partially account for the between-group differences. Multivariate Cox regression analysis (only for OS) and other analysis methods were used to try to balance differences between groups. The clinical experts consulted by CADTH indicated that the differences in baseline characteristics signalled that the niraparib and abiraterone acetate group had more serious disease than the control arm. Therefore, if the identified differences in characteristics were not fully accounted for in the analyses, the likely direction of the bias would be to the null (i.e., against niraparib and abiraterone acetate). There were major protocol deviations identified in the trial; however, the magnitude and direction of potential bias was unclear due to the lack of reported patient numbers affected by these deviations within the *BRCA* subgroup. Furthermore, the niraparib and abiraterone acetate with prednisone group received more treatment cycles than the placebo with abiraterone acetate with prednisone group (33.0% versus 23. 7%), which could artificially inflate the perceived effectiveness of niraparib and abiraterone acetate with prednisone. However, this difference in cycles of treatment received also reflects the observed higher percentage of patients in the placebo and abiraterone acetate group who had disease progression. The difference in treatment cycles may also increase the likelihood of reporting AEs with additional treatments in the niraparib and abiraterone acetate group. The CADTH reviewers could not determine

whether the efficacy and safety results were influenced by this imbalance based on the available information, although it is anticipated to have a limited effect, if any.

According to clinical experts, the patients in the MAGNITUDE trial were considered generally representative of patients with mCRPC. Patients in the cohort 1 *BRCA* subgroup of the MAGNITUDE trial all had *BRCA* mutations confirmed before being enrolled in the trial, which aligns with the indicated population and reimbursement request. However, there are potential gaps and implementation challenges related to the evidence from the MAGNITUDE trial versus the population of patients included in the approved indication. CADTH noted that the indication is line agnostic, whereas all patients in the MAGNITUDE trial had not received prior systemic therapy in the mCRPC setting (i.e., received niraparib and abiraterone acetate with prednisone or placebo and abiraterone acetate with prednisone as first-line treatment in this setting). Additionally, the clinical experts indicated that although patients who are asymptomatic can be easily identified, determining whether a patient is "mildly symptomatic" is a subjective judgment and may vary between clinicians. It is unclear if the patients enrolled in the MAGNITUDE trial would be classified as asymptomatic or mildly symptomatic because the trial did not have eligibility criteria nor did it report baseline characteristics directly related to this. Likewise, the clinical experts indicated that there is no objective definition for patients "in whom chemotherapy is not clinically indicated." Health Canada reported that the definition of this component of the indication is based on the clinical judgment of the treating physician and was included to reflect the MAGNITUDE study exclusion criteria, where no prior chemotherapy in the mCRPC setting was allowed. However, the clinical experts consulted by CADTH for this review noted that any patient with mCRPC who is well enough for cytotoxic chemotherapy could be interpreted as having a clinical indication for it, although they and/or their clinicians may not wish to treat these patients with chemotherapy due to the associated adverse effects.

In addition, the clinical experts noted that the exclusion criteria of the MAGNITUDE trial reduce the generalizability of the results as many patients with mCRPC in Canada would now have received a second-generation androgen receptor-targeted therapy in an earlier stage of the disease. The clinical experts indicated that this might impact the choice of niraparib and abiraterone acetate in the mCRPC setting because there would be a small population that would not be considered for taxane chemotherapy as first-line mCRPC treatment. Therefore, the CADTH review team noted the trial population could reflect a relatively small population in clinical settings based on treatment history and eligibility. The outcomes measured in the MAGNITUDE trial are those recommended by the Prostate Cancer Working Group 3 (i.e., OS, rPFS, patient-reported outcomes such as symptoms and HRQoL) and some are clinically relevant and important to patients. According to clinical experts consulted by CADTH, although rPFS is a relevant end point for assessing efficacy in trials, it is not an ideal primary efficacy outcome. It should be noted that despite the improvement in rPFS, there did not appear to be a substantial OS advantage. This is because the emphasis on radiographic results to determine disease progression and treatment benefit in the mCRPC setting does not adequately reflect clinical practice, which involves a broader more holistic assessment of determining treatment benefit. Although the experts noted that abiraterone acetate with prednisone was an appropriate comparator when the MAGNITUDE trial was designed, there are gaps in the direct comparative evidence as there are additional clinically relevant comparators that are now more commonly used (e.g., chemotherapy)

to treat patients with mCRPC in Canada. Therefore, the absence of head-to-head evidence between niraparib and abiraterone acetate versus chemotherapy represents an evidence gap. The clinical experts also noted that enrolling patients with ECOG PS scores of 0 and 1 in the MAGNITUDE trial is not entirely representative of patients with mCRPC as they expect patients with higher ECOG scores in Canadian practice.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For the pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for the outcomes considered most relevant to inform CADTH's 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 OS and rPFS were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review; for FACT-P total score, they were set according to the presence or absence of an important effect based on thresholds identified in the literature. The target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for TSP and TPP due to the lack of a formal minimal important difference estimate, and for harm events due to the unavailability of the absolute difference in effects, and was summarized narratively.

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 (i.e., OS, rPFS, TSP, TPP)
- HRQoL outcome (i.e., FACT-P total score)
- harms (i.e., WDAEs, SAEs).

Table 3 and Table 4 present the GRADE summary of findings for niraparib and abiraterone acetate with prednisone versus placebo and abiraterone acetate with prednisone.

Table 3: Summary of Findings for Niraparib and Abiraterone Acetate With Prednisone vs. Placebo and Abiraterone Acetate With Prednisone for Patients With mCRPC Who Have a *BRCA* Mutation — Efficacy Outcomes

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Niraparib and abiraterone acetate with prednisone	Placebo and abiraterone acetate with prednisone	Difference		
OS — randomized analysis set							
Probability of death[a] at 12 months Median follow-up: 24.8 months	225 (1 RCT)	NR	159 per 1,000	161 per 1,000 (NR)	2 fewer per 1,000 (108 fewer to 104 more)	Low[b]	Niraparib and abiraterone acetate with prednisone may result in little to no clinically important difference in the probability of death at 12 months when compared with placebo and abiraterone acetate with prednisone.
Probability of death[a] at 24 months Median follow-up: 24.8 months	225 (1 RCT)	NR	344 per 1,000	434 per 1,000 (NR)	90 fewer per 1,000 (245 fewer to 65 more)	Low[c]	Niraparib and abiraterone acetate with prednisone may result in a clinically important decrease in the probability of death at 24 months when compared with placebo and abiraterone acetate with prednisone.
rPFS — randomized analysis set							
Probability of radiographic progression[d] at 12 months Median follow-up: 24.8 months	225 (1 RCT)	NR	309 per 1,000	539 per 1,000 (NR)	230 fewer per 1,000 (370 fewer to 89 fewer)	Moderate[e,f]	Niraparib and abiraterone acetate with prednisone likely increases the probability of rPFS at 12 months when compared with placebo and abiraterone acetate with prednisone. The clinical importance of the difference is unknown.
Probability of radiographic progression[d] at 24 months	225 (1 RCT)	NR	579 per 1,000	748 per 1,000 (NR)	169 fewer per 1,000 (329 fewer to 8 fewer)	Moderate[e,f]	Niraparib and abiraterone acetate with prednisone likely increases the probability of rPFS at 24 months when compared with placebo and abiraterone acetate with prednisone.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Niraparib and abiraterone acetate with prednisone	Placebo and abiraterone acetate with prednisone	Difference		
Median follow-up: 24.8 months							The clinical importance of the difference is unknown.
TSP — randomized analysis set							
Probability of symptom progression[g] at 12 months Median follow-up: 24.8 months	225 (1 RCT)	NR	166 per 1,000	249 per 1,000 (NR)	83 fewer per 1,000 (203 fewer to 35 more)	Low[h,i]	Niraparib and abiraterone acetate with prednisone may result in a decrease in the probability of symptomatic progression at 12 months when compared with placebo and abiraterone acetate with prednisone. There is some uncertainty about the clinical importance of the estimates.
TPP — randomized analysis set							
Probability of pain progression[j] at 12 months Median follow-up: 24.8 months	225 (1 RCT)	NR	271 per 1,000	306 per 1,000 (NR)	35 fewer per 1,000 (174 fewer to 105 more)	Very low[h,k]	The evidence is very uncertain about the effect of niraparib and abiraterone acetate with prednisone on pain progression at 12 months when compared with placebo and abiraterone acetate with prednisone.
FACT-P (total score) — randomized analysis set							
LS mean change from baseline in FACT-P (total score), range of scores is 0 to 156 and a higher overall score indicates better HRQoL Time point: at cycle 25	225 (1RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[h,l]	Niraparib and abiraterone acetate with prednisone likely results in little to no difference in HRQoL at cycle 25 when compared with placebo and abiraterone acetate with prednisone. There is some uncertainty about the clinical importance of the estimates.

CI = confidence interval; FACT-P = Functional Assessment of Cancer Therapy-Prostate questionnaire; HRQoL = health-related quality of life; LS = least mean; mCRPC = metastatic castration-resistant prostate cancer; NR = not reported; OS = overall survival; RCT = randomized controlled trial; rPFS = radiographic progression-free survival; TPP = time to pain progression; TSP = time to symptomatic progression; 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 following footnotes. The details included in the table are from the sponsor's Summary of Clinical Evidence.

[a]The sponsor provided the probability of an event at the time point (i.e., death).

[b]Rated down 2 levels for very serious imprecision. The 95% CI for the difference between groups includes the possibility of both benefit and harm when compared with placebo and abiraterone acetate with prednisone. A between-group difference of greater than 5% was clinically significant according to the clinical experts. We did not rate down OS due to the risk of bias as there is a multivariate analysis for OS, adjusting for important imbalanced characteristics.

[c]Rated down 2 levels for very serious imprecision. The 95% CI for difference between groups includes the possibility of a trivial effect (little to no difference) and important harm when compared with placebo and abiraterone acetate with prednisone. A between-group difference of 5% (50 fewer or more events per 1,000 patients) was clinically significant according to the clinical experts.

[d]The sponsor provided the probability of an event at the time point (i.e., radiographic progression).

[e]We did not rate down for risk of bias due to important baseline imbalances as differences in baseline characteristics signalled that the niraparib and abiraterone acetate group had more serious disease than the control arm and the point estimate is showing a benefit; we are then more confident that the result is true. The results are based on an interim analysis; however, we did not detect potential overestimation of the true effect.

[f]Rated down 1 level for serious imprecision. The clinical experts were uncertain of what the exact threshold for clinical importance would be; therefore, the null was used. The point estimate and entire CI excluded the null. However, it was based on a small number of events.

[g]The sponsor provided the probability of an event at the time point (i.e., symptomatic progression).

[h]Rated down 1 level for serious risk of bias due to important baseline imbalances; the direction of bias is potentially toward the placebo and abiraterone acetate with prednisone group. The point estimate is showing little to no difference.

[i]Rate down 1 level for serious imprecision. The 95% CI includes the possibility of little to no difference. No known minimal important difference so the target of certainty appraisal was any effect.

[j]The sponsor provided the probability of an event at the time point (i.e., pain progression).

[k]Rated down 2 levels for very serious imprecision due to the 95% CI including the possibility of both important benefit and important harm. No known minimal important difference so the target of certainty appraisal was any effect.

[l]There is no imprecision in the estimate (the entire CI shows little to no difference). The point estimate and both the lower and upper boundaries of the 95% CI of the between-group comparison indicate trivial or no clinically meaningful difference; based on the literature, a 10-point change from baseline in FACT-P total score was clinically important.

Source: MAGNTIUDE IA2 Clinical Study Review and the sponsor's response to requested additional information.

Table 4: Summary of Findings for Niraparib and Abiraterone Acetate With Prednisone vs. Placebo and Abiraterone Acetate With Prednisone for Patients With mCRPC Who Have a *BRCA* Mutation — Harms Outcomes

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
SAEs	225 (1 RCT)	In the total population, there were 46 (40.7%) SAEs in the niraparib and abiraterone acetate with prednisone group vs. 28 (25%) in the placebo and abiraterone acetate with prednisone group.	Moderate[a]	Niraparib and abiraterone acetate with prednisone likely results in an increase in the proportion of patients who experience SAEs when compared with placebo and abiraterone acetate with prednisone. The clinical significance of the magnitude of the effect is uncertain.
WDAEs	225 (1 RCT)	In the total population, there were 17 (15%) WDAEs in the intervention group vs. 6 (5.4%) in the comparator group.	Moderate[a]	Niraparib and abiraterone acetate with prednisone likely results in an increase in the proportion of patients who withdraw due to adverse events when compared with placebo and abiraterone acetate with prednisone. The clinical significance of the magnitude of the effect is uncertain.

RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal from treatment due to adverse event.

[a]Rated down 1 level for serious imprecision. The number of events did not meet the optimal information size.

Source: The MAGNTIUDE IA2 Clinical Study Review and the sponsor's response to requested additional information.

Economic Evidence

Table 5: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Adult patients with deleterious or suspected deleterious *BRCA*-mutated (germline and/or somatic) mCRPC, who are asymptomatic or mildly symptomatic, and in whom chemotherapy is not clinically indicated.
Treatment	Niraparib and abiraterone acetate with prednisone
Dose regimen	200 mg niraparib with 1,000 mg abiraterone acetate (i.e., two 100 mg/500 mg tablets) daily, to be taken with 10 mg prednisone or prednisolone
Submitted price	Niraparib and abiraterone acetate, 100 mg/500 mg: $147.10 per tablet Niraparib and abiraterone acetate, 50 mg/500 mg: $147.10 per tablet
Treatment cost	$8,239 per 28-day cycle

Component	Description
Comparators	Abiraterone acetate with prednisone Enzalutamide
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (10 years)
Key data source	The MAGNITUDE trial's second interim data analysis to inform clinical efficacy of niraparib and abiraterone acetate with prednisone, and abiraterone acetate with prednisone Sponsor-conducted indirect treatment comparison to inform clinical efficacy of enzalutamide
Key limitations	• The sponsor modelled patients receiving first-line treatment for mCRPC; however, the indicated population for niraparib and abiraterone acetate with prednisone is line agnostic, and thus broader than the modelled population. As such, the cost-effectiveness of niraparib and abiraterone acetate with prednisone used as a subsequent therapy is unknown. • The definition of chemotherapy eligibility in clinical practice is uncertain and based on the judgment of the treating physician rather than consistent clinical criteria. This leads to uncertainty in cost-effectiveness for the patient population that is most likely to receive niraparib and abiraterone acetate with prednisone in Canada. • The long-term extrapolation of OS in the submitted model is uncertain and the methods used to select parametric survival curves did not align with best practices. • The relative efficacy of niraparib and abiraterone acetate with prednisone compared to enzalutamide was based on a sponsor-submitted indirect treatment comparison that was highly uncertain due to several major limitations, including patient comparability across studies, violation of the proportional hazards assumption, and outcome definitions. • The health state utility values used in the sponsor's submission lacked face validity and the methods to estimate them were not aligned with best practices. • The sponsor's selected time to treatment discontinuation distribution for abiraterone acetate with prednisone resulted in patients being treated until progression; however, niraparib and abiraterone acetate with prednisone was discontinued before progression. This resulted in patients receiving niraparib and abiraterone acetate with prednisone accruing health outcomes in the progression-free health state with no treatment cost. This introduced a bias that benefits niraparib and abiraterone acetate with prednisone. • The use of RDI estimates to calculate drug costs may underestimate the total treatment costs that would be seen in real-world clinical practice. • The health and cost outcomes associated with diagnostic tests were not adequately captured in the submitted model. The overall cost to the health care system was therefore underestimated.
CADTH reanalysis results	• To account for the identified key limitations, several changes were made to derive the CADTH base case: selecting the gamma distribution for OS for both niraparib and abiraterone acetate with prednisone and abiraterone acetate with prednisone; using the sponsor's EQ-5D-3L health state utility value from the MAGNITUDE trial for the progression-free health state; assuming that patients were treated to progression for all treatments; and removing RDI assumptions. • In the CADTH base case, the ICER for niraparib and abiraterone acetate with prednisone vs. abiraterone acetate with prednisone was $271,803 per QALY gained (incremental costs = $133,835; incremental QALYs = 0.49). A price reduction of approximately 61% would be required for niraparib and abiraterone with prednisone to be cost-effective at a $50,000 per QALY gained threshold.

EQ-5D-3L = 3-Level EQ-5D; ICER = incremental cost-effectiveness ratio; LY = life-year; mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; RDI = relative dose intensity.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the submitted model does not align with the reimbursement request, the eligible population is highly uncertain, the inclusion of docetaxel in the market share estimates was inappropriate, public drug coverage was underestimated, treatment duration was inappropriately estimated, and the inclusion of genetic testing costs does not align with the perspective of the analysis.

The CADTH reanalysis included adjusting the proportion of patients in whom chemotherapy is not clinically indicated, removing docetaxel as a comparator, modifying the public drug coverage rate, aligning the time on treatment with rPFS, and excluding diagnostic testing costs. Based on the CADTH reanalysis, the 3-year budget impact to the public drug plans of introducing niraparib and abiraterone acetate with prednisone for the treatment of adults with deleterious or suspected deleterious *BRCA*-mutated (germline and/or somatic) mCRPC who are asymptomatic or mildly symptomatic, and in whom chemotherapy is not clinically indicated is expected to be $9,085,054 (year 1: $1,581,059; year 2: $3,553,202; year 3: $3,950,792).

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik

Meeting date: November 8, 2023

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

Meeting date of deferred discussion: December 5, 2023

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

ISSN: 2563-6596

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.