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Reimbursement Review

Darolutamide (Nubeqa)

Sponsor: Bayer Inc.
Therapeutic area: Metastatic castration-sensitive prostate cancer

Summary

What Is Metastatic Castration-Sensitive Prostate Cancer?

- Metastatic prostate cancer is prostate cancer that has spread to other parts of the body. Metastatic castration-sensitive prostate cancer (mCSPC) refers to metastatic prostate cancer that responds to treatment that lowers testosterone levels in the body. Patients with mCSPC often have pain resulting from cancer spreading to the bones. It is estimated that 27,900 people will be diagnosed with prostate cancer in 2024.[1]

What Are the Treatment Goals and Current Treatment Options for mCSPC?

- Important end points identified by clinicians and patients included prolonging life, slowing disease progression, preventing or delaying progression to metastatic castration-resistant prostate cancer (mCRPC), maintaining quality life, reducing pain, and delaying or avoiding the need for chemotherapy.
- Although some patients with mCSPC in Canada receive androgen deprivation treatment (ADT) as monotherapy, the standard treatment for mCSPC is a doublet regimen consisting of a combination of an androgen receptor pathway inhibitor (ARPI) and ADT. Currently reimbursed ARPI plus ADT regimens in Canada include enzalutamide plus ADT, apalutamide plus ADT, and abiraterone acetate plus prednisone plus ADT. A small minority of patients with mCSPC may receive treatment with a triplet regimen consisting of either darolutamide or abiraterone plus prednisone plus ADT and docetaxel, or treatment with ADT alone.

What Is Nubeqa and Why Did Canada's Drug Agency Conduct This Review?

- Nubeqa is a medication available as a 300 mg oral tablet. At the time this review was conducted, Health Canada was reviewing Nubeqa in combination with ADT for the treatment of patients with mCSPC.
- Canada's Drug Agency (CDA-AMC) reviewed Nubeqa to inform a recommendation for the public drug programs on whether it should be reimbursed in combination with ADT for the treatment of mCSPC. The sponsor is seeking reimbursement for this patient group in accordance with the criteria currently used for the reimbursement of apalutamide and enzalutamide in combination with ADT.

Summary

How Did CDA-AMC Evaluate Nubeqa?

- CDA-AMC reviewed the clinical evidence on the beneficial and harmful effects, as well as the economic evidence, of Nubeqa in combination with ADT versus other ARPI treatments given in combination with ADT in Canada for mCSPC. Enzalutamide plus ADT, apalutamide plus ADT, and abiraterone acetate plus prednisone plus ADT were considered relevant treatments to compare with Nubeqa plus ADT.
- Nubeqa was reviewed through a tailored review process that focuses on whether the drug under review has similar beneficial and harmful effects to the most appropriate treatments for comparison.
- The review was informed by materials submitted by the sponsor, which included clinical and economic evidence.
- The review was also informed by 2 patient group submissions and 3 clinician group submissions in response to our call for input and by input from the participating public drug programs around issues that may impact their ability to implement a recommendation.
- Two clinicians with expertise in the management of prostate cancer were consulted as part of the review process.

What Did CDA-AMC Find?

Clinical Evidence

- CDA-AMC reviewed the following clinical evidence:
  - 1 randomized controlled phase III trial (ARANOTE) comparing Nubeqa plus ADT with placebo plus ADT in 669 patients with mCSPC (darolutamide plus ADT [N = 446] or placebo plus ADT [N = 223])
  - 1 network meta-analysis of Nubeqa plus ADT versus enzalutamide plus ADT, apalutamide plus ADT, and abiraterone acetate plus prednisone plus ADT.
- Evidence from a pivotal phase III clinical trial demonstrated that darolutamide plus ADT resulted in clinically meaningful improvements compared with placebo in outcomes that are relevant for the management of mCSPC, including radiographic progression-free survival (rPFS) and time to mCRPC. The estimates of effect from the sponsor's network meta-analysis for rPFS were limited by imprecision (i.e., wide credible intervals) making it challenging to evaluate if there are meaningful differences across the different ARPI plus ADT regimens (i.e., enzalutamide plus ADT, apalutamide plus ADT, and abiraterone acetate plus prednisone plus ADT). The clinical experts consulted by

Summary

CDA-AMC and the clinician groups that provided input noted that rPFS is an appropriate surrogate end point for overall survival for patients with mCSPC and that the results for rPFS suggest improvements in overall survival would likely be similar across the different ARPI plus ADT regimens. Overall, the available evidence and input suggest that darolutamide plus ADT may be associated with similar clinical benefit to the other available ARPI plus ADT regimens.

- The clinical experts emphasized that darolutamide plus ADT is expected to have similar clinical efficacy to the existing alternative ARPI plus ADT regimens (i.e., consistent with the sponsor's claim of no added clinical benefit). The clinical experts and clinician groups noted that reimbursement of darolutamide plus ADT would be beneficial as the potential for fewer adverse events could help ease the treatment burden for patients who are experiencing challenging or intolerable side effects with the alternative ARPI plus ADT regimens. In addition, reimbursement may ease the burden on clinicians when managing patients who are at risk of drug-drug interactions with the alternative regimens.

Economic Evidence

- At the submitted price of $28.34 per 300 mg tablet, the 28-day cycle cost of darolutamide is expected to be $3,175 per patient, based on the Health Canada–recommended dosage. When used in combination with ADT, the 28-day cost is expected to be $3,427 to $3,603 per patient.
- Using the sponsor's submitted price for darolutamide and publicly available list prices for all other drugs, the 28-day cost of darolutamide plus ADT is expected to be lower than the cost of apalutamide plus ADT and enzalutamide plus ADT, and higher than the cost of abiraterone plus prednisone plus ADT.
- CDA-AMC estimates that the budget impact of reimbursing darolutamide (for use in combination with ADT) for the treatment of mCSPC will be approximately $8 million over the first 3 years of reimbursement compared to the amount currently spent on comparators. The expenditure on darolutamide plus ADT is expected to be $73,071,529 over this period. The actual budget impact of reimbursing darolutamide will depend on the number of people eligible for treatment, market uptake of darolutamide plus ADT, displacement of each comparator, and confidentially negotiated drug prices.

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Abbreviations

AE	adverse event
ADT	androgen deprivation therapy
ARPI	androgen receptor pathway inhibitor
BPI-SF	Brief Pain Inventory-Short Form
CDA-AMC	Canada's Drug Agency
CI	confidence interval
CNS	central nervous system
DDI	drug-drug interaction
DIC	deviance information criterion
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FAS	full analysis set
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
ITC	indirect treatment comparison
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MID	minimal important difference
NMA	network meta-analysis
OS	overall survival
PACES	Pharmaceuticals With Anticipated Comparable Efficacy and Safety
PC	prostate cancer
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
RCT	randomized controlled trial
rPFS	radiographic progression-free survival
RR	rate ratio
SAE	serious adverse event
TEAE	treatment-emergent adverse event
TNM	tumour, node, metastasis
WDAE	withdrawal due to adverse event

Background

Sponsor's Summary of Disease Background and Current Management

This section was prepared by the sponsor in accordance with the tailored review process and has not been modified by CDA-AMC.

Application Summary

Table 1: Application Submitted for Review

Item	Description
Drug (product)	Darolutamide (Nubeqa), 300 mg, tablet, oral
Sponsor	Bayer Inc.
Health Canada indication	Proposed: Darolutamide (in combination with ADT) for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC).
Sponsor's reimbursement request	Reimbursement is requested with criteria similar to apalutamide + ADT and enzalutamide + ADT, which have been previously reviewed and recommended for reimbursement by the CDA-AMC for mCSPC.
Health Canada approval status	Under review (pre-NOC)
Health Canada review pathway	Standard review, Project Orbis (Type A)
NOC date	August 18, 2025

ADT = androgen deprivation therapy; mCSPC = metastatic castration-sensitive prostate cancer; NOC = Notice of Compliance.

Disease Background

Prostate cancer (PC) is the most common cancer among Canadian men, with approximately 27,900 new cases diagnosed annually, accounting for about 20% of all new cancer cases in males.[2] It is the third leading cause of cancer-related deaths in men, with an estimated 5,000 deaths each year.[2] The estimated 5-year prevalence of PC in Canada is 108,886,[3] and the age-standardized incidence rate is 119.7 per 100,000 males.[2]

mCSPC is a clinical state in which PC cells have spread to distant anatomical sites but remain sensitive to ADT.[4] Signs and symptoms of advanced prostate cancer include frequent urination, difficulty starting or stopping the flow of urine, blood in the urine or semen, painful ejaculation, and discomfort or pain in the lower back, hips, or pelvis due to widespread metastases, especially to bone.[5] Prostate cancer is clinically staged using the Tumour, Node, Metastasis (TNM) classification system.[6,7] The 5-year cancer-specific survival rates for prostate cancer decrease with disease progression, ranging from 54% to 30% based on the extent of disease.[8] Prognostic factors for mCSPC include disease volume, with high-volume disease indicating a poorer prognosis, and Gleason score, with a higher score (≥8) suggesting more aggressive cancer. Elevated prostate-specific antigen (PSA) levels are associated with worse outcomes. The presence of visceral metastases or extensive bone involvement also indicates a poorer prognosis.[9]

mCSPC patients inevitably develop resistance to ADT and progress to metastatic castration-resistant prostate cancer (mCRPC), which is associated with deterioration in health-related quality of life (HRQoL) and presents a high economic burden to healthcare systems.[10-12] In this setting of mCRPC, prostate cancer is aggressive and lethal.[13] As such, delaying disease progression to the lethal stage of prostate cancer is an important goal of treatment.[11,14-17] While there are treatment options for patients with mCSPC, treatment-related morbidity remains a significant issue. About 20% of mCSPC patients experience adverse outcomes unrelated to disease progression within two years of androgen receptor pathway inhibitor (ARPI)-based therapy.[18] Treatment selection must balance efficacy in delaying disease progression with the safety and tolerability of the treatment.[19-21] Current ARPI doublet regimens (e.g., apalutamide, enzalutamide, or abiraterone acetate-prednisone plus ADT) are linked to toxicities such as cognitive impairment, fatigue, bone health issues, and rash, leading to a poor quality of life.[22,23] Additionally, while some ARPIs can be combined docetaxel, this option is only suitable for patients who are appropriate for docetaxel, and some patients may prefer ARPI instead. Bayer submits that darolutamide plus ADT offers distinct advantages when balancing treatment selection considerations, as described below.

Diagnosis of the Condition

According to the Canadian Urological Association (CUA),[16] PC diagnosis is typically conducted in hospitals or outpatient clinics, through assessment of PSA blood levels, which could indicate the presence of PC, and obtaining a Gleason score from a biopsy to determine the cancer's aggressiveness. While the prostate biopsy is an invasive procedure performed in a hospital setting, patients are typically discharged on the same day, and most patients resume normal activities within a few days. Computed tomography (CT) scans assess the extent of disease spread to lymph nodes and other organs, while bone scans detect bone metastases.[24] Diagnostic tests such as PSA, Gleason scoring, CT scans, and bone scans are widely available across Canada in both hospitals and outpatient clinics. Prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT scans provide high sensitivity and specificity for detecting metastatic lesions but are not yet universally available.

Current Management and Place in Therapy of the Drug Under Review

Current Treatment Options

The primary treatment goals for mCSPC are to delay progression to mCRPC, prolong life, minimize adverse events without adding to the burden of ADT, and preserve long-term quality of life.[25] The long-term impact of treatment on quality of life is a key factor in guiding clinical decisions, as mCSPC patients are often elderly, have comorbidities, and can remain on treatment for years until disease progression. Therefore, there is a need for additional treatment options in mCSPC that are effective, have established and manageable safety and tolerability profiles, do not add to the treatment burden of ADT, and maintain health-related quality of life (HRQoL).

While ADT has remained the backbone therapy of prostate cancer, all mCSPC patients should be offered treatment-intensifying therapies in addition to ADT to delay progression to mCRPC,[26] as recommended by the CUA.[9,16] The majority of mCSPC patients are treated with ARPI doublet regimens (ARPIs plus ADT).

Other treatment options include triplet therapy (ARPI plus ADT plus docetaxel), docetaxel plus ADT and ADT monotherapy, as described below.

ARPIs have proven to be effective in delaying disease progression and improving survival and are established as preferred systemic treatment options. Despite the availability of multiple treatment options for mCSPC, treatment-related morbidity remains a limitation. One in five mCSPC patients experience non-progression-related adverse outcomes within two years of intensified therapy.[27] Currently available ARPI doublet regimens (such as apalutamide, enzalutamide or abiraterone acetate-prednisone plus ADT) are associated with treatment-related toxicities, including cognitive impairment, fatigue, bone health issues (falls and fractures), and rash among others. These toxicities contribute to a progressive clinical burden in mCSPC patients and result in poor quality of life.[23,28] Therapy selection needs to balance efficacy in delaying disease progression with the anticipated safety and tolerability profile of the treatment.[19-21] Furthermore, drug-drug interactions (DDIs) are a concern in the elderly mCSPC patient population, who often require polypharmacy. DDIs may occur more frequently with some ARPIs and can cause adverse reactions or impact the efficacy of interacting drugs, affecting the management of comorbidities,[29] and disrupting the stability of patients who are well-managed for their chronic disease.

The CUA clinical practice guidelines for mCSPC state: “In patients who can safely tolerate docetaxel and in whom docetaxel is felt to be appropriate, a triplet regimen [ARPI plus docetaxel plus ADT] should be considered as a treatment option.”[16] Clinician input indicates that appropriateness for chemotherapy is determined on a case-by-case basis between the patient and the treating physician, considering factors such as patient preference, fitness and functional status, comorbidities, drug toxicity profiles, among others.[30] Due to these factors ARPI doublets are more commonly used than triplet regimens.

Current clinical evidence demonstrates that the combination of ARPI plus docetaxel plus ADT provides superior clinical benefits to docetaxel plus ADT. Given that triplet regimen options are funded across Canada, docetaxel plus ADT is no longer a standard of care and is expected to be replaced by the triplet regimens (ARPI plus docetaxel plus ADT). Additionally, while ADT monotherapy continues to be used for mCSPC in Canada;[31-34] its use is declining with the broader adoption of ARPI regimens. According to the 2025 CDA-AMC provisional funding algorithm for prostate cancer and their respective reimbursement status, the aforementioned ARPI doublet and triplet regimens are funded for the treatment of mCSPC patients across CDA-AMC participating jurisdictions.[30,35]

Impact of the Drug Under Review on Treatment Options

Darolutamide plus ADT is proposed as a new standard of care option considering its favourable clinical profile for mCSPC. The phase III, pivotal study, ARANOTE, demonstrated that darolutamide plus ADT significantly reduced radiological progression or death while maintaining an adverse event (AE) profile similar to placebo.[36] Furthermore, indirect evidence from a network meta-analysis conducted by Bayer[37] indicates that darolutamide plus ADT offers comparable efficacy and may have a more favourable safety profile relative to other ARPI doublets. Darolutamide is a structurally distinct non-steroidal ARPI that offers potent and improved antagonism over existing ARPIs.[38,39] Based on a number needed to harm analysis of pivotal trial data for ARPIs, darolutamide has a lower risk of incremental harm versus apalutamide or enzalutamide,

for AEs such as fatigue, rash, falls, cognitive impairment and dizziness, which adversely impact patient and caregiver quality of life and increase health system burden.[40]

Darolutamide has low potential for clinically relevant drug-drug interaction (DDIs).[41-45] Refer to Appendix 1 in the supplemental materials for details. In addition, due to its low blood-brain barrier penetration,[29,39] darolutamide has a low potential for central nervous system (CNS)-related AEs.[46,47] Furthermore, among the ARPIs, darolutamide is associated with the fewest cardiovascular AEs.[48-51] These AEs are a concern for patients with mCSPC due to the high incidence of comorbid cardiovascular diseases.[49] These attributes of darolutamide contribute to a low treatment burden and provide flexibility for use in mCSPC.

Darolutamide plus ADT is expected to occupy the same place in therapy as other ARPI doublets currently funded for mCSPC. As described above, while triplet regimens are available, they are only suitable for mCSPC patients who can tolerate docetaxel and in whom treatment intensification with docetaxel-based therapy is felt to be appropriate. As these mCSPC patients will follow the same treatment selection process, it is expected that darolutamide plus ADT will not impact triplet regimens. Additionally, while ADT monotherapy use continues to decline given the broader adoption of ARPI regimens, this trend is expected to occur with or without the availability of darolutamide plus ADT. In other words, darolutamide plus ADT is not expected to change the current treatment paradigm but rather to displace the utilization of other ARPI doublets only: apalutamide, enzalutamide or abiraterone acetate-prednisone plus ADT.

Patients who progress to mCRPC following treatment with darolutamide plus ADT in mCSPC will be subject to the same subsequent therapies as other ARPI doublets (i.e. mCRPC therapies that can be used would be unchanged); therefore darolutamide plus ADT is not expected to impact subsequent lines of treatment. Given the above and as CDA-AMC accepted Bayer's request to include only ARPI doublets as relevant comparators for this review, evidence submitted is specific to allow the comparison of darolutamide plus ADT with other ARPI doublets. Key characteristics of darolutamide and other ARPIs are summarized in the supplemental materials.

CDA-AMC Sources of Information and Summary of Input

The contents of this section were prepared by the review team based on materials submitted by the sponsor and input from interested parties.

The objective of the clinical review is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of darolutamide 300 mg oral tablets in combination with ADT for the treatment of mCSPC. The focus will be on comparing darolutamide to relevant comparators in clinical practice in Canada and identifying gaps in the current evidence. This application has been submitted through the tailored review process and the focus of these reviews is whether the evidence supports that the drug under review demonstrates comparable clinical benefit and harms to appropriate comparators. The comparators considered relevant to this review were enzalutamide plus ADT, apalutamide plus ADT, and abiraterone acetate plus prednisone plus ADT.

Darolutamide is an androgen receptor axis-targeted therapy available as a 300 mg oral tablet; the dosage recommended in the product monograph is 600 mg taken twice daily, equivalent to a total daily dose of 1,200 mg, until disease progression or unacceptable toxicity. Patients receiving darolutamide should also receive a gonadotropin-releasing hormone analogue concurrently or have had a bilateral orchiectomy.

The relevant comparators in the same therapeutic class for which CDA-AMC issued a recommendation to reimburse for the same (or similar) indication include enzalutamide and apalutamide. CDA-AMC also issued a reimbursement recommendation (through the nonsponsored reimbursement review process) for abiraterone acetate and prednisone or dexamethasone for the treatment of adults with mCSPC in combination with docetaxel and ADT.

Sources of Information

The contents of the report are informed by materials submitted by the sponsor and input received from interested parties.

Calls for patient group and clinician group input are issued for each reimbursement review. CDA-AMC received 2 patient group submissions from the Canadian Cancer Society and the Canadian Cancer Survivor Network, and 3 clinician group submissions from the Genitourinary Medical Oncology Group at the Arthur J.E. Child Comprehensive Cancer Centre, the British Columbia Cancer Genitourinary Medical Oncologists' Group, and the Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee. The Canadian Cancer Society gathered input through surveys and interviews and the Canadian Cancer Survivor Network used a virtual focus group, as well as a survey that was conducted in 2022 as part of a submission to CDA-AMC for the use darolutamide in combination with ADT and docetaxel (i.e., a triplet regimen for mCSPC). Clinician input was based on a review of the literature (e.g., clinical trials) and clinician experience in the treatment of patients with mCSPC.

The full submissions received are available on the project landing page in the consolidated input document. The drug programs provide input on each drug being reviewed through the reimbursement review process by identifying issues that may impact their ability to implement a recommendation.

Input from patient and clinician groups is considered throughout the review, including in the selection of outcomes to include in the clinical review and in the interpretation of the clinical evidence. Relevant patient and clinician group input is summarized in the Summary of Input section.

Each review team includes at least 1 clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Two clinical specialists with expertise in the diagnosis and management of prostate cancer participated as part of the review team, with representation from Ontario and British Columbia.

Summary of Input

Impacts of the Disease

Similar to previously reviewed applications for drugs indicated for the treatment of mCSPC, patient groups identified that the symptoms associated with mCSPC had a negative impact on their ability to engage in sexual activity, work, exercise, travel, and fulfill or participate in family activities and obligations. Respondents also noted that the diagnosis and disease symptoms can have a negative impact on the mental well-being of patients and their loved ones. Patients also identified a number of important financial implications and barriers that resulted from their mCSPC diagnosis and the need to access therapy. Refer to the Patient and Clinician Group Input on the CDA-AMC website for complete details and results from the patient group survey.

Treatment Goals

Virtually all patients with mCSPC will ultimately progress to mCRPC and die of their disease. Treatment goals in patients with mCSPC include prolonging life while maintaining quality of life with minimal side effects, as well as preventing progression to mCRPC. Progression to castration resistance is associated with increased morbidity, including skeletal events, pain, deterioration of performance status, deterioration of quality of life, need for more intense therapies (including chemotherapy), and ultimately death from disease. It is therefore important to prevent progression to castration resistance for as long as possible while maintaining a patient's quality of life. As with previous submissions for metastatic prostate cancer, the patient groups are seeking future treatments that delay the onset of symptoms, delay the need for chemotherapy, have fewer side effects, improve survival, are easy to use, and allow patients to maintain their HRQoL.

Treatment Options

The clinical experts consulted by CDA-AMC noted that the combination of ADT plus an ARPI is now considered standard of care for mCSPC in all treatment guidelines.[16] The experts indicated that the majority of patients receive a doublet regimen (i.e., ADT plus an ARPI) while a small minority (e.g., those with very high disease burden and/or visceral metastases) would receive a triple therapy of darolutamide, ADT, and docetaxel (a regimen previously reviewed and recommended by CADTH in 2023).[52] Unfortunately, all ARPIs can cause toxicity and have drug interactions that limit their use in a sizable portion of patients. The most important side effects include, for enzalutamide, fatigue, confusion, and decrease of the seizure threshold; for apalutamide, fatigue, confusion, skin rash, and hypothyroidism; and for abiraterone acetate, need for prednisone with all associated side effects. A number of critical drug interactions exist with ARPIs, in particular with statins, factor Xa inhibitors, and antiarrhythmic drugs, all of which are very prevalent in the older adults with prostate cancer population.

The patient groups noted that common side effects following currently available treatments include changes in libido and sexual function, hot flashes, fatigue, loss of muscle mass, incontinence, difficulty concentrating, and weight gain. Several patients noted that their treatment regimens had to be switched and/or discontinued as the side effects were no longer manageable and had a negative impact on their quality of life.

Unmet Needs and Existing Challenges

The patient groups and clinicians identified that there is a need for mCSPC therapies that have fewer side effects to provide options for patients who are ineligible and/or intolerant to the existing ARPI plus ADT regimens. The benefit associated with ADT plus and ARPI versus ADT alone in the mCSPC setting is profound; hence, it is imperative to give access to these combinations to as many patients with mCSPC as possible.

The clinical specialists consulted by CDA-AMC and the clinician groups that provided input all noted that the ARPIs that are currently approved and reimbursed for use as a doublet regimen for mCSPC are associated with relevant drug interactions, in particular with statins (e.g., rosuvastatin), factor Xa inhibitors (direct oral anticoagulants), and cardiac therapies, all of which are commonly used in patients with mCSPC, which is most commonly diagnosed in an older adult patient population. The clinicians identified that darolutamide would be a useful treatment option, particularly for older adult patients with polypharmacy, as it has fewer treatment-limiting DDIs in comparison with the alternative ARPIs. The clinicians noted that abiraterone acetate must be administered in combination with prednisone, which can be associated with important AEs when used for mCSPC as patients receive the treatment for months or years.

The clinicians also noted that darolutamide does not penetrate the blood-brain barrier and, therefore, has a lower risk of CNS-related AEs, such as fatigue, decreased cognition, and seizures, than the alternative ARPIs. The potential reduction in fatigue was noted as being particularly important for the well-being and quality of life of patients.

Considerations for Using the Drug Under Review

The content of this section is informed by input from the clinical expert(s) consulted for the purpose of this review and from clinician groups. The implementation questions from the public drug programs and corresponding responses from the clinical experts consulted for this review are summarized in the Summary of Drug Program Input and Clinical Expert Responses table in Appendix 1 of the Supplemental Materials document. The following has been summarized by the review team.

This drug is being reviewed through the CDA-AMC pharmaceuticals with anticipated comparator efficacy and safety (PACES) process, based on the sponsor's claim that the drug does not offer additional benefit versus currently available ADT plus ARPI doublet regimens (i.e., ADT used in combination with apalutamide, enzalutamide, or abiraterone acetate plus prednisone). As such, a recommendation in favour of reimbursement would have the same reimbursement conditions as apalutamide and enzalutamide, which are reimbursed by all participating drug programs as restricted benefits where patients must meet specific clinical criteria to be eligible for coverage. Abiraterone acetate plus prednisone is a full benefit in 3 jurisdictions (Nova Scotia, New Brunswick, and Ontario) and a restricted benefit in all other jurisdictions. There are slight variations across jurisdictions for the criteria used for ARPIs, but in general the doublet regimens are available for those who meet the following criteria:

Initiation criteria (all of the following must be met):

- mCSPC

- no prior ADT in the metastatic setting; **or** have received ADT for no more than 6 months in the metastatic setting; **or** at least 1 year since prior ADT for early stage disease
- patient has not experienced disease progression on a prior ARPI regimen
- good performance status.

Discontinuation criteria (any of the following):

- disease progression
- development of castration-resistant disease
- unacceptable toxicity.

The clinical experts consulted by CDA-AMC noted that the existing reimbursement criteria for ARPI plus ADT doublet regimens would be appropriate for darolutamide plus ADT. The clinician groups that provided input to CDA-AMC similarly noted that darolutamide plus ADT would be used in a manner similar to other currently reimbursed doublet regimens and no respondents suggested the need for alternative reimbursement conditions for this product.

Sponsor's Summary of the Systematic Review Evidence

Objective and Methods

The objective is to perform a systematic review of the beneficial and harmful effects of darolutamide plus ADT for the treatment of patients with mCSPC versus relevant comparators in clinical practice in Canada. Refer to Appendix 2 in the supplemental materials for details on the systematic review protocol, literature search strategy, and study selection process. As presented in Appendix 3 of the supplemental materials, there are no excluded studies.

Included Studies

Table 2: Details of Included Study

Item	ARANOTE Trial
Study design and population	
Study design	A phase 3, randomized, double-blind, placebo-controlled study
Locations	133 sites in Asia, Europe, Latin America, Australia, New Zealand, Canada, and South Africa
Patient enrolment Dates	Start date: March 2021 End date: August 2022
Randomized (N)	N = 669. Patients were randomized 2:1 to darolutamide + ADT (N = 446) or placebo + ADT (N = 223)

Item	ARANOTE Trial
Inclusion criteria	• Men, with histologically or cytologically confirmed adenocarcinoma of the prostate. • Metastatic disease documented by conventional imaging, either by a positive bone scan or, for soft tissue or visceral metastases, CT or MRI assessed by central review. Metastatic disease was defined as either malignant lesions on bone scan or measurable lymph nodes above the aortic bifurcation or soft tissue or visceral lesions according to RECIST v1.1. • Started ADT within 12 weeks of random assignment. • Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 – 2.
Exclusion criteria	• Presence of regional lymph node metastases only. • Prior treatment with the following: ◦ ADT started more than 12 weeks before random assignment, except neoadjuvant or adjuvant therapy, or both, for a maximum of 24 months and completed at least 12 months before random assignment. ◦ Second-generation androgen receptor inhibitors such as enzalutamide, darolutamide, apalutamide, or other investigational androgen receptor inhibitors. ◦ Cytochrome P450 (CYP) 17 enzyme inhibitor such as abiraterone acetate or oral ketoconazole as anticancer treatment for prostate cancer. ◦ Chemotherapy including docetaxel or immunotherapy for prostate cancer. ◦ A systemic corticosteroid with a dose greater than the equivalent 10 mg of prednisone/day within 28 days before random assignment. ◦ Radiopharmaceuticals ◦ Any other anticancer treatment for prostate cancer, excluding local therapies and ADT. • Treatment with radiotherapy (external beam radiation therapy or brachytherapy) within 2 weeks before random assignment.
Drugs	
Intervention	Darolutamide (600 mg twice daily; oral; until disease progression, start of subsequent cancer therapy, unacceptable toxicity) + ADT
Comparator(s)	Placebo + ADT
Duration	
Screening phase	Participant screening occurred within 28 days prior to randomization.
Treatment phase	The start of the double-blind treatment phase was defined by first administration of the study drug.
Follow-up phase	The Active Follow-up period was the interval from the end-of-study drug intake to the end of all protocol-specified post-treatment interventions. After completing the Active Follow-up period, participants entered the Long-term Follow-up period and were contacted approximately every 12 weeks. The end of the Long-term Follow-up was defined as when the participant died, was lost to follow-up, withdrew consent, or the end-of-study.

Item	ARANOTE Trial
Outcomes	
Primary end point	Radiological progression-free survival (rPFS), from random assignment to the first documentation of radiological progressive disease in soft tissue or bone or death due to any cause.
Publication status	
Publications	Saad F, et al., Darolutamide in combination with Androgen-Deprivation Therapy in patients with metastatic Hormone-Sensitive Prostate Cancer from the Phase III ARANOTE Trial. Journal of Clinical Oncology. 2024 Sep:JCO-24. https://ascopubs.org/doi/10.1200/JCO-24-01798

ADT= Androgen deprivation therapy; BPI-SF = Brief Pain Inventory-Short Form questionnaire; ECOG PS= Eastern Cooperative Oncology Group performance status; EOT= End of treatment; LHRH = luteinizing hormone-releasing hormone; FACT-P= Functional Assessment of Cancer Therapy – Prostate Cancer; mCRPC= metastatic castration-resistant prostate cancer; PSA = Prostate specific antigen; rPFS= Radiological progression free survival. Source: Saad et al 2024.[53] Study duration obtained from ARANOTE Clinical Study Report on file.[54]

ARANOTE (NCT04736199) is a global, randomized, double-blind, placebo-controlled phase III trial designed to evaluate the efficacy and safety of darolutamide plus ADT in mCSPC.[53] ARANOTE is the third trial of darolutamide in prostate cancer and the second trial to investigate darolutamide in mCSPC. The ARAMIS phase III trial demonstrated the life-prolonging effect of darolutamide in non-metastatic castration-resistant prostate cancer (nmCRPC) versus placebo plus ADT, while the ARASENS phase III trial demonstrated that darolutamide (as triplet regimen) conferred a statistically significant benefit in overall survival (OS) (primary endpoint) when added to docetaxel plus ADT, versus docetaxel plus ADT, in mCSPC. Despite the benefit established in ARASENS, not all mCSPC patients are eligible or considered appropriate to receive treatment intensification with darolutamide in combination docetaxel plus ADT. Hence, ARANOTE was designed to evaluate the treatment effect of darolutamide plus ADT without docetaxel in mCSPC (i.e. as doublet regimen).

In ARANOTE, darolutamide plus ADT was compared to placebo plus ADT, like other pivotal trials of ARPI doublets in mCSPC.[55-57] At the time of study design and enrolment, ADT was an appropriate comparator given that many mCSPC patients in the real world were still treated with ADT alone, with access to ARPI doublets gradually increasing.[58] As ARASENS had established survival benefit of darolutamide in mCSPC, the primary endpoint for ARANOTE was rPFS. rPFS is a validated clinical surrogate for OS in mCSPC and allowed for expedited trial conduct.[36,59] OS would have required a long evaluation period at a time when the therapeutic space was evolving. Therefore, there was a narrow window for ARANOTE to enroll and maintain patients until primary analysis, while still offering all patients an appropriate, standard of care option. ARANOTE was the only mCSPC pivotal trial to follow a 2:1 randomization ratio – implemented to support enrolment by providing two-thirds of the study population with access to darolutamide plus ADT.

Treatment with darolutamide plus ADT or placebo plus ADT continued until progressive disease, change of antineoplastic therapy, unacceptable toxicity, death, or withdrawal. Once the primary analysis results from the double-blind phase were available, the study was unblinded and patients who were in the placebo group were offered the opportunity to cross-over to darolutamide during the open-label phase until the final analysis. Patients were stratified by the presence of visceral metastases and prior local therapy. The data cutoff date for the primary analysis was June 7, 2024. An amendment was made to the clinical study protocol

to add the open label phase to the study design and to update the sample size, among other rationale. (This information is included in the submitted protocol.) Specific measures were implemented to facilitate study conduct during the COVID-19 pandemic. There is no significant impact of the COVID-19 pandemic on the overall quality of the data or the outcomes of the study.

Interventions

All patients started ADT of the investigator's choice within 12 weeks prior to initiating study treatment. Patients were randomly assigned in a 2:1 ratio to receive darolutamide 600 mg twice daily plus ADT or matched placebo plus ADT from the start of the treatment phase and all patients received study drug until radiological disease progression, unacceptable toxicity, initiation of new anticancer therapy, patient or physician decision, or study drug interruption of more than 28 consecutive days. This study design included investigator/study site personnel, sponsor, and participant masking.[54]

Outcomes

Table 3: Summary of Outcomes Relevant to the Systematic Review

Outcome measure	Timepoint	ARANOTE Trial
rPFS	Time from the date of randomization to the date of first documentation of radiological progressive disease (using conventional imaging[a] assessed by central review based on RECIST v1.1 criteria [for soft tissue metastases] and PCWG3 criteria [for bone metastases]) or death due to any cause, whichever occurs first	Primary[a]
OS	Time from the date of randomization to the date of death from any cause	Key Secondary[a]
Time to initiation of subsequent anticancer therapy	Time from the date of randomization to initiation of first subsequent antineoplastic therapy for PC	Secondary[a]
Time to CRPC	Time from the date of randomization to the date of first castration-resistant event (radiological progression, PSA progression, or symptomatic skeletal events, whichever occurs first)	Secondary[a]
Time to PSA progression	Time from the date of randomization to the date of first PSA progression,[b] defined as a ≥25% increase above the nadir (lowest at or after baseline) value, which is confirmed by a second value 3 or more weeks later, and an increase in absolute value of ≥2 ng/mL above nadir, at least 12 weeks from baseline	Secondary[a]
PSA undetectable rates (<0.2 ng/mL)	Percentage of patients with detectable PSA values (≥0.2 ng/mL) at baseline, which become undetectable (<0.2 ng/mL) during the period between randomization and the earlier of 30 days after last dose of study drug or change of anticancer therapy	Secondary[a]
Time to pain progression	Time from the date of randomization to the date of first pain progression.	Secondary[a]
AE assessments	Any event, classified by the investigator as related to the study drug, arising or worsening after the first dose of study drug until 30 days after the last dose of study drug	Secondary[a]

mCRPC = metastatic castration-resistant prostate cancer; NR = not reported; OS = overall survival; PSA = prostate-specific antigen; rPFS = Radiological progression-free survival. Source: Saad et al 2024[53] ARANOTE Statistical Analysis Plan.

[a]Statistical testing for these endpoints was adjusted for multiple comparisons (e.g., hierarchal testing). As specified in the ARANOTE SAP, the secondary efficacy endpoints in ARANOTE were tested with a hierarchical gatekeeping procedure in the order shown, as the primary endpoint rPFS was significant.

Sample Size and Power Calculation

The ARANOTE Statistical Analysis Plan assumed a one-sided alpha of 0.025 for rPFS, a hazard ratio of 0.625 and a randomization ratio of 2:1 between the experimental and control arms and determined that 214 events were required to achieve a power of 90% for a statistically positive outcome for the primary endpoint. Based on an exponential distribution of rPFS events and a control arm median time of 20 months, the active arm median was estimated to be approximately 32 months, which is a 60% increase in median time. The expected study duration was estimated to be 36 months assuming approximately 665 participants were randomized at a rate of 45 participants per month, an enrollment ramp-up time of 6 months, 18 months until randomization is complete, a dropout rate of 33% for rPFS follow-up, exponentially distributed event times, and 20-month median time of rPFS for the control group. OS was included as a secondary endpoint in ARANOTE, however the study was not designed or powered to show statistical significance in this endpoint. As such, ARANOTE had fewer patients than other mCSPC studies powered for OS.

Statistical Testing

The full analysis set (FAS) was analyzed for rPFS using a stratified log-rank test with the random assignment stratification factors (visceral metastases and prior local therapy). The Cox regression model was used to determine stratified hazard ratios (HRs) and 95% confidence intervals [CIs] for the treatment comparison, and Kaplan-Meier estimates present rPFS at various time points with 95%CIs for both groups. Secondary time-to-event end points were analyzed in a similar manner as the primary end point, and rates of PSA <0.2 ng/mL were compared between treatment groups using a stratified Cochran-Mantel–Haenszel test. To account for multiple comparisons, secondary efficacy end points were tested for statistical significance using a hierarchical gatekeeping procedure only if the primary end point was statistically significant (two-sided alpha of 0.05) using the same alpha in the following order: OS, time to initiation of subsequent systemic anticancer therapy, time to mCRPC, time to PSA progression, rates of PSA <0.2 ng/mL, and time to pain progression.[53] No formal interim analysis for the primary endpoint was planned. An interim analysis for secondary endpoint OS was conducted at the time of primary completion analysis. As per the Statistical Analysis Plan, the final OS analysis was planned to occur with approximately 180 OS events. OS was the only efficacy endpoint evaluated at final analysis. The superiority of darolutamide treatment over placebo was set for rPFS (FAS) at the prespecified alpha significance level of 0.025 (one-sided). Detailed descriptions of statistical analysis methods are presented in Appendix 4 of the supplemental materials. This summary of clinical evidence includes the final rPFS analysis, the interim OS analysis and the final OS analysis. The final OS analysis is submitted as Bayer data on file in the ARANOTE Final OS Results Summary Report and contains new data collected after ARANOTE's S/NDS to Health Canada.

Subgroup Analyses

Pre-specified subgroups in ARANOTE included race, geographic region, and high and low volume disease subgroups.

Analysis Populations

Table 4: Analysis Populations of ARANOTE Trial

Study	Population	Definition	Application
ARANOTE trial	Full analysis set	Included all randomly assigned patients grouped according to their treatment at random assignment, irrespective of actual treatment.	Used for efficacy analysis.
	Safety analysis set	Included all randomly assigned patients who received at least one dose of study drug and are analyzed according to the treatment they received.	Used for safety analysis.

Source: Saad et al 2024[53]

Patient Population

Baseline Characteristics

The broad inclusion criteria and diverse patient population enrolled in ARANOTE, including 10% Black and 31% Asian patients, is generally representative of the real-world patient population in Canada. In ARANOTE, patient baseline characteristics and demographics were well-balanced across treatment arms. Table 5 provides details of the baseline characteristics in ARANOTE.

Table 5: Summary of Baseline Characteristics of the ARANOTE Trial (FAS set)

Characteristic		ARANOTE Trial	
		Darolutamide + ADT (N = 446)	Placebo + ADT (N = 223)
Median age (range), year		70 (43-93)	70 (45-91)
ECOG performance status, No. (%)	0	235 (52.7)	98 (43.9)
	1	199 (44.6)	117 (52.5)
	2	12 (2.7)	8 (3.6)
Race, No. (%)	White	251 (56.3)	125 (56.1)
	Asian	144 (32.3)	65 (29.1)
	Black	41 (9.2)	24 (10.8)
	Other	10 (2.2)	9 (4.0)
Region, No. (%)	Asia	141 (31.6)	63 (28.3)
	Latin American	119 (26.7)	72 (32.3)
	Europe and rest of the world	186 (41.7)	88 (39.5)
Gleason score at initial diagnosis ≥8, No. (%)		311 (69.7)	146 (65.5)
Median PSA level (range), ng/mL		21.4 (0.02-15,915)	21.2 (0.02-8,533)
Metastasis stage at initial diagnosisa No. (%)	De novo	317 (71.1)	168 (75.3)
	Recurrent	100 (22.4)	45 (20.2)

Characteristic		ARANOTE Trial	
		Darolutamide + ADT (N = 446)	Placebo + ADT (N = 223)
Visceral metastases, No. (%)	Yes	53 (11.9)	27 (12.1)
	No	393 (88.1)	196 (87.9)
Disease volumeb, No. (%)	High volume	315 (70.6)	157 (70.4)
	Low volume	131 (29.4)	66 (29.6)
Prior local therapy, No. (%)	Yes	80 (17.9)	40 (17.9)
	No	366 (82.1)	183 (82.1)

ADT=Androgen deprivation therapy; BICR=Blinded independent central review; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FAS= Full analysis set; PSA= Prostate specific antigen.

[a]Recurrent is defined as Stage I to IV A and de novo is defined as Stage IV B.

[b]High disease volume at baseline was defined as the presence of visceral metastases or 4 or more bone lesions (including superscans), with at least 1 metastasis beyond the vertebral column and pelvic bones. If none of these criteria were met, the participant had low disease volume at baseline.

Source: Saad et al 2024[53] and ARANOTE Clinical Study Report on file[54]

Patient Disposition

Table 6: Patient Disposition

Patient disposition	ARANOTE Trial	
	Darolutamide + ADT (N = 446)	Placebo + ADT (N = 223)
Screened, N	889	
Reason for screening failure and premature discontinuation of screening, N (%)	220 (24.7)	
Screen failure	202	
Withdrawal by subject	13	
Other	2	
Death, lost to follow-up, and subject decision (COVID-19 pandemic related)	3	
Randomized, N (%)	446	223
Discontinued from study, N (%)	203 (45.5)	160 (71.7)
Reason for discontinuation, N (%)		
Disease progression, radiologic	80 (39.4)	69 (43.1)
Disease progression, clinical	40 (19.7)	32 (20.0)
Withdrawal by patient	34 (16.7)	22 (13.75)
Adverse event	28 (13.8)	22 (13.75)
Death	9 (4.4)	3 (1.9)
Physician decision	5 (2.5)	9 (5.6)
Others	7 (3.5)	3 (1.9)
FAS, N	446	223

Patient disposition	ARANOTE Trial	
	Darolutamide + ADT (N = 446)	Placebo + ADT (N = 223)
Safety, N	445	221

FAS = Full Analysis Set; NR= Not reported; PP= Per-protocol

Source: Saad et al 2024[53] and ARANOTE Clinical Study Report on file.[54]

Exposure to Interventions

The median treatment duration was 24.2 months in the darolutamide group compared with 17.3 months in the placebo group, with a greater proportion of the darolutamide group (53.8%) still receiving study treatment than in the placebo group (28.3%).

Study Treatments

At the primary analysis, the overall median time under treatment was longer for darolutamide plus ADT versus the placebo plus ADT arm (24.2 vs. 17.3 months, respectively). Overall, a higher percentage of participants had ≥24 months study drug exposure in the darolutamide arm than in the placebo arm (50.3% vs. 34.4%, respectively). The percent of planned dose received (mean) was 98.6% for darolutamide plus ADT and 99.3% in the placebo plus ADT treatment arms.

Concomitant Medications and Co-Interventions

ARANOTE participants received an ADT started ≤12 weeks before randomization, on a continuous basis. Use of concomitant medications was generally well-balanced between the treatment arms (93.5% of participants in the darolutamide plus ADT arm and 91.0% in the placebo plus ADT arm).[54] Additional information on concomitant medications has been included in Appendix 5 of the supplemental materials.

Subsequent Treatment

The double-blind phase of ARANOTE lasted until the primary analysis and was followed on by an open-label phase where patients on study treatment (double-blind darolutamide or placebo) were permitted to crossover and offered the opportunity to receive open-label darolutamide. This phase of the study is described further in the ARANOTE Final OS Results Summary Report. In ARANOTE, the proportion of patients who received subsequent life-prolonging anticancer therapy was 32.5% in the darolutamide plus ADT arm and 42.5% in the placebo plus ADT arm. A table summarizing the overall use of subsequent treatments and breakdown of specific treatments and/or interventions has been included in Appendix 5 of the supplemental materials.

Results

Efficacy

Summary of Key Efficacy Outcomes

Table 7: Summary of Key Efficacy Results (FAS set)

Variable	ARANOTE Trial	
	Darolutamide + ADT (N = 446)	Placebo + ADT (N = 223)
Primary end point		
Radiological progression-free survival		
rPFS (months), median (95% CI)	NR	25 (19 to NR)
Events, n (%)	128 (28.7)	94 (42.2)
HR (95% CI)[a]	0.54 (0.41 to 0.71)	
P-value	<0.0001	
Secondary end points		
OS (interim)		
OS (months), median (95% CI)	NR	NR (33.8 to NR)
Events, n (%)	103 (23.1)	60 (26.9)
HR (95% CI)[a]	0.81 (0.59 to 1.12)	
P-value	0.1007	
Probability of OS (95% CI)	0.798 (0.759 to 0.837)	0.755 (0.696 to 0.813)
Timepoint	24 months	
Time to initiation of subsequent systemic anticancer therapy		
Time to initiation of subsequent systemic anticancer therapy (months), median (95% CI)	NR	NR (27.7 to NR)
Events, n (%)	68 (15.2)	74 (33.2)
HR (95% CI)[a]	0.40 (0.29 to 0.56)	
P-value	<0.0001	
Time to mCRPC		
Time to mCRPC (months), median (95% CI)	NR	13.8 (12.0 to 16.8)
Events, n (%)	154 (34.5)	143 (64.1)
HR (95% CI)[a]	0.40 (0.32 to 0.51)	
P-value	<0.0001	
Rate difference (darolutamide minus placebo) (%), [95% CI][b]	44.3 (37.4 to 51.2)	
P-value	<0.0001	
Time to PSA progression		

Variable	ARANOTE Trial	
	Darolutamide + ADT (N = 446)	Placebo + ADT (N = 223)
Time to PSA progression (months), median (95% CI)	NR	16.8 (13.9 to 20.1)
Events, n (%)	93 (20.9)	108 (48.4)
HR (95% CI)[a]	0.31 (0.23 to 0.41)	
P-value	<0.0001	
Rates of PSA <0.2 ng/mL in patients with baseline PSA ≥0.2 ng/mL		
Number of patients contributing to the analysis	425	211
Events, n (%) (95% CI)	266 (62.6) (57.8 to 67.2)	39 (18.5) (13.5 to 24.4)
Rate difference (darolutamide minus placebo) (%), [95% CI][b]	44.3 (37.4 to 51.2)	
P-value	<0.0001	
Time to pain progression		
Time to pain progression (months), median (95% CI)	NR	29.9 (29.7 to NR)
Events, n (%)	124 (27.8)	79 (35.4)
HR (95% CI)[a]	0.72 (0.54 to 0.96)	
P-value	0.0115	

ADT = androgen-deprivation therapy; CI = Confidence interval; HR = Hazard ratio; NA = not applicable; NR = not reached.

[a]Hazard ratio and 95% CI were based on Cox regression model, stratified by visceral disease (present v absent) and prior local therapy (yes v no).

[b]The rate difference and 95% CI were based on a Cochran-Mantel-Haenszel test comparing between the treatment arms, stratified by IWRS stratification factors: visceral metastases (present vs. absent) and prior local therapy (yes vs. no). Note: Since OS was not statistically significant at the prespecified alpha significance level of 0.0185 (one-sided) based on 163 OS events observed, the other secondary endpoints were not formally tested for statistical significance according to the hierarchical gatekeeping procedure.

Source: Saad et al 2024 and ARANOTE Clinical Study Report on file.

Primary End Point: Radiological Progression-Free Survival

ARANOTE met its primary endpoint of rPFS. At the primary analysis (data cutoff date June 7, 2024), darolutamide plus ADT demonstrated a clinically meaningful and statistically significant reduction in the risk of radiological progression or death of 46% versus ADT (HR, 0.54 [95% CI, 0.41 to 0.71]; P < 0.0001), with median rPFS not reached in the darolutamide group versus 25.0 months in the placebo group. The median follow-up for rPFS was 25.3 months in the darolutamide plus ADT arm and 25.0 months in the placebo plus ADT arm. The rPFS rates at 24 months were 70.3% in the darolutamide group and 52.1% in the placebo group. The benefit of darolutamide plus ADT on rPFS was consistent across prespecified patient subgroups, including patients with high- and low-volume disease. This was the final analysis for rPFS. Further details are presented in Appendix 6 of the supplemental materials.

Key Secondary End Point: Overall Survival

At the interim OS analysis (data cutoff date June 7, 2024), after 163 deaths (occurring in 23.1% of the darolutamide group and in 26.9% of the placebo group), the results showed a 19% relative reduction in the risk of death in patients treated with darolutamide plus ADT compared to placebo plus ADT; however, it

did not reach statistical significance (HR, 0.81 [95% CI, 0.59 to 1.12]). This benefit was observed despite a higher proportion of patients receiving subsequent life-prolonging anticancer therapy in the placebo plus ADT arm (42.5%) vs the darolutamide plus ADT arm (32.5%; refer to Appendix 4 of the supplemental materials for further information on subsequent anticancer therapy). The median OS was not reached in either treatment group. The median follow-up time for OS was 25.3 months in the darolutamide plus ADT group and 25 months in the placebo plus ADT group. In total, 79.8% and 75.5% of participants were estimated to be alive at 24 months in the darolutamide plus ADT and placebo plus ADT groups, respectively.

The final OS analysis (data cutoff date January 10, 2025), based on 185 events, maintained the positive trend favouring darolutamide plus ADT; however, it was not statistically significant (HR, 0.78 [95% CI, 0.58 to 1.05]).

As described above, ARANOTE was not powered to show significance in OS. It had a smaller patient sample than other ARPI trials in mCSPC and was conducted over a relatively shorter follow-up period. With fewer patients and a shorter duration, fewer OS events occurred in ARANOTE. Of note, at the two-year landmark for ARANOTE, 80% of patients on darolutamide were still alive – this survival rate is consistent with the pivotal studies for apalutamide and enzalutamide in mCSPC (86% and 82% of patients who were on enzalutamide [ARCHES trial] and apalutamide [TITAN trial] respectively were alive at the same time point).[55,56,60,61] According to clinical expert opinion, this suggests a comparable OS benefit between darolutamide plus ADT and other ARPIs.

Other Secondary Endpoints

As OS was not statistically significant, other secondary endpoints were not formally tested for significance. Darolutamide plus ADT showed a numerical benefit vs placebo plus ADT across all other secondary endpoints. Further details are presented in Appendix 6 of the supplemental materials.

Time to Initiation of Subsequent Systemic Anticancer Therapy for Prostate Cancer

68 (15.2%) patients in the darolutamide plus ADT group and 74 (33.2%) patients in the placebo plus ADT group started subsequent systematic anticancer therapy for prostate cancer (HR, 0.40 [95%CI, 0.29 to 0.56]). The median time to initiation of subsequent systemic anticancer therapy for prostate cancer was not reached in either of the treatment arms.

Time to mCRPC

A smaller percentage of patients in the darolutamide plus ADT group (34.5%) had progressed to mCRPC than in the placebo plus ADT arm (64.1%) (HR, 0.40 [95% CI, 0.32 to 0.51]). The median time to mCRPC was not reached in the darolutamide plus ADT arm and was 13.8 (95% CI, 12.0 to 16.8) months in the placebo plus ADT arm.

Time to PSA Progression

A smaller percentage of patients in the darolutamide plus ADT group (20.9%) than in the placebo plus ADT group (48.4%) (HR, 0.31 [95% CI, 0.23 to 0.41]) had PSA progression. The median time to PSA progression was not reached in the darolutamide plus ADT group and was 16.8 (13.9 to 20.1) months in the placebo

plus ADT group. This benefit, although not statistically significant, is important as higher PSA is a prognostic factor for worse disease outcomes.

Rates of PSA <0.2 ng/mL in Patients With Baseline PSA ≥0.2 ng/mL

Among patients with detectable PSA ≥0.2 ng/mL at baseline, a higher percentage of patients in the darolutamide plus ADT group (62.6%) than in the placebo plus ADT group (18.5%) had undetectable PSA values of <0.2 ng/mL at any time during the treatment period.

Time to Pain Progression

Pain progression was assessed using the Brief Pain Inventory-Short Form (BPI-SF) questionnaire and/or the initiation of short- or long-acting opioid use for malignant disease for ≥7 consecutive days after randomization. 27.8% of patients in the darolutamide plus ADT group and 35.4% of patients in the placebo plus ADT group experienced pain progression (HR, 0.72 [95% CI, 0.54 to 0.96]). The median time to pain progression was not reached in the darolutamide plus ADT group and was 29.9 months in the placebo plus ADT group.

Harms

The safety analysis (data cut-off date June 7, 2024) reconfirms the established tolerability profile of darolutamide observed in earlier prostate cancer trials, with no new safety findings. The safety data showed that darolutamide was well tolerated and had a favorable safety profile, reconfirming the favourable tolerability and safety profile of darolutamide observed in the previous ARAMIS and ARASENS Phase III trials. In ARANOTE, the incidences of AEs with darolutamide were low and comparable to placebo. Darolutamide had lower discontinuation rates due to AEs, a measure of treatment tolerability, versus placebo. The majority of AEs are of low grade with similar incidence between the treatment arms. Notably, the frequency of grade 3/4 or 5, and serious AEs showed no difference between treatment arms. Rates of fatigue were lower with darolutamide when compared to placebo. The most common treatment-emergent adverse events (TEAEs) reported with a higher incidence (≥2% points) in the darolutamide arm than in the placebo arm were anemia, urinary tract infection, AST increased, constipation, hot flush, insomnia, hyperglycemia, blood bilirubin increased, pneumonia, and hyperlipidemia.

Overview of Safety

In ARANOTE, an independent data monitoring committee reviewed unblinded safety data throughout the study. The safety analysis set included 666 patients, 445 in the darolutamide group and 221 in the placebo group. Detailed results for harms are presented in Appendix 5 of the supplemental materials. The overall incidence of TEAEs was similar in the darolutamide and placebo arms (91.0% and 90.0%). Most AEs were grade 1 or 2 and similar rates were reported for grades 3, 4 or 5. The most commonly reported TEAEs were generally comparable between the treatment arms. The most common adverse events in ≥10% of participants in either the darolutamide and placebo arms were anemia (20.4% vs. 17.6%, respectively), arthralgia (12.4% vs. 11.3%), urinary tract infection (11.7% vs. 7.7%), back pain (9.7% vs. 10.4%), and bone pain (7.4% vs. 12.2%). Detailed results for harms are presented in Appendix 7 of the supplemental materials. At the final analysis, safety results showed consistency with the data at primary analysis completion and confirmed that darolutamide plus ADT was well-tolerated.

Withdrawals Due to Adverse Events

A smaller proportion of patients receiving darolutamide plus ADT (27/445; 6.1%) versus placebo plus ADT (20/221; 9.0%) discontinued treatment because of adverse events.

Adverse Events of Special Interest

AEs commonly associated with ARPIs occurred at low rates in the darolutamide group, similar to placebo. The median duration of study treatment was longer in the darolutamide arm than in the placebo arm (24.2 vs. 17.3 months, respectively). Thus, it was necessary to consider the exposure-adjusted incidence rates (EAIR) between the treatment arms. EAIR per 100 patient-years (PY) were also low and similar between the darolutamide plus ADT arm and placebo plus ADT arm for most AEs of special interest.

Additional Results From the Included Studies

Table 8: Summary of Final OS Analysis

Results (FAS)	Darolutamide (N = 446)	Placebo (N = 223)
Number (%) of participants with event	115 (25.8%)	70 (31.4%)
Number (%) of participants censored	331 (74.2%)	153 (68.6%)
Median (days) (95% CI)[a]	A (A to A)	A (A to A)
Range (days) (including censored values)	(1 to 1397)	(7 to 1334)
Range (days) (without censored values)	(37 to 1181)	(48 to 1171)
OS Rate		
Month 6 (95% CI)	0.984 (0.972 to 0.996)	0.973 (0.951 to 0.994)
Month 12 (95% CI)	0.942 (0.920 to 0.964)	0.894 (0.853 to 0.935)
Month 18 (95% CI)	0.853 (0.819 to 0.887)	0.841 (0.791 to 0.890)
Month 24 (95% CI)	0.798 (0.759 to 0.836)	0.756 (0.698 to 0.814)
Month 30 (95% CI)	0.736 (0.693 to 0.780)	0.694 (0.630 to 0.757)
Month 36 (95% CI)	0.714 (0.668 to 0.760)	0.644 (0.573 to 0.714)
Month 42 (95% CI)	0.687 (0.629 to 0.745)	0.610 (0.517 to 0.703)
Month 48 (95% CI)	A (A to A)	A (A to A)
HR (Daro vs. Pla) (95% CI)[b]	0.776 (0.577 to 1.045)	
One-sided p-value c	0.0473	

A = Value cannot be estimated due to censored data; CI = confidence interval; CRPC = castration-resistant prostate cancer; Daro = darolutamide; FAS = Full analysis set; HR = Hazard ratio; IWRS = interactive web response system; N = Total number of participants (100%); NA = not applicable; OS = overall survival; Pla = Placebo; PSA = Prostate-specific antigen

[a]Median and 95% CI were computed using Kaplan-Meier estimates.

[b]A hazard ratio <1 indicates superiority of darolutamide over placebo. The HR and 95% CI were based on a Cox regression model, stratified by IWRS stratification factors: visceral metastases (present vs. absent) and prior local therapy (yes vs. no).

[c]One-sided p-value from stratified log-rank test.

Source: Clinical Study Report

CDA-AMC Critical Appraisal of the Systematic Review Evidence

The contents of this section were prepared by the review team based on the sponsor's summary of the systematic review evidence and other material submitted by the sponsor.

Internal Validity

Treatment allocation: Randomization was performed using an Interactive Web Response System for concealment and stratified by important prognostic factors (i.e., presence of visceral metastases versus absence of visceral metastases [assessed by blinded independent central review] and according to prior use of local therapy versus no prior local therapy). The clinical experts consulted by CDA-AMC noted that the stratification factors were clinically relevant and they did not identify other factors that should have been included for a phase III trial in patients with mCSPC.

Patient characteristics: The baseline characteristics of patients were generally well balanced between treatment groups. One exception was potential differences in baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) across the treatment groups. Compared with the placebo plus ADT group, the darolutamide plus ADT group had a greater proportion of patients with an ECOG PS of 0 at baseline (52.7% versus 43.9%) and a lower proportion of patients with an ECOG PS of 1 at baseline (44.6% versus 52.5%). Subgroup analysis for rPFS based on baseline ECOG PS were similar for those with a baseline score of 0 (HR = 0.552; 95% CI, 0.367 to 0.832) and those with a score of 1 or 2 (HR = 0.557; 95% CI, 0.391 to 0.795), although statistical tests for interaction were not conducted. The sponsor similarly reported that subgroup analyses for TEAEs did not reveal differences based on baseline ECOG PS (0 versus 1 or 2). The clinical experts consulted by CDA-AMC noted that the imbalances were unlikely to introduce meaningful bias or substantially affect the internal validity of the ARANOTE results for any of the end points, noting that an ECOG PS of both 0 and 1 reflect good functional status and are treated similarly in clinical practice.

Blinding: Treatments were administered in a double-blind manner. The frequency and distribution of AEs across the darolutamide plus ADT and placebo plus ADT groups was generally similar and unlikely to compromise blinding in the study. The clinical experts consulted by CDA-AMC did not believe that the AE profile would significantly compromise blinding in the ARANOTE trial.

Statistical testing: The efficacy analysis was conducted in the FAS, in which all randomized patients were included and analyzed by treatment assignment. A hierarchical gatekeeping approach was used to account for multiplicity for secondary efficacy end points. As the study did not demonstrate a statistically significant difference between darolutamide plus ADT and placebo plus ADT for OS (the first secondary end point tested), no other secondary end points were formally tested for statistical significance. Though the statistical testing hierarchy was stopped at OS, the sponsor reported nominal P values for all of the other secondary end points that are associated with an increased risk of type I error due to the lack of control for multiplicity.

Final analyses were submitted for both rPFS (primary end point) and OS (key secondary end point). With respect to the Cox proportional hazards model for the rPFS and OS analyses, the sponsor clarified that formal statistical tests of the proportional hazards assumption were conducted in a post hoc manner as part of the European Medicines Agency review. The sponsor reported that the results of the supremum tests for

rPFS (P = [redacted]) and the interim and final analyses of OS (P = [redacted] and P = [redacted] respectively) indicated that there was no significant evidence against the proportional hazards assumption for both OS analyses. For the OS analyses, the sponsor reported that the ARANOTE study was not designed or statistically powered to detect a difference between the darolutamide plus ADT and placebo plus ADT groups. This makes it challenging to interpret the non–statistically significant difference between the treatment groups and limits the reliability of the sponsor's indirect treatment comparison.

Discontinuations: A higher proportion of patients discontinued treatment in the placebo plus ADT group (71.7%) compared with darolutamide plus ADT group (45.5%). The most common reasons for treatment discontinuation were related to disease progression, both radiologic and clinical. There were no concerns identified related to the approach for censoring the analyses to account for discontinuations.

HRQoL: The sponsor reported high adherence with the Functional Assessment of Cancer Therapy – Prostate Cancer questionnaire used to assess HRQoL (i.e., adherence of 95% or greater at each visit during the treatment period). No data imputation was involved. It should also be noted that the instrument has not been validated in patients with mCSPC and most items in the questionnaire were measuring symptoms. As such, it is uncertain if the instrument can adequately capture the HRQoL of the study population. Time to pain progression was assessed based on the BPI-SF questionnaire and a minimal important difference (MID) estimate of 2 points was used to define pain progression. It should be noted that evidence for validity, reliability, and responsiveness of the BPI-SF instrument was not available for mCSPC, as most available evidence was for mCRPC. An MID for mCSPC has not yet been established. In consultation with the clinical experts, the MID estimate of 2 points used by the sponsor for defining time to pain progression was considered reasonable, although the patient perspective on this is unknown.

External Validity

Target population: According to the clinical experts consulted by CDA-AMC, the eligibility criteria of the ARANOTE trial were reflective of the selection criteria for patients with mCSPC in clinical practice who would be treated with a doublet regimen, except that the requirement for ECOG PS is less stringent in clinical practice. Overall, the clinical experts indicated that the ARANOTE trial population is a reasonable reflection of the target population in Canada for the baseline and demographic characteristics. There were no concerns that the results of the ARANOTE trial would not be generalizable to the practice setting in Canada (noting that darolutamide is already used in Canada as part of a triplet regimen in this patient population).

Intervention: Dosing of darolutamide and ADT was consistent with the Canadian product monograph and clinical practice. Darolutamide was administered until disease progression (i.e., symptomatic disease progression or change in antineoplastic therapy) or unacceptable toxicity. The clinical experts consulted by CDA-AMC noted that this is consistent with how darolutamide would be administered in practice in Canada.

Comparator: Placebo plus ADT alone is no longer a relevant comparator for mCSPC in Canada as nearly all patients would receive either doublet or triplet therapy. This is reflected in commentary in the sponsor's indirect comparison that states that ADT monotherapy is not a relevant comparator and was only included in the indirect treatment comparison (ITC) to provide a common comparator to connect darolutamide plus

ADT, enzalutamide plus ADT, and apalutamide plus ADT in a network. The sponsor stated that placebo plus ADT alone was a relevant comparator at the time the ARANOTE trial initiated patient enrolment in February 2021. The sponsor stated that many patients with mCSPC in the real world were still treated with ADT alone, with access to ARPI doublets gradually increasing at that time.[62] CDA-AMC notes that before initiation of the ARANOTE trial, the pan-Canadian Oncology Drug Review Expert Review Committee issued recommendations in favour of reimbursement for apalutamide and enzalutamide (final recommendation issued in April 2020 and September 2020, respectively);[63,64] however, pan-Canadian Pharmaceutical Alliance negotiations were not completed when the trial was initiated (August 2021 for apalutamide and July 2021 for enzalutamide) and jurisdictions may not have been providing reimbursement for the doublet regimens at that time.[65]

Trial setting: In response to a question from Health Canada about the geographic distribution of enrolment in the ARANOTE study, the sponsor stated that Brazil, China, India, and Russia were the top recruiters for the study, along with Europe and Latin America. The countries chosen were where ADT monotherapy was still considered a standard of care for mCSPC in clinical practice. Although 2 patients were enrolled from sites in Canada, the clinical experts consulted by CDA-AMC noted that recruitment may have been challenging in North American as ARPI plus ADT doublet regimens had been shown to be clinically superior to ADT monotherapy and had been approved by Health Canada and the FDA. Despite the limited participation from sites in North America, the clinical experts considered the results to be generalizable.

Outcomes: The clinical experts consulted by CDA-AMC noted that the outcomes studied in the ARANOTE trial were appropriate to demonstrate that darolutamide plus ADT will offer similar clinical benefits to other doublet regimens that are currently reimbursed by the public drug programs. Given that ARPI plus ADT doublet regimens are considered the current standard of care in Canada for most patients, the experts were not concerned that the ARANOTE trial was not designed to show a different in OS versus ADT plus placebo. They noted that, although OS is the preferred end point, rPFS represents a clinically important outcome because of the increased morbidity and mortality associated with more advanced stages of prostate cancer (versus mCSPC).

Concomitant medications: The clinical experts consulted by CDA-AMC indicated that concomitant medications used in the ARANOTE trial were a reasonable reflection of what may be used in practice in Canada and there were no issues identified that could limit the generalizability of the study results to the target population in Canada.

Patient disposition: The clinical experts consulted by CDA-AMC felt that the patient disposition of the ARANOTE trial was a reasonable reflection of what would be anticipated for patients in Canada.

Summary of Findings and Certainty of the Evidence

For a tailored review application, CDA-AMC only applies the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach when the sponsor submits direct evidence comparing the drug under review with a relevant comparator. The sponsor has submitted an indirect comparison to support

the comparative effectiveness of darolutamide versus the appropriate comparators; therefore, the GRADE approach has not been used.

Sponsor's Summary of the Indirect Evidence

Description of Indirect Treatment Comparison

Objectives

The primary objective of the indirect treatment comparison (ITC) is to bridge the evidence gap in comparative effectiveness between darolutamide (DAR) plus ADT and other ARPIs plus ADT in mCSPC. This analysis is particularly relevant in the absence of direct randomized controlled trial (RCT) comparisons between darolutamide plus ADT and the comparators relevant to this analysis.

Study Selection and Review Methods

Briefly, the scope of the indirect treatment comparisons includes:

- **Population:** Adult patients with mCSPC.
- **Comparators:** Relevant treatments included in the ITC are doublet regimens (ARPIs plus ADT): apalutamide (APA), enzalutamide (ENZ) and abiraterone acetate-prednisone (ABI-PRED). As described above, doublet ARPI regimens are the relevant comparators for darolutamide plus ADT (aligned with the approved request for deviation for this review).
- **Outcomes:** The key outcomes assessed in the ITC include PFS, OS, and safety outcomes (grade 3-5 AEs, serious AEs, discontinuation due to AEs). It is noted that ARANOTE was not designed or powered to show statistical significance in OS and median OS was not reached in either treatment arm, hence results for indirect treatment effects in this endpoint should be interpreted taking this into consideration.

Details on study selection criteria and review methods are presented in Appendix 8 of the supplemental materials.

Indirect Treatment Comparison Analysis Methods

A network meta-analysis (NMA) was conducted by Bayer to estimate relative treatment effects across multiple interventions based on available RCT evidence. Considering the relevant comparators (ARPI doublets) for the review of darolutamide plus ADT in mCSPC, the following trials were included in the network: ARANOTE (darolutamide plus ADT vs. ADT), TITAN (apalutamide plus ADT vs. ADT), ARCHES (enzalutamide plus ADT vs. ADT), LATITUDE and STAMPEDE G vs. A (abiraterone acetate-prednisone plus ADT vs. ADT). The NMA was conducted using the Bayesian generalized linear model framework implemented in the OpenBUGS software.[66,67] This method is described in the NICE DSU TSD on evidence synthesis and is the approach recommended by CDA-AMC.[68,69] For OS and PFS, a proportional hazards assumption was made in the NMA conducted. For OS, crossover unadjusted HRs from ARCHES, TITAN and LATITUDE were used - in line with prior published NMAs in mCSPC.[70,71] For ARANOTE, final OS (crossover

unadjusted HR) and safety results reported in the ARANOTE Final OS Summary Results Report were used for the analysis.

The selection between fixed- and random-effects models was guided by the goodness of fit statistics (lower Deviance Information Criterion [DIC] and residual deviance) and an assessment of heterogeneity. When the DIC values were similar, a fixed-effects model was preferred given the star-shaped network structure in this analysis and considering that random-effects model typically yield wider credible intervals because of the increased uncertainty driven from limited direct evidence and reduced pooling efficiency. When DIC values show a difference, a random-effects model was used. Details on analysis methods for the indirect comparison(s) are presented in Appendix 8 of the supplemental materials. For a full description of the ITC methods and results, please refer to the ARANOTE NMA Report.

Results

Overall, the NMA suggests a comparable efficacy between darolutamide plus ADT and the other ARPI doublet therapies. The safety NMA found that darolutamide plus ADT has at least equivalent safety versus other ARPI doublets (with statistically significant differences in favour of darolutamide plus ADT over selected ARPI doublets for Grade ≥3 AEs and discontinuation due to AEs). These results should be interpreted with caution as sources of heterogeneity were identified.

Summary of Included Studies

A summary of the assessment of homogeneity from the 5 eligible studies is provided in Table 8. The studies were comparable in terms of study design and target populations, despite some heterogeneity. All the studies included a similar definition of castration-sensitive disease: patients who have not been treated with ADT or who received limited ADT, suspended before randomization. In terms of active comparators, all the studies used ADT either biochemical or surgical castration. In terms of baseline characteristics, the studies included participants with similar age and ECOG status. However, other characteristics, such as Gleason score, de novo disease, disease volume, and risk category varied across the studies. ARANOTE, ARCHES and TITAN enrolled all mCSPC patients, while STAMPEDE and LATITUDE only included mCSPC subpopulations (de novo and de novo high-risk mCSPC, respectively). Available outcomes included PFS, OS, and safety. PFS definition was variable, including clinical, biochemical and radiologic progression. OS was reported across all studies using the same definition, despite heterogeneity in follow-up duration. Safety was less frequently and more heterogeneously reported by STAMPEDE and LATITUDE. Based on the comparability of study populations, alignment in key outcome definitions, and the structure of the evidence network, it was feasible to conduct an NMA to estimate the relative efficacy and safety of darolutamide plus ADT compared to other ARPI doublets in mCSPC. The NMA evaluated the exclusion of STAMPEDE from the network in a sensitivity analysis due to the heterogeneity in its trial design, study population and outcome definition (PFS) compared to other trials in the network.

Table 9: Assessment of Homogeneity

Trial Name		ARCHES[55,72]	TITAN[56,61]	LATITUDE[57,73]	STAMPEDE G vs A[74,75]	ARANOTE[53]
Characteristics		**Description and handling of potential effect modifiers**				
ARPI doublet regimen		ENZ + ADT	APA + ADT	ABI-PRED + ADT	ABI-PRED + ADT	DAR + ADT
Study design		RCT, double blind	RCT, double blind	RCT, double blind	RCT, open label	RCT, double blind
Sample size		1150	1052	1199	1003	669
≥8 Gleason score (%)	Treatment	386 (67.2)	351 (66.9)	584 (98.0)	366 (73.0)	311 (69.7)
	Control	373 (64.8)	358 (67.9)	586 (97.0)	377 (75.0)	146 (65.5)
Age (yr), median	Treatment	70	69	68	67	70
	Control	70	68	67	67	70
ECOG status 0, n (%)	Treatment	448 (78.0)	328 (62.5)	NR	376 (75.0)	235 (52.7)
	Control	443 (76.9)	348 (66.0)	NR	371 (74.0)	98 (43.9)
White ethnicity, n (%)	Treatment	466 (81.2)	354 (67.4)	NR	NR	251 (56.3)
	Control	460 (79.9)	365 (69.3)	NR	NR	125 (56.1)
Prior Docetaxel use, n (%)	Treatment	103 (17.9)	58 (11.0)	None	None	None
	Control	102 (17.7)	55 (10.4)			
Median follow-up (months)		OS: 44.6 PFS: 44.6	OS: 44.0 PFS: 44.0	OS: 51.8 PFS: 30.4	OS: 73.2 PFS: 73.2	OS: 31.4 (final) PFS: 25.0
Type of PFS		rPFS	rPFS	rPFS	cPFS, bPFS	rPFS
Multi-arm, multi-stage		No	No	No	Yes	No
Randomization ratio		1:1	1:1	1:1	1:1	2:1

CT = computed tomography; MRI = Magnetic Resonance Imaging; ECOG = Eastern Cooperative Oncology Group; ADT= Androgen-deprivation therapy; RCT = randomized control trial; ENZ = Enzalutamide; APA = Apalutamide; ABI = Abiraterone acetate; DAR = Darolutamide; OS = overall survival; rPFS = radiographic progression-free survival; cPFS = clinical progression-free survival; bPFS = biochemical progression-free survival; RCT = randomized controlled trial; PSA = prostate-specific antigen.

In terms of model selection, the random effects model was selected for PFS, and for all other endpoints analyzed, the fixed effects model was selected. Please refer to Appendix 8 in the supplemental materials for more details.

Efficacy

Table 10: Summary of NMA Results for Efficacy Results, Darolutamide Plus ADT Versus Comparators

Comparator	PFS[a] HR (95% CrI)	OS HR (95% CrI)
ADT	[redacted]	[redacted]
ENZ + ADT	[redacted]	[redacted]
ABI-PRED + ADT	[redacted]	[redacted]
APA + ADT	[redacted]	[redacted]

ABI-PRED = Abiraterone acetate-prednisone; AEs = adverse events; ADT = Androgen-deprivation therapy; APA = Apalutamide; CrI = credible interval; DAR = Darolutamide; ENZ = Enzalutamide; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

Values below 1 favour darolutamide plus ADT.

[a]Random Effects.

PFS

Random-effects results comparing darolutamide plus ADT with other treatments are presented in Table 10, with hazard ratios below 1 favouring darolutamide plus ADT. The results suggest that treatment effects between darolutamide plus ADT and apalutamide, enzalutamide or abiraterone acetate-prednisone plus ADT in mCSPC are comparable. While there are numeric differences, these differences were not statistically significant. The credible intervals of the pairwise comparisons were wide and overlap. When excluding the STAMPEDE trial (sensitivity analysis), the HR was consistent with the base case ([redacted]) for the comparison against abiraterone acetate plus prednisone plus ADT.

OS

Fixed-effects results comparing darolutamide plus ADT with other treatments are presented in Table 10, with hazard ratios below 1 favouring darolutamide plus ADT. Results show no evidence of a difference between darolutamide plus ADT and other comparators. While there were numeric differences, these differences were not statistically significant. As in PFS, the credible intervals of the pairwise comparisons were wide and overlap. When excluding the STAMPEDE trial (sensitivity analysis), HR was consistent with the base case ([redacted]) for the comparison against abiraterone acetate plus prednisone plus ADT.

Harms

The safety NMAs generally favoured darolutamide plus ADT over comparators (Table 11). The results suggest that the incidence rate of grade 3-5 AEs is higher with enzalutamide and abiraterone acetate plus prednisone plus ADT, and discontinuation due to AEs is higher with abiraterone acetate plus prednisone plus ADT and apalutamide plus ADT, compared to darolutamide plus ADT. For the serious AEs (SAEs), darolutamide plus ADT showed a lower incidence rate when compared to abiraterone acetate plus

prednisone plus ADT and apalutamide plus ADT, although this difference was not statistically significant. When the STAMPEDE trial was excluded, the rate ratio (RR) remained consistent with the base case for the comparison of AE grades 3-5 between abiraterone acetate plus prednisone plus ADT ( ), supporting the comparative favourability of darolutamide plus ADT in grade 3-5 AEs. For the other safety outcomes, the STAMPEDE trial did not provide data.

Table 11: Summary of NMA Results for Harms Results, Darolutamide Plus ADT Versus Comparators

Comparator	AEs 3-5 RR (95% CrI)	SAEs RR (95% CrI)	Discontinuation due to AEs RR (95% CrI)
ADT			
ENZ + ADT			
ABI + ADT			
APA + ADT			

ABI-PRED = Abiraterone acetate-prednisone; AEs = adverse events; ADT = Androgen-deprivation therapy; APA = Apalutamide; CrI = credible interval; DAR = Darolutamide; ENZ = Enzalutamide; OS = overall survival; PFS = progression-free survival; RR = rate ratio; SAEs = serious adverse events.

Values above 1 favour darolutamide plus ADT.

CDA-AMC Critical Appraisal of the Indirect Evidence

The contents of this section were prepared by the review team based on the sponsor's summary of the systematic review evidence and other material submitted by the sponsor.

Critical Appraisal

Study Selection Methods

The sponsor-submitted NMA was informed by a global systematic literature review that included planned searches of multiple databases. The inclusion of studies was based on prespecified eligibility criteria (i.e., population, intervention, comparators, outcomes, and study designs [PICOS]). CDA-AMC is not aware of any relevant studies that were excluded from the systematic literature review. The sponsor did not report on the quality (risk of bias) of the clinical studies included in the NMA; however, these were phase III RCTs, and the risk of bias is expected to be lower for objective outcomes such as rPFS and OS. The eligibility criteria used for study selection were appropriate and reflect the relevant comparators for the Canadian context.

Analyses Methods

Feasibility assessment: The sponsor conducted a feasibility assessment to evaluate heterogeneity based on study design, target populations, and baseline characteristics, including age and ECOG PS. The sponsor noted that heterogeneity across baseline Gleason score, de novo disease, disease volume, and

risk category varied across the studies. In addition, while the ARANOTE, ARCHES, and TITAN trials enrolled all patients with mCSPC, the STAMPEDE and LATITUDE trials only included an mCSPC subpopulations (patients with de novo disease and patients with de novo disease who are considered high risk, respectively). The sponsor did not exclude any studies based on heterogeneity from the reference case but conducted sensitivity analysis removing the STAMPEDE trial due to differences with the patient population and outcomes reported (cPFS and bPFS).

Model fit: Base-case analyses were conducted using fixed-effects models based on the lowest DIC. While DIC is an important consideration in choosing between fixed- and random-effects models, other factors, like network geometry and number of nodes and studies included, should be considered. In this NMA, the star shape with 4 nodes and mostly 1 RCT per node could support use of a fixed-effects model to avoid model instability and potentially biased results from random-effects models in such circumstances. However, the use of a fixed-effects model implies that there is no between-study heterogeneity and that effect modifiers are evenly distributed across all of the studies in the analysis. It does not appear that these assumptions were corroborated by other empirical evidence or expert opinion; thus, it is uncertain if fixed-effects models were truly most appropriate. Regardless, sensitivity analyses using random-effects models with varying alternative prior distributions were conducted, for which the results were consistent with the base case, though point estimates were associated with wide credible intervals, highlighting the uncertainty in the results.

Proportional hazards: The sponsor acknowledged that the primary limitation of their NMA models for rPFS and OS was that the HRs are assumed to be constant, which relies on the proportional hazard assumption. However, no formal testing (e.g., Schoenfeld residuals, time-varying covariates) was conducted to assess this assumption. As noted in the critical appraisal section for the ARANOTE trial, visual inspection of the Kaplan-Meir curves for the analyses of OS suggest that the proportional hazards assumption may have been violated, which would likely bias HR estimates and affect the validity of the NMA results for this outcome.

Imprecise estimates of effect: The credible intervals were wide for all of the NMAs comparing darolutamide plus ADT against the other ARPI regimens, suggesting imprecision and limited statistical power to accurately quantify potential differences between the treatments. This is an important limitation that limits the ability to interpret the results of the NMA.

Study Characteristics

The ARANOTE (darolutamide plus ADT), ARCHES (enzalutamide plus ADT), TITAN (apalutamide plus ADT), and LATITUDE (abiraterone acetate plus prednisone plus ADT) trials were generally similar in their overall design (i.e., phase III, double-blind, placebo-controlled trials). The STAMPEDE trial (abiraterone acetate plus prednisone plus ADT) had a different design with the treatments being administered in an open-label manner.

Patient Characteristics

There was some heterogeneity across the trials' patient populations with respect to disease status, with the ARANOTE, ARCHES, and TITAN trials enrolling patients with mCSPC, the LATITUDE trial only enrolling patients with de novo high-risk mCSPC, and the STAMPEDE trial enrolling patients with de novo, locally

advanced, and metastatic prostate cancer (the sponsor only extracted the subgroup of patients with de novo mCSPC for the NMA). The sponsor noted that there was variability in the proportion of patients with bone metastases at baseline, with approximately 77% of patients having bone metastases in the ARANOTE trial, and ranging from 47% to 100% in the other trials. All of the trials were multinational, but the ARANOTE trial included very few patients from North America (n = 2). The clinical experts considered the results of the ARANOTE trial to be generalizable to the target population in Canada for rPFS; though the differences in geographical region remain an area of heterogeneity in the NMA that could not be investigated through sensitivity analyses.

End Points

The efficacy outcomes included in the NMA were relevant to the treatment of mCSPC (i.e., PFS and OS). No outcomes related to HRQoL were evaluated, but several safety end points were included (AEs, SAEs, and withdrawals due to AEs [WDAEs]).

rPFS: The ARANOTE, ARCHES, TITAN, and LATITUDE trials examined rPFS as the primary end point (with a similar definition). In contrast, the primary end point for the STAMPEDE trial was failure-free survival (defined as the time from randomization to the first of biochemical, lymph node, distant metastatic progression, or prostate cancer death). A sensitivity analysis was performed by removing the STAMPEDE trial and the results were similar to the reference case (i.e., HR = [redacted] for darolutamide plus ADT versus abiraterone acetate plus prednisone plus ADT). The estimates of effect from the NMA for rPFS were limited by imprecision (i.e., wide credible intervals), making it challenging to evaluate if there are meaningful differences across the different ARPI plus ADT regimens. Unlike the indirect comparisons for OS, AEs, SAEs, and WDAEs, CDA-AMC did not identify clear sources of heterogeneity across the studies that would likely bias the NMA results for rPFS in favour or against darolutamide plus ADT.

OS: Median follow-up was considerably shorter in the ARANOTE trial (31.4 months) in comparison with all the other studies (range, 44.0 months to 51.8 months). Similarly, at the time of the OS analysis, deaths in the placebo group were lower in the ARANOTE trial (26.9%) than in all other trials included in the NMA (35.1% in the ARCHES trial, 44.6% in the TITAN trial, 57% in the LATITUDE trial). The shorter duration of follow-up and lower OS events in the placebo arm could bias the ITC against darolutamide plus ADT in comparison with the other treatments.

AEs and SAEs: The overall exposure to the drug — and time for AEs and SAEs to be accrued — in the ARANOTE trial was at least 1 year less than the TITAN and ARCHES trials (44.0 and 44.6 months, respectively) and 20 months less than the LATITUDE trial (51.8 months). As patients with metastatic disease would likely experience more AEs as the disease progresses, the indirect comparisons with the other treatments may be biased in favour of darolutamide plus ADT.

WDAEs: Although overall exposure to the drug — and time for WDAE events to occur — was reduced in the ARANOTE trial compared with the other studies, the clinical experts consulted by CDA-AMC noted that discontinuations from ARPIs as a result of tolerability issues would typically begin shortly after treatment initiation. As such, the differential duration of follow-up across the trials was not perceived as being a major source of potential bias for this end point. However, the results remain highly uncertain given the absence

of information submitted regarding the timing of these events across the different trials, the wide credible intervals for the indirect estimates of effect, and the potential variation across trials with respect to definition and documentation of withdrawal status.

CDA-AMC Clinical Review Discussion and Conclusion

The contents of this section were prepared by CDA-AMC based on the preceding sections.

Discussion

Efficacy

The clinical experts consulted by CDA-AMC noted that the results from the ARANOTE trial suggested that darolutamide plus ADT resulted in clinically meaningful improvements in rPFS, time to mCRPC, and time to pain progression. The sponsor reported that the ARANOTE trial was not designed or statistically powered to demonstrate an improvement in OS versus placebo plus ADT and no statistically significant difference between darolutamide plus ADT and placebo plus ADT was demonstrated in the interim or final analyses of OS. Given that ARPI plus ADT doublet regimens are considered the current standard of care in Canada for most patients, the experts were not concerned that the ARANOTE trial was not designed to show a different in OS versus ADT plus placebo. They noted that, although OS is the preferred end point, rPFS represents a clinically important outcome because of the increased morbidity and mortality associated with more advanced stages of prostate cancer than mCSPC. Overall, there was consensus across the clinical experts consulted by CDA-AMC, the clinician groups that provided input, and regulatory authorities that rPFS is a reasonable surrogate end point for mCSPC. In addition, a recent meta-analysis of 31 clinical trials also supported rPFS as a valid surrogate end point for OS in mCSPC.[76] Overall, the clinicians who provided input felt that the improvements in the rPFS surrogate end point were sufficient to conclude that darolutamide plus ADT was efficacious for the treatment of mCSPC as a doublet regimen. This is similar to the input that was received from clinician groups, which noted that the data from the ARANOTE trial suggested a class-level effect for the ARPI plus ADT doublet regimens.

Although the ARANOTE trial was conducted almost exclusively in centres outside of North American, the clinical experts noted that the results should be generalizable to Canada. The clinical experts noted that the use of placebo plus ADT as a comparator likely limited the ability and willingness of centres in North America to participate as doublet therapy was beginning to be viewed as the standard therapy for patients with mCSPC and there would likely have been concerns regarding clinical equipoise in the treatment groups.

The sponsor submitted an NMA comparing darolutamide plus ADT versus other ARPI plus ADT doublet regimens (i.e., enzalutamide plus ADT, apalutamide plus ADT, abiraterone acetate plus prednisone plus ADT). The sponsor reported that the results showed no evidence of differences across treatments for rPFS and OS. The estimates of effect from the sponsor's NMA for rPFS were limited by imprecision (i.e., wide credible intervals), making it challenging to evaluate if there are meaningful differences across the different ARPI plus ADT regimens for rPFS. The sponsor's ITC for OS had too many limitations to draw conclusions

(most notably the fact that the ARANOTE trial was not designed to detect differences in OS; hence, the duration of follow-up and number of deaths were far lower than in the trials for the comparators).

In June 2025, the US FDA issued approval for the indication of this review based on the ARANOTE trial, and the European Medicines Agency's Committee for Medicinal Products for Human Use adopted a positive opinion to expand the label to include the new indication. Health Canada was still reviewing the file at the time of this review. The Australian Pharmaceutical Benefits Advisory Committee recommended reimbursement for darolutamide plus ADT for mCSPC in 2023 while reviewing the triplet regimen of darolutamide, ADT, and docetaxel for mCSPC. Although, no data for the doublet regimen were reviewed, the Australian Pharmaceutical Benefits Advisory Committee recommended coverage. The rationale for the decision was that darolutamide has the same mechanism of action as apalutamide and as darolutamide and apalutamide were considered noninferior in nmCRPC, they concluded there was not likely to be a clinically meaningful difference in efficacy between the drugs and recommended that darolutamide could be used in combination with ADT (doublet therapy) or in combination with ADT and docetaxel (triplet therapy) in patients with mCSPC.

Harms

The product monograph for darolutamide includes warnings regarding a risk of ischemic heart disease, drug-induced liver injury, and seizures. The product monograph recommends that patients be monitored for signs and symptoms of ischemic heart disease, that the management of cardiovascular risk factors (e.g., hypertension, diabetes, or dyslipidemia) be optimized, that serum transaminases and bilirubin be measured as clinically indicated, and that health care professionals consider withholding darolutamide if the patient experiences a seizure.

The clinical experts consulted by CDA-AMC and the clinician groups that provided input all noted that the AE profile of darolutamide may offer advantages in comparison with the existing doublet regimens, most notably for patients who are considered to be at risk for CNS AEs (e.g., the product monograph for enzalutamide [Xtandi] contains a backbox warning regarding the risk of neurologic AEs) and for those receiving polypharmacy where the use of the alternative ARPIs may be associated with important DDIs. It was noted that the DDIs for existing ARPIs can be significant and can require health teams to coordinate changing other medications (e.g., cardiology medications) to provide the ARPI plus ADT regimen. As such, the addition of darolutamide plus ADT would be valued by clinicians and patients as it may be a preferred option for patients considered to be at risk of AEs with the existing alternative regimens and those receiving medications that have known DDIs with the alternative ARPIs. The clinical experts consulted by CDA-AMC noted that the AE profile for darolutamide could increase the number of patients who may be eligible for ARPI plus ADT treatment in Canada.

The clinical experts consulted by CDA-AMC noted that laboratory monitoring for patients receiving darolutamide plus ADT would generally be similar to the other doublet regimens, which would likely be less overall testing than currently required for those receiving abiraterone acetate plus prednisone plus ADT (e.g., the product monograph for abiraterone acetate recommends monthly monitoring of blood pressure, serum potassium, and fluid retention).

The sponsor submitted an ITC comparing darolutamide plus ADT against the other doublet regimens for grade 3 to 5 AEs, SAEs, and discontinuations due to AEs. The sponsor claimed that the ITCs suggest that darolutamide plus ADT is associated with fewer grade 3 to 5 AEs compared with enzalutamide plus ADT (rate ratio = [redacted]) and abiraterone acetate plus prednisone plus ADT (rate ratio = [redacted]). The ITC for SAEs showed overlapping and wide credible intervals for all comparisons, suggesting considerable uncertainty and imprecision with the estimates of effect. CDA-AMC concluded that the results of the ITCs for grade 3 to 5 AEs and SAEs cannot be interpreted as the median time for AEs to be accrued in the ARANOTE trial was at least 1 year less than the TITAN and ARCHES trials (44.0 and 44.6 months, respectively) and 20 months less than the LATITUDE trial (51.8 months), limiting the time at risk for AE accrual. As patients with metastatic disease would likely experience more AEs over time and, especially as the disease progresses, this difference between trials in median follow-up may introduce bias in favour of darolutamide plus ADT. Furthermore, although the ITCs adjust for differences in follow-up duration (by modelling total number of events over treatment exposure), this adjustment may not account for event rates that increase over time, and the wide, overlapping credible intervals for SAEs indicate substantial uncertainty in the ITC results. Given these limitations, in addition to the limitations identified with the efficacy comparisons, the results of the ITCs cannot be reliably interpreted. The clinical experts agreed that the ITCs for analyses for AEs and SAEs may be biased in favour of darolutamide plus ADT.

The sponsor's ITC also reported that darolutamide plus ADT was associated with a reduced risk of WDAEs compared with apalutamide plus ADT (rate ratio = [redacted]) and abiraterone acetate plus prednisone plus ADT (rate ratio = [redacted]), with the lower bound of the credible interval estimate for enzalutamide plus ADT just below the null (rate ratio = [redacted]). The clinical experts consulted by CDA-AMC noted that WDAEs typically occur shortly after the initiation therapy; therefore, the shorter duration of follow-up in the ARANOTE trial may not be a serious limitation for the submitted ITC for this particular end point. However, not all discontinuations occur early, and the ITC did not appear to adjust for differences in treatment exposure or follow-up duration, which may bias the results in favour of darolutamide. Overall, based on these limitations, in addition to the previously mentioned ones related to the ITCs, CDA-AMC considered the results to be associated with too much uncertainty to quantify any potential improvements in WDAEs with darolutamide plus ADT compared with the alternative regimens. In addition, as the sponsor has submitted the application through the CDA-AMC PACES process, the comparative cost-effectiveness of darolutamide plus ADT versus the alternative doublet regimens has not been evaluated. In accordance with CDA-AMC reimbursement review procedures, a recommendation in favour of reimbursement would include a pricing condition that the total cost of the drug under review should not exceed the total cost of the appropriate comparators (i.e., no pricing premium is considered through the PACES process).

Conclusion

Evidence from a pivotal phase III clinical trial demonstrated that darolutamide plus ADT resulted in clinically meaningful improvements compared with placebo in outcomes that are relevant for the management of mCSPC, including rPFS and time to mCRPC. The estimates of effect from the sponsor's NMA for rPFS were

limited by imprecision (i.e., wide credible intervals), making it challenging to evaluate if there are meaningful differences across the different ARPI plus ADT regimens (i.e., enzalutamide plus ADT, apalutamide plus ADT, and abiraterone acetate plus prednisone plus ADT). The clinical experts consulted by CDA-AMC and the clinician groups that provided input noted that rPFS is an appropriate surrogate end point for OS for patients with mCSPC and that the results for rPFS suggest that improvements in OS would likely be similar across the different ARPI plus ADT regimens. Overall, the available evidence and input suggest that darolutamide plus ADT may be associated with similar clinical benefit as the other available ARPI plus ADT regimens.

The clinical experts emphasized that darolutamide plus ADT is expected to have similar clinical efficacy to the existing alternative ARPI plus ADT regimens (i.e., consistent with the sponsor's claim of no added clinical benefit). The clinical experts and clinician groups noted that reimbursement of darolutamide plus ADT would be beneficial as the potential for fewer AEs could help ease the treatment burden for patients who are experiencing challenging or intolerable side effects with the alternative ARPI plus ADT regimens. In addition, reimbursement may ease the burden on clinicians when managing patients who are at risk of DDIs with the alternative regimens.

CDA-AMC Pharmacoeconomic Evaluation

The objective of the economic review undertaken by CDA-AMC is to review and critically appraise the submitted cost information and budget impact of darolutamide in combination with ADT compared to other relevant treatment regimens for mCSPC. This review was summited via the PACES tailored review pathway; as such, the economic information provided within this report is limited to cost tables and budget impact.

Summary of the Submitted Cost Information

The sponsor submitted a cost-minimization analysis for darolutamide plus ADT compared with apalutamide plus ADT, enzalutamide plus ADT, and abiraterone plus prednisone plus ADT.[77] The costs included a comparison of the drug acquisition costs, calculated by the sponsor using the submitted price for darolutamide and publicly available list prices for other drugs. Health care costs were assumed by the sponsor to be equivalent for darolutamide plus ADT and its comparators and were not included in their submission.

The sponsor reported a drug cost of $3,174.53 per 28-day cycle for darolutamide based on a unit price of $28.34 per tablet (darolutamide plus ADT: $3,427 to $3,664 per 28-day cycle). Drug costs for the comparators ranged from $1,111 to $3,947 per 28-day cycle.

CDA-AMC Cost Comparison

Based on the publicly available list prices of all comparators and the sponsor's submitted price of darolutamide, reimbursement of darolutamide for use in combination with ADT is expected to be associated with lower drug costs to the health care system than apalutamide plus ADT and enzalutamide plus ADT (incremental savings: $95 to $313 per 28-day cycle) and higher costs than abiraterone plus ADT and prednisone (incremental costs: $2,568 to 2,744 per 28-day cycle) (Table 12).

Table 12: CDA-AMC Cost Comparison Table

Treatment	Strength and/or concentration	Form	Price ($)	Recommended dosage	Per 28-day cycle[a] drug cost ($)	Difference in 28-day cycle drug[a] cost vs. darolutamide plus ADT ($)
Darolutamide (Nubeqa)	300 mg	Tablet	28.3440[a]	600 mg twice daily	3,175	—
Darolutamide plus ADT	—	—	—	—	3,427 to 3,603[b]	Reference
Apalutamide plus ADT						
Apalutamide (Erleada)	240 mg	Tablet	124.5600[c]	240 mg once daily	3,488	—
Apalutamide plus ADT	—	—	—	—	3,740 to 3,916[b]	313
Enzalutamide plus ADT						
Enzalutamide (Xtandi)	40 mg	Capsule	29.1954[c]	160 mg daily	3,270	—
Enzalutamide plus ADT	—	—	—	—	3,522 to 3,698[b]	95
Abiraterone plus prednisone						
Abiraterone (generics)	250 mg, 500 mg	Tablet	7.6563 15.3125	1,000 mg daily	858	—
Prednisone (generics)	5 mg	Tablet	0.0220	5 mg daily	0.62	—
Abiraterone plus prednisone	—	—	—	—	859	–2,568 to –2,744

ADT = androgen deprivation therapy; CDA-AMC = Canada's Drug Agency; vs. = versus.

Notes: Prices are from the Ontario Drug Benefit Formulary (accessed June 2025) unless otherwise indicated and do not include dispensing fees. A year was assumed to last 365 days, and a month was assumed to be 30.42 (365/12) days. Dosage intervals were as specified in the Health Canada product monograph (e.g., 3 months was assumed to be 91.25 days ([365/12] x 3).

[a]Sponsor's submitted price.

[b]The cost of ADTs is provided in Table 2 of the Supplemental Materials document.

[c]Ontario Exceptional Access (June 2025).

Summary of the Budget Impact

The sponsor submitted a budget impact analysis to estimate the 3-year (2026 to 2028) budget impact of reimbursing darolutamide plus ADT for the treatment of mCSPC.[78] The sponsor assumed that the payer would be CDA-AMC–participating public drug plans and derived the size of the eligible population using an epidemiologic approach. The price of darolutamide plus ADT was aligned with the price included in the sponsor's economic evaluation, while the prices of comparators were based on the publicly available list prices. Additional information pertaining to the sponsor's submission is provided in Appendix 11 of the Supplemental Materials document. CDA-AMC identified a number of issues with the sponsor's estimated budget impact and made changes to the model parameters and assumptions in consultation with the clinical experts to derive the CDA-AMC base case (refer to the Supplemental Materials document). CDA-AMC estimated that 319 patients will initiate treatment with darolutamide plus ADT in year 1, 653 patients will initiate this regimen in year 2, and 834 patients will initiate this regimen in year 3. The estimated incremental budget impact of reimbursing darolutamide (for use in combination with ADT) is expected to be approximately $8 million over the first 3 years (expenditure on darolutamide plus ADT: $73,071,529). The actual budget impact of reimbursing darolutamide will depend on the number of people eligible for treatment, the market uptake of darolutamide plus ADT, the displacement of each comparator, and the confidentially negotiated drug prices.

Conclusion

- At the submitted price of $28.34 per tablet, the 28-day cycle of darolutamide is expected to be $3,175 per patient, based on the Health Canada–recommended dosage. When used in combination with ADT, the per-cycle cost is expected to be $3,427 to $3,603 per patient.
- Using the sponsor's submitted price for darolutamide and publicly available list prices for all other drugs, the 28-day cost of darolutamide plus ADT is expected to be lower than the cost of apalutamide plus ADT and enzalutamide plus ADT and higher than the cost of abiraterone plus prednisone plus ADT.
- CDA-AMC estimates that the budget impact of reimbursing darolutamide for use in combination with ADT for the treatment of mCSPC will be approximately $8 million over the first 3 years of reimbursement compared to the amount currently spent on comparators. The actual budget impact of reimbursing darolutamide will depend on the number of people eligible for treatment, the market uptake of darolutamide plus ADT, the displacement of each comparator, and the confidentially negotiated drug prices.

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