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## Reimbursement Recommendation

# Darolutamide (Nubeqa)

**Indication:** In combination with androgen deprivation therapy for the treatment of metastatic castration-sensitive prostate cancer

**Sponsor:** Bayer Inc.

**Recommendation:** Reimburse with conditions

# Summary

## What Is the Reimbursement Recommendation for Nubeqa?

Canada's Drug Agency (CDA-AMC) recommends that Nubeqa be reimbursed by public drug plans for use in combination with androgen deprivation therapy (ADT) for the treatment of metastatic castration-sensitive prostate cancer (mCSPC) if certain conditions are met.

## Why Did CDA-AMC Recommend Reimbursement?

A subcommittee of the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) determined that Nubeqa plus ADT demonstrates acceptable clinical value versus other androgen receptor pathway inhibitors (ARPIs) plus ADT in patients with mCSPC. This determination was sufficient for the pERC subcommittee to recommend that Nubeqa plus ADT be reimbursed.

Given that Nubeqa is expected to be an alternative to other ARPI plus ADT regimens, acceptable clinical value refers to at least comparable value versus apalutamide plus ADT, enzalutamide plus ADT, and abiraterone acetate and prednisone plus ADT. Evidence from a pivotal phase III clinical trial demonstrated that darolutamide plus ADT resulted in clinically meaningful improvements compared with placebo plus ADT in outcomes that are relevant for the management of mCSPC, including time to progression to more advance disease. Although limited by imprecision, evidence from an indirect comparison suggested similar effects for darolutamide plus ADT versus the other ARPI plus ADT regimens.

## Which Patients Are Eligible for Coverage?

Nubeqa should only be covered for patients who currently meet the eligibility criteria used by each of the public drug plans for the other ARPI plus ADT regimens used in the treatment of mCSPC.

## What Are the Conditions for Reimbursement?

Nubeqa should only be reimbursed in accordance with the criteria used by each of the participating drug programs for other ARPI plus ADT regimens and if the drug program cost of Nubeqa does not exceed that of the least costly ARPI plus ADT regimen for the treatment of mCSPC.

## Review Background

- **Disease background:** Metastatic prostate cancer is prostate cancer that has spread to other parts of the body. mCSPC refers to metastatic prostate cancer that responds to treatment that lowers testosterone levels in the body. Patients with mCSPC often have pain due to cancer spreading to the bones. The Canadian Cancer Society estimated that 27,900 people would be diagnosed with prostate cancer in 2024.
- **Indication and reimbursement request:** Darolutamide has been approved by Health Canada for use in combination with ADT for the treatment of mCSPC. The sponsor is seeking reimbursement with conditions similar to those for apalutamide plus ADT and enzalutamide plus ADT, which have been previously reviewed and recommended for reimbursement by CDA-AMC for mCSPC.
- **Drug under review:** Darolutamide is an androgen receptor pathway inhibitor that is 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.
- **Treatment costs:** At the submitted price of $28.34 per 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 of darolutamide plus ADT is expected to be $3,427 to $3,603 per patient.
- **Tailored review process:** This application was reviewed through the tailored review process. When submitting an application for a tailored review, the sponsor does not claim added clinical benefit with the drug under review compared with the most appropriate comparators, and the sponsor requests alignment in the recommendation with the existing reimbursement criteria for the most appropriate comparators. A subcommittee of the relevant expert committee deliberates and, when there is unanimous agreement, issues the recommendation for tailored review applications. The focus of the subcommittee deliberations is whether the evidence supports that the drug under review demonstrates comparable clinical benefit and harms to 1 or more appropriate comparators, and whether the evidence supports that the drug should be reimbursed in accordance with the existing reimbursement criteria for the most appropriate comparators.

## Highlights From Interested Parties' Input

The patient groups (the Canadian Cancer Society and the Canadian Cancer Survivor Network) noted the following regarding impacts of the disease, unmet needs, and important outcomes:

- The patient groups identified that the symptoms associated with mCSPC had a negative impact on their ability to engage in sexual activity, work, exercise, and 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.

- 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 them to maintain their quality of life.

The clinician groups (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) and the clinical experts consulted by CDA-AMC noted the following regarding unmet needs arising from the disease and place in therapy for the drug under review:

- Clinicians and patient groups identified that there is a need for mCSPC therapies that have fewer side effects to provide options for patients who are ineligible or intolerant to the existing ARPI plus ADT regimens. The benefit associated with ADT plus ARPIs 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 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 darolutamide plus ADT reimbursement would be beneficial as the potential for fewer adverse events (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 drug-drug interactions with the alternative regimens.

The participating public drug programs raised potential implementation issues related to considerations for initiation, generalizability of trial populations to broader populations, care provision issues, and the potential need for a provisional funding algorithm.

## Recommendation

The pERC subcommittee recommends that darolutamide be reimbursed for use in combination with ADT for the treatment of mCSPC only if the conditions listed in Table 1 are met.

### Table 1: Reimbursement Conditions and Reasons

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Initiation** | | |
| 1. Eligibility for darolutamide + ADT should be based on the criteria used by each of the public drug plans for the reimbursement of other ARPI + ADT regimens for the treatment of mCSPC. | There is insufficient evidence that darolutamide + ADT is clinically superior or inferior to the other ARPI + ADT regimens currently reimbursed for mCSPC. | **Existing criteria:** The reimbursement criteria for an ARPI + ADT may vary across participating drug programs, but are summarized as 1 of the following:<br>• no prior ADT in the metastatic setting<br>• have received ADT for no more than 6 |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| | | months in the metastatic setting<br>• more than 1 year has elapsed since prior ADT for early-stage disease.<br>**Switching ARPIs:** Patients who are currently receiving an alternative ARPI + ADT regimen may switch to darolutamide + ADT if there are concerns about tolerability or toxicity, provided they have not met the discontinuation criterion.<br>**Prior ARPI:** Reimbursement of darolutamide + ADT could be appropriate for those treated with an ARPI in the non-mCSPC setting, and should be authorized in accordance with the reimbursement criteria currently used for other ARPI + ADT regimens. |
| **Discontinuation** | | |
| 2. Discontinuation for darolutamide + ADT should be based on the criteria used by each of the public drug plans for the reimbursement of other ARPI + ADT regimens in the treatment of mCSPC. | The existing discontinuation criteria for ARPI + ADT regimens are appropriate for darolutamide + ADT. | **Existing criteria:** The discontinuation criteria used by the drug programs include:<br>• disease progression based on clinical, PSA, and radiographic factors<br>• unacceptable toxicity. |
| **Prescribing** | | |
| 3. Darolutamide + ADT should be prescribed by clinicians with expertise in managing prostate cancer. | This is meant to ensure that darolutamide is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner. | — |
| 4. Patients receiving darolutamide should also receive ADT (i.e., a gonadotropin-releasing hormone analogue concurrently or have had a bilateral orchiectomy). | This is in accordance with the indication under review. | — |
| **Pricing** | | |
| 5. The drug program cost of darolutamide + ADT should be negotiated so that it does not exceed the drug program cost of treatment with the least costly ARPI + ADT for the same indication. | Based on the subcommittee's assessment of the evidence, darolutamide + ADT is expected to have comparable clinical benefits and harms vs. relevant comparators. Therefore, darolutamide should be priced no more than the least costly ARPI. | Reimbursement of darolutamide + ADT may lead to an expansion in the number of patients who receive ARPI + ADT. Therefore, even if the price of darolutamide + ADT is negotiated to not exceed the drug program cost of treatment with the least costly ARPI, the expenditure on darolutamide may increase the overall budgetary amount spent by the drug plans. Additional price reductions beyond that recommended in the pricing condition may be necessary to avoid increasing the overall budget. |

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; mCSPC = metastatic castration-sensitive prostate cancer; PSA = prostate-specific antigen; vs. = versus.

## Rationale for the Recommendation

The subcommittee deliberated on whether the evidence supports that darolutamide plus ADT demonstrates comparable clinical benefit and harms to 1 or more appropriate comparators in patients with mCSPC.

Based on the totality of the evidence, the subcommittee determined that darolutamide plus ADT demonstrates comparable clinical benefit and harms to other ARPI plus ADT regimens (i.e., apalutamide plus ADT, enzalutamide plus ADT, and abiraterone acetate and prednisone plus ADT) and therefore has acceptable clinical value. Evidence from a pivotal phase III clinical trial demonstrated that darolutamide plus ADT resulted in clinically meaningful improvements compared with placebo plus ADT in outcomes that are relevant for the management of mCSPC, including radiographic progression-free survival (rPFS) and time to metastatic castration-resistant prostate cancer. Although limited by imprecision, evidence from a network meta-analysis suggested similar effects for improving rPFS with darolutamide plus ADT versus the other ARPI plus ADT regimens.

Patients and clinicians identified the need for additional treatment options for patients who experience challenging or intolerable side effects with the alternative ARPI plus ADT regimens and for those who are at risk of drug-drug interactions with the alternative regimens. The subcommittee noted that darolutamide plus ADT has the potential for fewer AEs and fewer drug-drug interactions than the alternative ARPI plus ADT regimens.

Further information on the subcommittee's discussion around clinical value is provided in the Summary of Deliberation section.

The determination of acceptable clinical value was sufficient for the subcommittee to recommend reimbursement of darolutamide. As the subcommittee recommended that darolutamide be reimbursed, it also considered whether reimbursement conditions should be added to address important economic considerations, health system impacts, or social and ethical considerations, or to ensure clinical value is realized. The resulting reimbursement conditions, with accompanying reasons and implementation guidance, are stated in Table 1.

## Summary of Deliberation

The subcommittee considered all domains of value of the deliberative framework before developing its recommendation: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems. For further information on the domains of value, please refer to Expert Committee Deliberation at Canada's Drug Agency.

The subcommittee considered the following key discussion points, organized by the 5 domains of value.

## Clinical Value

- **Appropriate comparators:** Apalutamide plus ADT, enzalutamide plus ADT, and abiraterone acetate and prednisone plus ADT were considered the appropriate comparators.
- **Efficacy versus ADT alone:** One randomized controlled trial (ARANOTE; N = 669) demonstrated that treatment with darolutamide plus ADT resulted in a statistically significant improvement in rPFS (hazard ratio = 0.54; 95% confidence interval, 0.41 to 0.71) compared with ADT alone.
- **Clinical importance of treatment effects**: The subcommittee considered that the treatment effects for rPFS compared with ADT alone were clinically meaningful and aligned with expectations for the ARPI plus ADT regimens used for mCSPC.
- **Efficacy versus other ARPI plus ADT regimens**: The subcommittee noted that 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 and 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 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.
- **AEs:** The subcommittee noted that darolutamide plus ADT has the potential for fewer AEs and fewer drug-drug interactions than the alternative ARPI plus ADT regimens. As such, darolutamide plus ADT could help address some of the unmet needs identified by patients and clinicians.
- **Clinical value:** Based on all the preceding considerations, the subcommittee determined that darolutamide plus ADT demonstrates comparable clinical benefit and harms to other ARPI plus ADT regimens (i.e., apalutamide plus ADT, enzalutamide plus ADT, and abiraterone acetate and prednisone plus ADT).

## Unmet Clinical Need

- **Input on unmet clinical need:** Patients and clinicians identified the need for additional treatment options for patients who experience challenging or intolerable side effects with the alternative ARPI plus ADT regimens and for those who are at risk of drug-drug interactions with the alternative regimens.
- **Deliberation on significant unmet clinical need:** The subcommittee reviewed the considerations for unmet clinical need, and, given that deliberations for tailored reviews have a specific focus, further deliberation on whether there was significant unmet clinical need was not required.

## Distinct Social and Ethical Considerations

- **Deliberation on unmet nonclinical need and health inequity:** The subcommittee reviewed the considerations for unmet nonclinical need and health inequity and did not identify any specific issues that were relevant for darolutamide plus ADT in comparison with the existing ARPI plus ADT regimens. Given that deliberations for tailored reviews have a specific focus, further deliberation on whether the drug under review addresses a significant unmet nonclinical need or health inequity was not required.

## Economic Considerations

- **Cost of darolutamide plus ADT versus an ARPI plus ADT:** At the submitted price of $28.34 per 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 of darolutamide plus ADT is expected to be $3,427 to $3,603 per patient. The 28-day cost of darolutamide plus ADT is expected to be lower than the 28-day cost of apalutamide plus ADT and enzalutamide plus ADT (incremental savings: $95 to $313 per 28-day cycle) and higher than the 28-day cost of abiraterone plus prednisone and ADT (incremental costs: $2,568 to $2,744 per 28-day cycle).
- **Other considerations:** pERC discussed that generic versions of apalutamide and enzalutamide are under review by Health Canada and that reimbursement of these generic products would impact the budgetary impact of reimbursing darolutamide plus ADT.

## Impacts on Health Systems

- **Anticipated budget impact:** CDA-AMC estimates that, over the next 3 years, of the 5,596 patients eligible to receive darolutamide plus ADT, 1,806 patients will receive this regimen. The incremental budget impact of reimbursing darolutamide plus ADT at the submitted price would be $8,447,158 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, market uptake of darolutamide plus ADT, displacement of each comparator, and confidentially negotiated drug prices.

# Sources of Information Used by the Subcommittee

To make its recommendation, the subcommittee considered the following information (links to the full documents for the review can be found on the project webpage):

- the CDA-AMC review of the clinical and pharmacoeconomic evidence submitted by the sponsor (refer to the main report and Supplemental Material document)
- the sponsor's comments on the draft report and the CDA-AMC responses

- patients' perspectives gathered by 2 patient groups, the Canadian Cancer Society and the Canadian Cancer Survivor Network (refer to the Patient and Clinician Group Input document)
- input from 3 clinician groups, 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 (refer to the Patient and Clinician Group Input document)
- input from the public drug programs that participate in the reimbursement review process (refer to the Supplemental Material document)
- input from 2 clinical specialists with expertise in the management of prostate cancer.

# pERC Information

## Members of the Committee

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

A subcommittee composed of 4 pERC members was convened. None had a conflict of interest that precluded their participation.

**Meeting date:** September 3, 2025


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