pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug: Apalutamide (Erleada)

Submitted Funding Request:
In combination with androgen deprivation therapy (ADT) for the treatment of patients with castration-resistant prostate cancer (CRPC) who have no detectable distant metastases by either computed tomography (CT) scan, magnetic resonance imaging (MRI), or technetium-99m bone scan.

Submitted by:
Janssen Inc.

Manufactured by:
Janssen Inc.

NOC Date:
July 3, 2018

Submission Date:
April 16, 2018

Initial Recommendation Issued:
August 30, 2018

Approximate per Patient Drug Costs, per Month (28 Days)	Apalutamide costs:
Submitted list price Apalutamide: $28.34 per 60 mg tablet	$3,174.53 per 28-day cycle

pERC RECOMMENDATION

pERC conditionally recommends reimbursement of apalutamide (Erleada) in combination with ADT for the treatment of patients with CRPC who have no detectable distant metastases by either CT, MRI, or technetium-99m bone scan and who are at high risk of developing metastases only if the following condition is met:

- cost-effectiveness being improved to an acceptable level.

If the aforementioned condition cannot be met, pERC does not recommend reimbursement of apalutamide plus ADT. High risk is defined as a prostate-specific antigen doubling time (PSADT) of ≤ 10 months during continuous ADT. Patients should have good performance status and no risk factors for seizures. Treatment should continue until unacceptable toxicity or radiographic disease progression.

pERC made this recommendation because it was satisfied that compared with ADT monotherapy, there is a net clinical benefit of apalutamide plus ADT based on statistically significant and clinically meaningful improvements in metastasis-free survival (MFS), significant improvements

	in time to symptomatic progression, a manageable toxicity profile, no significant detriment in quality of life (QoL), and a need for treatment options in this population of patients, who are at increased risk for developing metastases. pERC was also satisfied that apalutamide aligns with patient values because of the delay in disease and symptom progression, manageable side effects, an additional treatment choice, and lack of detriment in QoL. pERC concluded that, at the submitted price and with a lack of a statistically significant overall survival (OS) benefit, apalutamide plus ADT is not cost-effective compared with ADT monotherapy. pERC also highlighted that the submitted potential budget impact of apalutamide plus ADT is underestimated.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Decrease Budget Impact** Given that pERC was satisfied that there is a net clinical benefit of apalutamide plus ADT, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of apalutamide plus ADT to an acceptable level. pERC noted that a substantial reduction in the price of apalutamide would be required in order to improve the cost-effectiveness to an acceptable level and to decrease the predicted substantial budget impact. **Generalizability of Results to Patients With Other High Risk Factors** pERC discussed that there is currently insufficient evidence to make an informed recommendation on the use of apalutamide plus ADT in patients with high risk features, other than those defined in the SPARTAN trial. Therefore, the Committee noted that a separate submission to pCODR for apalutamide in patients with high risk features (other than those defined in the SPARTAN trial) would be required. **Sequencing of Treatments for Metastatic Castration-Resistant Prostate Cancer** pERC was unable to make an informed recommendation on the optimal sequencing of treatments for metastatic CRPC after treatment with apalutamide in the non-metastatic setting, noting that there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of apalutamide plus ADT, and noted that a national approach to developing evidence-based clinical practice guidelines addressing sequencing of treatments would be of value. **Time-Limited Need for Apalutamide After Abiraterone/Enzalutamide in Non-Metastatic Castration-Resistant Prostate Cancer** pERC was unable to make an informed recommendation on the use of apalutamide for patients who have been treated with abiraterone, enzalutamide, or other second-generation antiandrogens through a clinical trial or private drug insurance, as there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of apalutamide plus ADT, and noted that a national approach to developing evidence-based clinical practice guidelines addressing this time-limited need would be of value. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

Prostate cancer is the most common cancer diagnosed in Canadian men (excluding non-melanoma skin cancers). The number of new prostate cancer cases in 2017 has been estimated at approximately 22,000, with a 34% annual progression to metastatic castration-resistant prostate cancer (mCRPC) and an overall mortality rate of 16%. This represents a significant patient group with a high risk for progression to metastatic disease. CRPC is defined as disease progression in the setting of castrate testosterone levels. Biochemical progression, as manifested by a rise in prostate-specific antigen (PSA) alone, is often the initial sign of disease progression before developing metastatic disease to bone or visceral organs. No accepted standard treatment options have been defined for patients with non-metastatic castration-resistant prostate cancer (nmCRPC). In the absence of proven treatment options, observation or ADT are often recommended for patients with biochemical-only progression and no evidence of metastases. pERC acknowledged input by registered clinicians for this submission, noting that patients with nmCRPC must progress to having metastatic disease before they are eligible to receive other therapies. pERC agreed with the pCODR Clinical Guidance Panel (CGP) and the registered clinicians providing input that there is a need for new treatment options that delay the development of metastases and disease symptoms.

pERC deliberated on the results of one randomized, placebo-controlled, phase III trial (SPARTAN) that evaluated the efficacy and safety of apalutamide (Erleada) in combination with ADT compared with ADT alone in men with nmCRPC. pERC considered that the results of MFS, the primary outcome of the trial, were statistically significant and clinically meaningful in favour of apalutamide plus ADT. The secondary outcomes — progression-free survival (PFS) and time to symptomatic progression — were also statistically significant in favour of apalutamide. pERC noted that the results for OS (a secondary outcome) are immature at present. In the absence of OS data, pERC discussed the clinical meaningfulness of MFS in the nmCRPC setting. pERC discussed that the transition from nmCRPC to detectable metastatic disease is a clinically relevant event and often heralds the onset of pain and a potential for rapid decline in overall QoL. pERC agreed with the CGP that the improvement in MFS of the magnitude observed in the SPARTAN trial (i.e., approximately a two-year delay in occurrence of metastasis or death), is of clinical importance in a patient population for whom there are currently no standard treatments. pERC noted that further support for the MFS outcome was observed in the prolonged time to symptomatic progression in the apalutamide arm compared with the placebo arm. pERC concluded that, given that patients with nmCRPC are at risk of progressing to metastatic disease within one to two years, a two-year increase in median MFS of apalutamide over placebo is a meaningful outcome in this setting.

pERC deliberated on the toxicity profile of apalutamide in combination with ADT and noted that the incidence and severity of adverse reactions with apalutamide plus ADT were similar to those in the apalutamide plus placebo group. The most frequently reported treatment-emergent adverse events (TEAEs) included fatigue, hypertension, skin rash, diarrhea, falls, fractures, and hypothyroidism. pERC noted that a very small number of patients suffered a seizure during treatment with apalutamide and agreed that apalutamide was contraindicated in patients with risk factors for seizures. pERC discussed that a small increased fracture risk was observed with the use of apalutamide. pERC agreed with the CGP that increased osteopenia can potentially be mitigated with the use of bone-conserving therapies. Overall, pERC agreed with the CGP that apalutamide has a manageable safety profile.

pERC discussed the available patient-reported outcomes data from the SPARTAN trial and noted that the QoL scores showed no clinically meaningful differences between treatment arms in the treatment phase. pERC noted uncertainty in the utility values for the post-progression state. pERC discussed that the utilities from the SPARTAN trial may apply only to the early phase (not the later phases) of the metastatic disease state, as there were only three QoL assessment points during the follow-up phase of the trial, and it is unclear how many patients completed questionnaires at each of these follow-up assessments. The Committee concluded that the SPARTAN trial did not show a negative effect of apalutamide plus ADT on

QoL compared with ADT plus placebo. pERC considered this to be reasonable in the nmCRPC setting, where patients' QoL is expected to be relatively high and stable.

pERC discussed that there is a net clinical benefit to apalutamide plus ADT compared with ADT plus placebo in the treatment of men with nmCRPC. In making this conclusion, pERC considered the clinically meaningful results in MFS as well as time to symptomatic progression, a manageable toxicity profile, no significant detriment in QoL, and a need for treatment options that delay the onset of disease symptoms and metastases.

pERC deliberated upon input from three patient advocacy groups and concluded that apalutamide aligns with patient values. pERC noted that, according to patients, key symptoms of concern among patients with nmCRPC are sexual dysfunction/impotence/loss of sexual activity and intimacy, urinary incontinence, fatigue, depression, stress, and anxiety. Although few patients had direct experience using apalutamide, patients indicated that side effects were minimal and manageable and that the benefits of apalutamide outweighed the risk of the side effects, which aligned with the results of the SPARTAN trial. pERC considered that patients value having access to effective treatment options that delay disease and symptom progression, have manageable side effects, provide additional treatment choice, and improve QoL. In addition pERC commented on the ease of taking apalutamide orally at home. As a result, the Committee concluded that apalutamide aligned with patient values.

pERC deliberated upon the cost-effectiveness of apalutamide plus ADT in men with nmCRPC and concluded that at the submitted price, apalutamide is not cost-effective when compared with ADT monotherapy. pERC noted that the submitter's base-case incremental cost-effectiveness ratio (ICER) was lower than the pCODR Economic Guidance Panel's (EGP's) reanalyzed ICER. The Committee noted that the EGP made the following changes to the model to address some of its limitations:

- Shorter time horizon to address the uncertainty in survival estimates based on extrapolation of short-term trial data;
- Equal treatment compliance for all drugs, as CGP indicated that this would more closely reflect the real-world setting; and
- Choosing the Gamma instead of the Weibull parametric curve for the time to treatment discontinuation to produce a better fit with trial data.

In addition, pERC noted that the factors that most influence the incremental effectiveness of apalutamide plus ADT compared with ADT monotherapy include the duration of treatment effect, the time horizon, and the source of utilities. The key cost drivers are the time-to-treatment-discontinuation curve and the duration of treatment effect. Furthermore, pERC discussed the following main limitations of the submitted economic analyses:

- Lack of statistically significant OS data from the SPARTAN trial: pERC noted that an OS benefit of apalutamide could not be readily assumed given that the surrogacy of MFS for OS has not been established and that OS data observed in the SPARTAN trial were immature. pERC concluded that incorporating OS extrapolation likely overestimated the incremental effectiveness gains and that the ICER was likely underestimated.
- Structural uncertainty of the submitted model: There was a variance of up to 3% in the mean ICER when running the probabilistic analyses at 5,000 iterations. pERC agreed with the EGP that this variance may originate from the large variability in the incremental gains in quality-adjusted life-years (QALYs) in the submitted base case (with the 95% confidence interval [CI] extending into negative numbers). pERC concluded that this structural limitation increased the uncertainty in the cost-effectiveness estimates.
- Uncertainty in the utility values for the post-progression state: pERC discussed that the utilities from the SPARTAN trial seemed relatively high and may only apply to the early phase (not the later phases) of the metastatic disease state, as there were only three QoL assessment points during the follow-up phase of the trial and it is unclear how many patients completed questionnaires at each of these follow-up assessments. In addition, pERC noted that the submitter ran scenario analyses with markedly lower literature based utility values for metastatic disease and that the trial utilities were inconsistent and seemed high in comparison.

Overall, pERC agreed with the EGP's reanalyses and the limitations identified in the submitted economic model. pERC noted that not all limitations noted previously could be addressed by the EGP's scenario analyses, notably the structural uncertainty in the model. pERC concluded that apalutamide with ADT was not cost-effective compared with ADT monotherapy at the submitted price.

pERC considered the feasibility of implementing a reimbursement recommendation for apalutamide in men with nm-CRPC. pERC discussed that the submitted three-year budget impact was underestimated due to the assumption that patients whose disease becomes metastatic would be ineligible to receive APA+ADT or ADT monotherapy during the year in which they progress. pERC discussed that patients who progress to the metastatic state part-way through a year were excluded from the year upfront. For each year, the submitter excludes a certain proportion of patients receiving APA+ADT and ADT monotherapy from the BIA based on the assumption that these patients would be expected to progress to metastatic disease and would therefore be ineligible for treatment in the non-metastatic setting. pERC agreed with the EGP that this assumption underestimated the true budget impact. In reality, patients would be eligible to receive apalutamide for a portion of the year before they progressed to metastatic disease and became ineligible for further apalutamide treatment. pERC acknowledged that, according to the EGP's reanalysis, the submitted incremental three-year budget impact: (1) increased by about 5% if treatment compliance was set as equal for all drugs; and (2) increased by about 160% if the budget impact was estimated for the whole of Canada as opposed to just Ontario, which represents 38.5% of all prostate cancer patients in Canada. In addition, pERC discussed that the number of patients confirmed as being "true" non-metastatic may decrease in the future with newer diagnostic imaging tests. This would affect the budget impact as it would reduce the number of patients eligible for apalutamide. However, pERC noted that at the present time, this is an unknown quantity. The Committee agreed that jurisdictions will need to consider the factors mentioned previously upon implementation, and that the submitted budget impact is underestimated.

pERC discussed PAG's request for guidance on a number of clinical scenarios to assist with implementation.

- pERC discussed that there is currently insufficient evidence to make an informed recommendation on the use of apalutamide plus ADT in patients with high risk features, other than those defined in the SPARTAN trial. Therefore, the Committee noted that a separate submission to pCODR for apalutamide in patients with high risk features (other than those defined in the SPARTAN trial) would be required.
- pERC discussed the optimal sequencing of treatments for metastatic CRPC after treatment with apalutamide in the non-metastatic setting. pERC agreed with the CGP and with the registered clinicians providing input for this submission that adding apalutamide to the available drug options may affect which treatment a patient will receive if they progress to metastatic disease. pERC considered input from the CGP that, based on its clinical expert opinion, treatments belonging to the same drug class would likely not be used in sequence (i.e., apalutamide followed by enzalutamide). However, pERC noted that there is insufficient evidence to inform this clinical situation. As a result, the Committee was unable to make an informed recommendation on the optimal sequencing of treatments for metastatic CRPC after treatment with apalutamide in the non-metastatic setting. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of apalutamide plus ADT, and noted that a national approach to developing evidence-based clinical practice guidelines would be of value.
- pERC was unable to make an informed recommendation on the use of apalutamide for patients who have been treated with abiraterone, enzalutamide, or other second-generation antiandrogens through a clinical trial or private drug insurance, as there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of apalutamide plus ADT, and noted that a national approach to developing evidence-based clinical practice guidelines would be of value.
- pERC agreed with the CGP that the SPARTAN trial results were not generalizable to patients with a PSADT greater than 10 months. pERC noted that there was insufficient evidence to make an informed recommendation on the use of apalutamide plus ADT in this patient group.
- pERC agreed with the CGP that the SPARTAN trial results were generalizable to the following patient populations as long as PSADT ≤ 10 months, during continuous ADT:
  - Patients who had received adjuvant or neoadjuvant chemotherapy
  - Patients who had already started ADT plus an antiandrogen (SPARTAN allowed these patients if there was PSA progression after a four-week washout period)
  - Patients who are undergoing secondary hormonal manipulation (e.g., changing bicalutamide to megestrol acetate, or antiandrogen withdrawal).
- Input from PAG indicated that there are different definitions of CRPC (e.g., the prostate cancer working group [PCWG] definition), some of which may differ slightly from that used in the SPARTAN trial. pCODR agreed with the CGP that the PCWG definition is generally accepted in

clinical practice and that the SPARTAN trial used that definition and then selected the high risk group. Hence, the results of the SPARTAN trial can be generalized to the PCWG definition.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Input from three patient advocacy groups: PROSTAID Calgary, the Canadian Cancer Survivor Network, and the Prostate Cancer Centre
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the efficacy and safety of apalutamide (Erleada) in combination with androgen deprivation therapy (ADT) compared with ADT alone in men with non-metastatic castrate resistant prostate cancer (nmCRPC).

Studies included: One randomized, placebo-controlled, phase III trial

The pCODR systematic review included one randomized, placebo-controlled, phase III trial: SPARTAN. The SPARTAN trial evaluated the efficacy and safety of apalutamide (Erleada) in combination with ADT compared with ADT alone in men with nmCRPC.

A total of 1,207 patients were randomized (2:1) in SPARTAN, with 806 assigned to apalutamide plus ADT and 401 to placebo plus ADT. Patients in the experimental group were treated with oral apalutamide (240 mg once daily as four 60 mg tablets) and continuous ADT with gonadotropin-releasing hormone (GnRH) analogue or surgical castration (bilateral orchiectomy) to maintain castrate concentrations of testosterone (< 50 ng/dL). Patients in the placebo group received continuous ADT and matched placebo tablets. All patients received treatment until documented radiographic progression, withdrawal of consent, or the development of unacceptable toxicity. Dose interruption was permitted. If adverse events (AEs) recurred, the dose could be reduced to 180 mg (three 60 mg tablets) and then to 120 mg (two 60 mg tablets) once daily. Dose re-escalation was not permitted unless discussed with the sponsor. Patients experiencing AEs that could not be managed adequately with dose modifications and patients requiring dose interruptions longer than 28 days could discontinue before study completion if they met the protocol-specified discontinuation criteria.

The median duration of treatment was 16.9 months in the apalutamide arm and 11.2 months in the placebo arm. Eighty-eight per cent of patients in the apalutamide arm and 93% of those in the placebo arm had more than 80% compliance.

To be eligible for inclusion in the trial, patients had to have testosterone levels of less than 50 ng/dL, no evidence of symptomatic local or regional nodal disease, no malignant pelvic lymph nodes > 2 cm in the short axis, no prior treatment with next-generation antiandrogens, and an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. Randomization was stratified by prostate-specific antigen doubling time (PSADT) (> 6 months versus ≤ 6 months), use of bone-sparing drugs (yes versus no), and the presence of loco-regional disease (N0 versus N1).

Patient populations: Median age 74 years, median PSA doubling time at baseline less than five months

SPARTAN included 1,207 men with nmCRPC. The baseline characteristics were well balanced between the study groups. The median age in the intention-to-treat population was 74 years (range: 48 years to 94 years in the apalutamide arm and 52 years to 97 years in the placebo arm). The median prostate-specific antigen (PSA) doubling time at baseline was 4.4 months in the apalutamide arm and 4.5 months in the placebo arm. The median time from initial prostate cancer diagnosis to randomization was 7.95 years in the apalutamide arm and 7.85 years in the placebo arm. About 10% of patients in each arm had a history of treatment with a bone-sparing drug; around 16% of patients in each arm presented with lymph nodes <

2cm. The proportions of patients with a history of any prior therapy were well balanced between the study arms. Overall, 76.6% of patients had prior surgery or radiation therapy; 99.5% had received prior hormonal therapy; and 2% had a history of chemotherapy.

Key efficacy results: Clinically meaningful improvement in metastasis-free survival in favour of apalutamide

pERC deliberated on the key efficacy outcomes in the SPARTAN trial. The primary outcome of the study was metastasis-free survival (MFS) as assessed by blinded independent central review (BICR). Secondary outcomes included: time to metastasis (as assessed by BICR), progression-free survival (PFS) as assessed by BICR, time to symptomatic progression, overall survival (OS), and time to the initiation of cytotoxic chemotherapy. Exploratory outcomes included time to PSA progression, PSA response rate, quality of life (QoL) outcomes, second PFS, and treatment-emergent adverse events (TEAEs).

The trial met its primary outcome and demonstrated a statistically significant improvement in MFS in the apalutamide plus ADT group after a median follow-up time of 20.3 months; median MFS was 40.5 months in the apalutamide plus ADT arm and was 16.2 months in the placebo plus ADT group (hazard ratio [HR] = 0.28; 95% confidence interval [CI], 0.23 to 0.35; $P < 0.0001$). Distant metastasis or death was observed in 184 patients (22.8%) in the apalutamide arm and 194 patients (48.4%) in the placebo arm. Of the patients who had metastases, 60.5% in the apalutamide arm and 54.4% in the placebo arm were reported to have bone metastases. The MFS benefit was consistent across pre-specified subgroups based on patients' ECOG performance status, age group, geographic region, number of prior hormonal therapies, baseline PSA value, PSA doubling time, bone-sparing drug use, and loco-regional disease.

Time to symptomatic progression was a secondary outcome in the SPARTAN trial. The median time to symptomatic progression was not reached in either of the apalutamide or placebo arms. The stratified HR indicated that apalutamide resulted in a statistically significant decrease in risk of symptomatic progression when compared with placebo (HR = 0.447; 95% CI, 0.315 to 0.634; P <0.0001).

OS was a secondary outcome in the trial and was immature at the median follow-up time of 20.3 months. The median OS was not reached in the apalutamide arm and was 39.0 months in the placebo arm. The stratified HR indicated that OS was not statistically different between the treatment groups (HR = 0.700; 95% CI, 0.472 to 1.038; $P = 0.0742$).

Patient-reported outcomes: No difference between treatment arms

QoL outcomes were collected in SPARTAN. Health-related QoL was assessed using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) (for physical well-being, social/family well-being, emotional well-being, pain, and prostate cancer-specific symptoms) and the EuroQol 5-Dimensions questionnaire (EQ-5D) (for health status, mobility, self-care, usual activity, pain or discomfort, and anxiety and depression). Baseline FACT-P and EQ-5D scores were reported to be comparable between the study arms, although no formal statistical testing was conducted to test potential differences between the study groups at the baseline. No statistically significant differences were reported between the apalutamide and placebo arms in change from baseline in FACT-P or EuroQol Visual Analogue Scale (EQ-VAS) scores during the treatment and follow-up phases. The EQ-5D index scores seemed similar between the study groups; however, no formal statistical testing was performed to confirm this. The compliance rates for completion of both the FACT-P and EQ-5D questionnaires were ≥ 92% (range: 92% to 100%) at any assessment visit during the treatment phase and 63% or greater (range: 63% to 76%) for the "end of treatment" and follow-up visits.

Safety: Manageable toxicity profile, similar between groups

The incidence and severity of adverse reactions with apalutamide plus ADT were similar to those in the apalutamide plus placebo group. TEAEs (any grade) were reported in 96.5% of patients in the apalutamide arm and in 93.2% of those in the placebo arm. The most frequently reported TEAEs included fatigue (30% with apalutamide versus 21% with placebo), hypertension (25% with apalutamide versus 20% with placebo), skin rash (24% with apalutamide versus 5.5% with placebo), diarrhea (20% with apalutamide versus 15% with placebo), falls (16% with apalutamide versus 9% with placebo), fractures (12% with apalutamide versus 6.5% with placebo), and hypothyroidism (2% with apalutamide versus 8% with placebo). The proportion of patients with grade 3 or grade 4 TEAEs was 45.1% in the apalutamide arm and 34.2% in the placebo arm. Mortality due to AEs was reported in 1.2% of patients in the apalutamide arm and in 0.3% of those in the placebo arm; serious TEAEs occurred in 24.8% and 23.1% of patients in the apalutamide and placebo arms, respectively. At a median follow-up time of 20.3 months, 10.36% of

patients in the apalutamide arm and 7.0% of those in the placebo arm had discontinued treatment due to the incidence of AEs.

Most fractures were grade 1 or 2 AEs and did not require surgical intervention. Approximately 10% of patients were receiving bone-sparing drugs for osteoporosis or osteopenia at study entry. In patients who were not receiving a bone-sparing drug at study entry, the incidence of fracture was reported to be 11% (82 out of 722) in the apalutamide arm and 6% (22 out of 359) in the placebo arm. In patients who were receiving a bone-sparing drug at study entry, fractures were reported in 15% of patients (12 out of 81) in the apalutamide arm and in 10% of patients (4 out of 39) in the placebo arm.

A very small number of patients (0.2%) suffered a seizure during treatment with apalutamide.

Need and burden of illness: Need for treatment that delays development of metastases and disease symptoms

Prostate cancer is the most common cancer diagnosed in Canadian men (excluding non-melanoma skin cancers). The number of new prostate cancer cases in 2017 has been estimated at approximately 22,000 men, with a 34% annual progression to metastatic CRPC and an overall mortality rate of 16%. Therefore, a significant patient group is at high risk for progression to metastatic disease. CRPC is defined as disease progression in the setting of castrate testosterone levels. Biochemical progression as manifested by a rising PSA alone is often the initial sign of disease progression before developing metastatic disease to bone or visceral organs. No accepted standard treatment options have been defined for patients with nmCRPC. In the absence of proven treatment options, observation or ADT are often recommended for patients with biochemical-only progression and no evidence of metastases. There is an urgent need for new treatment options that delay the development of metastases and disease symptoms.

Registered clinician input: Need for treatment options

The six registered clinicians providing input all expressed that there is currently no funded standard of care for patients with nmCRPC and that apalutamide does fill an unmet need. It was noted repeatedly that there is a gap in treatment options for patients in this stage of disease because patients must progress to having metastatic disease before they are eligible to receive most treatment options. In terms of sequencing, it was reported by the clinicians that apalutamide would be used in combination with ADT before a patient with nmCRPC has developed metastases. It was noted that adding apalutamide to the available drug options may affect which treatment patients receive if they progress to metastatic disease. There is no diagnostic testing required for this drug.

PATIENT-BASED VALUES

Values of patients with nmCRPC: Improved quality of life, delayed disease progression, improved overall survival

Three patient advocacy groups provided input on the apalutamide (Erleada) submission for the treatment of nmCRPC. Patients expressed a number of negative sentiments about their experiences with prostate cancer. Survey participants perceived the following issues to have a negative impact on their QoL: urinary incontinence, challenges with intimacy and sexual dysfunction, and negative psychological feelings regarding their “manhood.” Survey results suggested that patients felt strongly about being given treatment options other than surgery.

In terms of expectations for alternative treatment options, focus was placed on improving QoL, managing or reducing side effects, delaying disease and symptom progression, and additional treatment choice. Patients reported feeling anxious about whether they would qualify for further treatment and worrying about how prostate cancer might affect their future.

Patient values on treatment: Minimal side effects, benefits outweigh risk of side effects

Respondents who had experience with apalutamide had a positive attitude toward it. They indicated that side effects were minimal and manageable and that the benefits outweighed the risk of side effects.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility and cost-effectiveness analyses

The pCODR Economic Guidance Panel (EGP) assessed one cost-utility analysis (clinical effects measured by quality-adjusted life-years [QALYs] gained) and one cost-effectiveness analysis (clinical effects measured by life-years gained) of apalutamide in combination with ADT compared with ADT monotherapy for the treatment of men with nmCRPC.

Basis of the economic model: Clinical and economic inputs

The key clinical outcomes considered in the cost-utility analysis were MFS and OS and utilities.

Costs considered in the analysis included those related to drug acquisition, disease management, diagnosis of metastasis, end of life, and AEs.

Drug costs: Treatment cost of apalutamide and comparators

Apalutamide costs $0.4724 per mg or $28.34 per 60 mg tablet. At the recommended dose of 240 mg (four 60 mg tablets) administered orally once daily, apalutamide costs $113.38 per day and $3,174.53 per 28-day cycle.

ADTs:

- Leuprolide costs $39.60 per mg tablet. At the recommended dose of 22.5 mg once every three months, leuprolide costs $10.60 per day and $297 per 28-day cycle.
- Bicalutamide costs $1.27 per 50 mg tablet. At the recommended dose of 50 mg once daily, bicalutamide costs $1.27 per day and $35.56 per 28-day cycle.
- Goserelin costs $111.55 per mg. At the recommended dose of one 10.8 mg depot injection administered every 13 weeks, goserelin costs $13.23 per day and $370.69 per 28-day cycle.
- Degarelix costs $3.19 per mg. At the recommended dose of one 10 mg depot injection per month, degarelix costs $9.12 per day and $255.00 per 28-day cycle.

Cost-effectiveness estimates: Not cost-effective at the submitted price

pERC deliberated upon the cost-effectiveness of apalutamide plus ADT in men with nmCRPC and concluded that apalutamide is not cost-effective when compared with ADT monotherapy at the submitted price. pERC noted that the submitter's base-case incremental cost-effectiveness ratio (ICER) was lower than the EGP's reanalyzed ICER. This was primarily due to three factors: (1) shorter time horizon to address the uncertainty in survival estimates based on extrapolation of short-term trial data; (2) equal treatment compliance for all drugs, as CGP indicated that this would more closely reflect real-world use; and (3) choosing the Gamma instead of the Weibull parametric curve for the time to treatment discontinuation to produce a better fit with trial data.

pERC noted that according to the EGP's one-way scenario analyses, the factors that most influence the incremental effectiveness of apalutamide plus ADT compared with ADT monotherapy include the duration of treatment effect, the time horizon, and the source of utilities. The key cost drivers are the time-to-treatment-discontinuation curve and the duration of treatment effect.

Further, the Committee noted the following main limitations of the submitted economic analyses: (1) lack of statistically significant OS data from the SPARTAN trial and the resulting extrapolation of OS using short-term data; (2) structural uncertainty resulting in uncertainty in the ICER estimates; (3) including only one line of subsequent treatment; (4) the fact that disease management costs did not account for the increased number of tests in the apalutamide arm.

Overall, pERC agreed with the EGP's reanalyses and the limitations identified in the submitted economic model. pERC noted that not all limitations noted previously could be addressed by the EGP's scenario analyses, notably the structural uncertainty in the model. pERC concluded that apalutamide with ADT was not cost-effective compared with ADT monotherapy at the submitted price.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact underestimated, exclusion of patients expected to progress to metastatic disease

pERC considered the feasibility of implementing a reimbursement recommendation for apalutamide in men with nmCRPC. pERC discussed that the submitted three-year budget impact was underestimated due to the assumption that patients whose disease becomes metastatic would be ineligible to receive APA+ADT or ADT monotherapy during the year in which they progress. pERC discussed that patients who progress to the metastatic state part-way through a year were excluded from the year upfront. For each year, the submitter excludes a certain proportion of patients receiving APA+ADT and ADT monotherapy from the BIA based on the assumption that these patients would be expected to progress to metastatic disease and would therefore be ineligible for treatment in the non-metastatic setting. pERC agreed with the EGP that this assumption underestimated the true budget impact. In reality, patients would be eligible to receive apalutamide for a portion of the year before they progressed to metastatic disease and became ineligible for further apalutamide treatment. pERC acknowledged that, according to the EGP's reanalysis, the submitted incremental three-year budget impact: (1) increased by about 5% if treatment compliance was set as equal for all drugs; and (2) increased by about 160% if the budget impact was estimated for the whole of Canada as opposed to just Ontario, which represents 38.5% of all prostate cancers patients in Canada. In addition, pERC discussed that the number of patients confirmed as being "true" non-metastatic may decrease in the future with newer diagnostic imaging tests. This would affect the budget impact, as it would reduce the number of patients eligible for apalutamide. However, pERC noted that at the current time, this remains an unknown quantity. The Committee agreed that jurisdictions will need to consider the factors mentioned previously upon implementation, and that the submitted budget impact is underestimated.

pERC discussed PAG's request for guidance on a number of clinical scenarios to assist with implementation.

- pERC discussed that there is currently insufficient evidence to make an informed recommendation on the use of apalutamide plus ADT in patients with high risk features, other than those defined in the SPARTAN trial. Therefore, the Committee noted that a separate submission to pCODR for apalutamide in patients with high risk features (other than those defined in the SPARTAN trial) would be required.
- pERC discussed the optimal sequencing of treatments for metastatic CRPC after treatment with apalutamide in the non-metastatic setting. pERC agreed with the CGP and with the registered clinicians providing input for this submission that adding apalutamide to the available drug options may affect which treatment a patient will receive if they progress to metastatic disease. pERC considered input from the CGP that, based on its clinical expert opinion, treatments belonging to the same drug class would likely not be used in sequence (i.e., apalutamide followed by enzalutamide). However, pERC noted that there is insufficient evidence to inform this clinical situation. As a result, the Committee was unable to make an informed recommendation on the optimal sequencing of treatments for metastatic CRPC after treatment with apalutamide in the non-metastatic setting. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of apalutamide plus ADT, and noted that a national approach to developing evidence-based clinical practice guidelines would be of value.
- pERC was unable to make an informed recommendation on the use of apalutamide for patients who have been treated with abiraterone, enzalutamide, or other second-generation antiandrogens through a clinical trial or private drug insurance, as there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of apalutamide plus ADT, and noted that a national approach to develop evidence-based clinical practice guidelines would be of value.
- pERC agreed with the CGP that the SPARTAN trial results were not generalizable to patients with a PSADT greater than 10 months. pERC noted that there was insufficient evidence to make an informed recommendation on the use of apalutamide plus ADT in this patient group.
- pERC agreed with the CGP that the SPARTAN trial results were generalizable to the following patient populations as long as PSADT ≤ 10 months, during continuous ADT:
  - Patients who had received adjuvant or neoadjuvant chemotherapy
  - Patients who had already started ADT plus an antiandrogen (SPARTAN allowed these patients if there was PSA progression after a four-week wash out period)
  - Patients who are undergoing secondary hormonal manipulation (e.g., changing bicalutamide to megestrol acetate, or antiandrogen withdrawal).

- Input from PAG indicated that there are slightly different definitions of CRPC (e.g., the prostate cancer working group [PCWG] definition), some of which may differ slightly from that used in the SPARTAN trial. pCODR agreed with the CGP that the PCWG definition is generally accepted in clinical practice and that SPARTAN used that definition and then selected the high risk group. Hence, the results of the SPARTAN trial can be generalized to the PCWG definition.

DRUG AND CONDITION INFORMATION

Drug Information	• Apalutamide is a next-generation androgen receptor inhibitor. • Oral apalutamide is administered at a dose of 240 mg once daily (four 60 mg tablets). Apalutamide should be co-administered with continuous androgen deprivation therapy (ADT) with gonadotropin-releasing hormone (GnRH) analogue or surgical castration (bilateral orchiectomy) to maintain castrate concentrations of testosterone (< 50 ng/dL).
Cancer Treated	• Non-metastatic castration-resistant prostate cancer (nmCRPC)
Burden of Illness	• The number of new prostate cancer cases in 2017 has been estimated as approximately 22,000, with a 34% annual progression to metastatic CRPC and an overall mortality rate of 16%. Therefore, it represents a significant patient group with a high risk for progression to metastatic disease.
Current Standard Treatment	• ADT
Limitations of Current Therapy	• Most patients on ADT eventually progress to CRPC.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Christopher Longo, Economist
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

All members participated in deliberations and voting on the Initial Recommendation except:

- Dr. Anil Abraham Joy and Cameron Lane, who were not present for the meeting

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of apalutamide for non-metastatic castration-resistant prostate cancer, through their declarations, none of the members had a real, potential, or perceived conflict. Based on the application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

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APPENDIX 1: pERC RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendations
• PAG is seeking clarity on whether or not the following patients would be eligible for treatment with apalutamide: o Patients with PSA doubling times greater than 10 months o Patients who have received adjuvant or neoadjuvant chemotherapy o Patients who have already started ADT plus an antiandrogen (the trial allowed these patients if there was PSA progression after a four-week wash out period) o Patients who are undergoing secondary hormonal manipulation (e.g., changing bicalutamide to megestrol acetate, or antiandrogen withdrawal)	• SPARTAN required study participants to be at high risk for development of metastases, defined as PSADT≤ 10 months, during continuous ADT. pERC agreed with the CGP that currently there is insufficient evidence to make an informed recommendation on the use of apalutamide plus ADT in patients with PSADT greater than 10 months. • pERC agreed with the CGP that the SPARTAN trial results were generalizable to the following patient populations as long as PSADT≤ 10 months, during continuous ADT: o Patients who have received adjuvant or neoadjuvant chemotherapy o Patients who have already started ADT plus an antiandrogen o Patients who are undergoing secondary hormonal manipulation (e.g., changing bicalutamide to megestrol acetate, or antiandrogen withdrawal)
• PAG is seeking guidance on the definition of castration resistance, as there are different definitions (e.g., the definition offered by the PCWG, which may differ slightly from that used in the SPARTAN trial). For example, in some clinical trials, castration resistance has been defined by a serum PSA greater than 2 ng/mL and rising over one month, although some clinicians may initiate a discussion of treatment modification with a patient as soon as the PSA has risen twofold.	• pCODR agreed with the CGP that the PCWG definition is generally accepted in clinical practice and that SPARTAN used that definition and then selected the high risk group. Hence, the results of the SPARTAN trial can be generalized to the PCWG definition.
• PAG noted that there is potential for indication creep to use apalutamide in high risk patients (e.g., those with a Gleason score of 8 to 10, high PSA at diagnosis, etc.) who have not had a PSA progression in the non-metastatic setting.	• pERC discussed that there is currently insufficient evidence to make an informed recommendation on the use of apalutamide plus ADT in patients with high risk features, other than those defined in the SPARTAN trial. Therefore, the Committee noted that a separate submission to pCODR for apalutamide in patients with high risk features (other than those defined in the SPARTAN trial) would be required.

PAG Implementation Questions	pERC Recommendations
• PAG is seeking information on the appropriate treatment for metastatic disease after treatment with apalutamide in the non-metastatic setting. Treatments available for castration-resistant metastatic disease include abiraterone, enzalutamide, and chemotherapy. PAG noted that apalutamide and enzalutamide are the same class of drug and is seeking information on the use of enzalutamide in the metastatic castration-resistant setting after apalutamide or whether patients previously treated with apalutamide should be treated with abiraterone or chemotherapy in the castration-resistant metastatic setting.	• pERC discussed the optimal sequencing of treatments for metastatic CRPC after treatment with apalutamide in the non-metastatic setting. pERC agreed with the CGP and with the registered clinicians providing input for this submission that adding apalutamide to the available drug options may affect which treatment a patient will receive if they progress to metastatic disease. pERC considered input from the CGP that, based on its clinical expert opinion, treatments belonging to the same drug class would likely not be used in sequence (i.e., apalutamide followed by enzalutamide). However, pERC noted that there is insufficient evidence to inform this clinical situation; as a result, it was unable to make an informed recommendation on the optimal sequencing of treatments for metastatic CRPC after treatment with apalutamide in the non-metastatic setting. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of apalutamide plus ADT, and noted that a national approach to developing evidence-based clinical practice guidelines would be of value.
• PAG identified that there may be a small number of patients who have been treated with abiraterone, enzalutamide, or other second-generation antiandrogens (e.g., through a clinical trial or private drug insurance) for non-metastatic castration-resistant prostate cancer. PAG is seeking guidance on the appropriateness of using apalutamide following abiraterone, enzalutamide, or other second-generation antiandrogens after failure of these drugs in this therapeutic space, should these patients continue to remain non-metastatic.	• pERC was unable to make an informed recommendation on the use of apalutamide for patients who have been treated with abiraterone, enzalutamide, or other second-generation antiandrogens through a clinical trial or private drug insurance, as there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of apalutamide plus ADT, and noted that a national approach to develop evidence-based clinical practice guidelines would be of value.

ADT = androgen deprivation therapy; CGP = Clinical Guidance Panel; CRPC = castration-resistant prostate cancer; PAG = Provincial Advisory Group; pCODR = CADTH pan-Canadian Oncology Drug Review; PCWG = Prostate Cancer Working Group; pERC = CADTH pCODR Expert Review Committee; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time.