pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL 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.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Apalutamide (Erleada) **Submitted Reimbursement Request:** For the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC).	
Submitted By: Janssen Inc.	**Manufactured By:** Janssen Inc.
NOC Date: December 12, 2019	**Submission Date:** October 15, 2019
Initial Recommendation: April 2, 2020	**Final Recommendation:** April 22, 2020

Approximate per Patient Drug Costs	Apalutamide costs $28.35 per 60 mg tablet. At the recommended dose of four capsules per day taken orally (240 mg), apalutamide costs $113.38 per day, $3,175 per 28-day cycle, and $41,384 per year.

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

* If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends funding apalutamide (Erleada) in combination with androgen deprivation therapy (ADT) for patients with mCSPC only if the following condition is met:

- cost-effectiveness improved to an acceptable level.

Patients must be castration sensitive (i.e., no prior ADT or within six months of beginning ADT), with good performance status. Treatment should be continued until unacceptable toxicity or disease progression.

pERC made this recommendation because it was satisfied that apalutamide plus ADT has a net clinical benefit compared with ADT monotherapy based on a statistically significant and clinically meaningful improvement in radiographic progression-free survival (rPFS), an improvement in overall survival (OS), a manageable toxicity profile, no detriment to quality of life (QoL), and a need for less toxic treatment options in this population of patients.

pERC also concluded that apalutamide plus ADT aligns with the following patient values: disease control, no detriment to QoL, and additional treatment choice.

pERC concluded that apalutamide plus ADT was not cost-effective at the submitted price versus available comparators in Canada and that a reduction in drug price would be required to improve its cost-effectiveness to an acceptable level. pERC also noted that more mature data on clinical efficacy from the TITAN trial would help to decrease the uncertainty associated with OS extrapolations and further inform the true cost-

	effectiveness of apalutamide plus ADT. pERC noted that the budget impact of apalutamide plus ADT is potentially significantly 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. pERC noted that a substantial reduction in the price of apalutamide would be required in order to improve the cost-effectiveness and to decrease the predicted substantial budget impact. **Preferred Treatment Between Androgen Receptor-Axis Targeted Therapies** pERC discussed that there is currently insufficient evidence to make an informed decision on the use of apalutamide plus ADT compared to other androgen receptor-axis targeted (ARAT) therapies (e.g., abiraterone, enzalutamide). pERC was unable to comment on the preferred treatment choice for patients but recognized that provinces will need to address this issue upon implementation of reimbursement of other ARAT therapies. **Sequencing of Treatments following Treatment with Apalutamide plus ADT for mCSPC** pERC was unable to make an informed recommendation on the optimal sequencing of treatments for patients who progress after treatment with apalutamide plus ADT for mCSPC and enter the metastatic castration resistant prostate cancer setting. pERC noted 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 clinical practice guidelines addressing sequencing of treatments 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

Prostate cancer is the most common cancer diagnosed among Canadian men, not including non-melanoma skin cancers. Prostate cancer is the third leading cause of cancer-related death among Canadian men. It is estimated that there will be 22,900 new cases of prostate cancer (one in five cancers in men) and 4,100 deaths in Canada in 2020. Approximately 2,000 to 3,000 men in Canada will be diagnosed with mCSPC. Men with mCSPC are treated with first-line ADT. Nearly all patients with mCSPC will initially respond to ADT; however, patients will eventually progress to castration-resistant prostate cancer (CRPC). pERC noted that enzalutamide and abiraterone are currently under review at CADTH for mCSPC (though at the time of this publication, the abiraterone Initial Recommendation is suspended). Therefore, pERC discussed that treatments are needed to extend the period patients remain in the castration-sensitive setting.

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

pERC deliberated one multi-national, multi-centre, phase III, randomized, double-blind, placebo controlled trial (TITAN) comparing apalutamide plus ADT with placebo plus ADT among men with mCSPC. pERC considered that rPFS, one of two primary outcomes of this trial, was statistically significant and clinically meaningful in favour of apalutamide plus ADT. pERC noted that while OS, the other primary outcome, was statistically significant at the first interim analysis for OS, results were immature as median survival was not yet reached in either treatment group. pERC also noted that patients randomized to the ADT monotherapy group were able to cross over to the apalutamide plus ADT group; it is not clear how many patients were able to cross over, but pERC highlighted that this may bias OS results against apalutamide plus ADT. Secondary outcomes discussed by pERC included time to cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, and time to skeletal-related event, all of which favoured treatment with apalutamide plus ADT; however, these secondary end points were considered exploratory. Overall, pERC concluded that the statistically significant improvements in rPFS and the immature but promising OS results in the TITAN trial were clinically meaningful in this setting.

pERC deliberated the safety profile of apalutamide plus ADT and noted the incidence and severity of adverse events (AEs) were broadly similar between the two groups. pERC discussed that rash, which was an AE of special interest, was more commonly reported among patients randomized to the apalutamide plus ADT group and was the most common AE of grade 3 or higher. pERC discussed that rash was manageable with dose reduction and treated with topical steroids. pERC also highlighted the incidence of fractures, which was higher among patients receiving apalutamide plus ADT, and noted that this was of some concern given the short follow-up of these patients. pERC also discussed and agreed with the CADTH Clinical Guidance Panel (CGP), that additional monitoring of AEs may be required as hypothyroidism was also higher among patients in the apalutamide plus ADT group, and that this is not an AE that clinicians may routinely be looking for in this group of patients. Overall, pERC agreed with the CGP and registered clinicians that apalutamide plus ADT has a manageable safety profile.

pERC discussed the available patient-reported outcomes data from the TITAN trial and noted that QoL was similar between the two groups, which suggested a maintenance of health-related quality of life (HRQoL) with apalutamide plus ADT compared to placebo plus ADT. pERC considered this to be reasonable in the mCSPC setting, where patients' HRQoL is expected to be relatively high and stable.

pERC concluded that there is a net clinical benefit to apalutamide plus ADT compared to ADT monotherapy in the treatment of men with mCSPC. In coming to this conclusion, pERC considered the clinically meaningful results in rPFS, statistically significant results in OS, manageable toxicity profile, and lack of detriment in HRQoL.

pERC also noted that approximately two-thirds of patients enrolled in the TITAN trial had high-volume disease. pERC discussed the differences in treatment benefit among men with low- and high-volume disease burden and agreed that treatment choice would be based on patient preferences, side-effect profile, and treatment schedule. pERC also discussed sequencing of other therapies upon progression with

apalutamide plus ADT; pERC agreed with the CGP and registered clinicians that patient's responses to ARAT therapies following progression on apalutamide may be low as the treatments follow the same biological mechanism, and that treatment with docetaxel would most likely be the next treatment choice.

pERC deliberated the patient advocacy group input from the Canadian Cancer Survivor Network (CCSN). pERC noted that side effects most commonly reported by patients as a result of their prostate cancer included fatigue, hot flashes, and anxiety; however, some of these side effects may be a result of treatment. pERC considered that current treatments for prostate cancer are currently differentially covered across Canada, and that some patients reported some difficulty in accessing their treatments. Side effects considered unacceptable from treatment included fatigue, hot flashes, and erectile dysfunction. Patients with direct experience with apalutamide plus ADT reported that apalutamide plus ADT was better able to control their symptoms and manage their disease progression compared to previous therapies. pERC agreed that the benefits of apalutamide plus ADT outweighed the potential risk of side effects. pERC concluded that apalutamide plus ADT aligned with the following patient values: disease control, improved QoL, and additional treatment choice.

pERC highlighted that the TITAN trial did not compare apalutamide plus ADT to relevant treatments, such as chemotherapy, abiraterone plus prednisone, and enzalutamide; however, during the trial design for TITAN, pERC acknowledged that ADT was considered the standard of care. In the absence of a direct comparison, pERC considered the results of a submitted network meta-analysis (NMA) from the sponsor comparing apalutamide plus ADT to docetaxel plus ADT, abiraterone acetate with prednisone plus ADT, and ADT monotherapy. Results suggested that all active treatments were preferred over ADT monotherapy. However, no direct comparisons between active treatments were made. pERC acknowledged the limitations of the NMA noted by the CADTH Methods Team and agreed with its concerns regarding heterogeneity across the study designs and populations. pERC agreed with the CGP and CADTH Methods Team and cautioned against drawing conclusions from the NMA on the magnitude of effect of apalutamide plus ADT compared to other treatments in the absence of more robust direct evidence from randomized trials. pERC deliberated on the cost-effectiveness of apalutamide plus ADT compared with docetaxel plus ADT, abiraterone acetate with prednisone plus ADT, and placebo plus ADT. The Committee considered the evidence provided by the sponsor and the pCODR Economic Guidance Panel, in particular the exploratory analyses conducted by CADTH to assess the impact of treatment effect waning. Due to the lack of data informing the duration of treatment effect and long-term extrapolation of OS, estimating the true incremental treatment effect of apalutamide plus ADT was associated with uncertainty. pERC noted that apalutamide plus ADT was extendedly dominated and not considered cost-effective at the submitted price.

pERC discussed the feasibility of implementing a reimbursement recommendation for apalutamide plus ADT for patients with mCSPC. pERC noted that a key factor influencing the incremental budget impact was the apalutamide market shares provided by the sponsor, which was considered to be low given the limited usage (i.e., docetaxel plus ADT) or funding across jurisdictions (i.e., abiraterone acetate with prednisone plus ADT) of comparators. The predicted budget impact for apalutamide plus ADT was therefore considered to be underestimated in the sponsor's base case. pERC also addressed a number of implementation questions from PAG that are outlined in Appendix 1.

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 sponsor's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group: CCSN
- input from registered clinicians: three individual clinician inputs and one joint input from three oncologists on behalf of Cancer Care Ontario
- input from PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- One clinician group, [Cancer Care Ontario GU DAC]
- The PAG
- The sponsor Janssen Inc.

The pERC Initial Recommendation was to conditionally recommend reimbursement of apalutamide (Erleada) for the treatment of patients with mCSPC. Feedback on the pERC Initial Recommendation indicated that the sponsor, PAG, and registered clinician group agreed with the Initial Recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of apalutamide (Erleada) in combination with ADT compared with placebo plus ADT in men with mCSPC.

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

The pCODR systematic review included one multi-national, multi-centre, double-blind, placebo-controlled, phase III randomized control trial: TITAN. The TITAN trial evaluated the efficacy and safety of apalutamide (Erleada) in combination with ADT compared to placebo with ADT in men with mCSPC.

A total of 1,052 men with mCPSC were randomized (2:1) to receive either apalutamide (240 mg once daily) plus ADT (n = 525) or matched placebo plus ADT (n = 527), which comprised the intention-to-treat population. The safety population comprised of 1,051 patients (n = 524 in the apalutamide plus ADT group versus n = 527 patients in the placebo plus ADT group). Treatment with apalutamide plus ADT continued until disease progression, unacceptable toxicity, or patient withdrawal. Patients randomized to the ADT monotherapy group were able to cross over to the apalutamide plus ADT group; it is not clear how many patients were able to cross over.

Key inclusion criteria included patients with documented adenocarcinoma of the prostate; metastatic disease documented on the basis of at least one lesion on bone scanning, with or without visceral or lymph-node involvement; an Eastern Cooperative Oncology Group performance status score of 0 or 1; those who were castration sensitive (i.e., patients were not receiving ADT at the time of disease progression); and those who had discontinued antiandrogen therapy before randomization. Patients with previous treatment for prostate cancer were allowed so long as it was limited to a maximum of six cycles of docetaxel for low-volume mCSPC, ADT for no more than six months for mCSPC or no more than three years for localized prostate cancer, one course of radiation or surgical therapy for symptoms associated with metastatic disease, and other localized treatments for prostate cancer completed at least one year before randomization. Key exclusion criteria included patients with severe angina, myocardial infarction,

congestive heart failure, arterial or venous thromboembolic events, or having a history of or predisposition to seizure.

Patient populations: Median age 68 years; majority of patients with metastatic disease

The median age in the TITAN trial was 68 years (range: 43 to 94 years), with 23% of patients over the age of 75. A greater proportion of patients had an Eastern Cooperative Oncology Group performance status of 0 (62.5% vs. 66.0% in the apalutamide plus ADT and ADT monotherapy groups, respectively), Gleason score of higher than 7 at initial diagnosis (66.9% versus 67.9%), and high-volume disease (61.9% versus 63.6%). Median prostate-specific antigen levels were 5.97 mcg/L (range = 0 mcg/L to 2,682 mcg/L) in the apalutamide plus ADT group and 4.02 mcg/L (0 mcg/L to 2,229 mcg/L) in the placebo plus ADT group. Median treatment duration was 20.5 months for patients in the apalutamide plus ADT group and 18.3 months for patients in the placebo plus ADT group.

Key efficacy results: Clinically meaningful improvement in rPFS; OS in favour of apalutamide plus ADT

The primary efficacy outcomes in the TITAN trial were rPFS, defined as the time from randomization to first imaging-based documentation of progressive disease or death, whichever occurred first, and OS, defined as the time from randomization to the date of death from any cause. The analyses for both rPFS and OS was based on the intention-to-treat population. Secondary outcomes included time to pain progression, time to cytotoxic chemotherapy, time to chronic opioid use, and time to skeletal-related events.

At 24 months, 68.2% of patients in the apalutamide plus ADT group were found to have rPFS compared to 47.5% in the placebo plus ADT group (hazard ratio (HR) = 0.48; 95% CI, 0.39 to 0.60; P < 0.001), for a 52% lower risk of radiographic progression or death in the apalutamide plus ADT group. Median rPFS was not reached in the apalutamide plus ADT group and was 22.1 months in the placebo plus ADT group. At 24 months, the rate of OS was 82.4% in the apalutamide plus ADT group compared to 73.5% in the placebo plus ADT group (HR = 0.6; 95% CI, 0.51 to 0.89; P = 0.005), resulting in a 33% reduction in the risk of death in the apalutamide plus ADT group. However, median OS was not yet reached in either treatment group; a final analysis of OS will be conducted after 410 events have occurred. Subgroup analyses of efficacy on patients with low-volume or high-volume disease were pre-specified as a secondary objective. Subgroup analyses showed rPFS benefit among patients with low- and high-volume disease, but no statistical difference regarding OS; however, the CADTH Methods Team noted that these subgroup analyses should be considered exploratory and be interpreted with caution. All secondary outcomes tended to favour apalutamide plus ADT.

Patient-reported outcomes: No Detriment to QoL

HRQoL was an exploratory outcome in the TITAN trial. HRQoL was measured using the following instruments: Functional Assessment of Cancer Therapy–Prostate questionnaire, EuroQol 5-Dimensions 5-Levels questionnaire, Brief Pain Inventory (BPI), and BPI short form (BPI-SF).

Based on the Functional Assessment of Cancer Therapy–Prostate questionnaire and the EuroQol 5-Dimensions 5-Levels questionnaire, there was no detriment to QoL in both the apalutamide plus ADT and placebo plus ADT groups; there were no differences between the two treatment groups. Patients were mostly asymptomatic at baseline with low pain and fatigue scores. Based on the BPI and BPI-SF, experiences of pain and fatigue were similar between the apalutamide plus ADT and placebo plus ADT groups and remained stable throughout treatment. In the TITAN trial, all patient-reported and HRQoL outcomes were exploratory and descriptive in the TITAN trial.

Safety: Manageable toxicity profile, similar between groups

In general, the incidence of AEs of any grade was similar for both the apalutamide plus ADT and placebo plus ADT groups of the TITAN trial. AEs of grades 3 or 4 occurred similarly across both treatment groups (42.2% in the apalutamide plus ADT group versus 40.8% in the placebo plus ADT group). The most common grade 3 or higher AE was rash of any type and was considered by the investigator to be due to apalutamide plus ADT (6.3%). Serious AEs were reported for 19.8% of patients in the apalutamide plus ADT group and 20.3% of patients in the placebo plus ADT group. Treatment emergent AEs resulting in treatment discontinuation were more frequent in the apalutamide plus ADT group (8.0%) compared to the

placebo plus ADT group (5.3%). Treatment emergent AEs resulting in death occurred in 1.9% of patients in the apalutamide plus ADT group and 3.0% of patients in the placebo plus ADT group.

AEs of special interest were consistently more frequent in patients receiving apalutamide plus ADT than those receiving placebo plus ADT. These included rash (27.1% versus 8.5%), falls (7.4% versus 7.0%), fractures (6.3% versus 4.6%), hypothyroidism (6.5% versus 1.1%) and seizures (0.6% versus 0.4%). Skin rash led to treatment discontinuation, dose reduction, and dose interruption in 12 (2.3%), 28 (5.3%), and 44 (8.4%) of patients in the apalutamide plus ADT group, respectively, versus 1(0.2%), 4 (0.8%), and 5 (0.9%) of patients in the placebo plus ADT group, respectively. However, rash was considered by the CGP to be manageable with dose modification and treatment with topical steroids. There may be some concern of fracture among patients being treated with apalutamide plus ADT as there was a 50% greater fracture risk during a short follow-up period. Hypothyroidism did not lead to treatment discontinuation or dose modification and was monitored according to thyrotropin level and managed with levothyroxine.

Limitations: No direct comparative data to relevant treatment options

While no direct evidence exists to compare apalutamide plus ADT to relevant treatments comparators, three NMAs were critically appraised and summarized by the CADTH Methods Team. The sponsor-provided NMA compared apalutamide plus ADT and relevant comparators (e.g., abiraterone acetate with prednisone plus ADT and docetaxel plus ADT) to ADT monotherapy in patients with mCSPC. The CADTH Methods Team concluded that since no comparisons were made between active treatments, no conclusions could be made regarding the relative efficacy of apalutamide compared to abiraterone acetate or docetaxel. In addition, due to the clinical heterogeneity present between the four included trials, the estimates from the NMA may be biased, the magnitude of which cannot be established.

The CADTH Methods Team also identified two additional relevant published NMAs comparing apalutamide to additional comparators, including abiraterone, enzalutamide, docetaxel, bisphosphonates, docetaxel plus bisphosphonates, celecoxib, or celecoxib plus bisphosphonates (all of which were combined with ADT). The CADTH Methods Team concluded that the published NMAs also contained clinical heterogeneity related to prior therapies of patients, patients' disease characteristics, or whether patients received chemical versus surgical castration. While the published NMAs were able to compare apalutamide plus ADT to treatments other than ADT monotherapy, the uncertainty related to the direct and indirect comparisons warrants caution regarding interpretation of results.

Need and burden of illness: Need for treatment that delays development of CRPC

Prostate cancer is the most common cancer diagnosed among Canadian men, not including non-melanoma skin cancers. Prostate cancer is the third leading cause of cancer-related death among Canadian men. It is estimated that there will be 22,900 new cases of prostate cancer (one in five cancers in men) and 4,100 deaths in Canada in 2020. Approximately 2,000 to 3,000 men in Canada will be diagnosed with mCSPC. Men with mCSPC are treated with first-line ADT. Nearly all patients with mCSPC will initially respond to ADT; however, patients will eventually progress to CRPC. Enzalutamide and abiraterone are currently under review at CADTH for mCSPC (though at the time of this publication, the abiraterone Initial Recommendation is suspended). Therefore, pERC discussed that treatments are needed to extend the period patients remain in the castration-sensitive setting.

Registered clinician input: Apalutamide plus ADT is well tolerated, shows similar efficacy to other ARAT therapies

Four registered clinician input submissions were provided for apalutamide plus ADT for patients with mCSPC — three inputs from individual oncologists and one joint input on behalf of three oncologists from Cancer Care Ontario. Docetaxel and abiraterone acetate were acknowledged as current treatment options for patients with mCSPC but were also noted not to be available in all jurisdictions. Clinicians agreed that apalutamide plus ADT shows efficacy among this population of men with prostate cancer, is better tolerated compared to chemotherapy, and may require less monitoring compared to abiraterone acetate plus prednisone. Main toxicities were stated to be rash, fatigue, and hypertension. Contraindications were indicated in patients with history of seizure, hypothyroidism, and uncontrolled hypertension. Other contraindications, per the TITAN trial, were also acknowledged. Chemotherapy or radiation therapy were suggested as the next most likely treatments for patients upon progression with apalutamide plus ADT. One clinician indicated abiraterone acetate as another treatment possibility for patients upon progression, indicating that some patients in the TITAN trial appeared to benefit from abiraterone acetate as a second-line therapy. Clinicians suggested that patient preferences and characteristics may need to

be considered when deciding upon the choice of treatment between apalutamide, docetaxel, and other relevant comparators for patients with mCSPC in this line of treatment.

PATIENT-BASED VALUES

Experience of patients with prostate cancer: Variable access to treatments, impacted QoL
One patient submission was provided to CADTH from CCSN. Patients indicated a number of symptoms affecting their QoL and day-to-day living as a result of their prostate cancer. Fatigue, hot flashes, anxiety, erectile dysfunction, and loss of muscle mass were the most commonly reported symptoms. Caregivers of patients with prostate cancer cited anxiety or worrying and hours spent in medical appointments as the most commonly reported issues they encountered. They also indicated emotional drain, management of medication, management of side effects, lifestyle changes, fatigue, and monetary concerns (i.e., absence at work and driving expenses) as other challenges. Caregivers stated fatigue, urinary and rectal incontinence, severe rashes, and nose bleeds were the most challenging side effects related to their loved one's cancer or treatment. Patients valued treatments that helped to control their disease, that lessened side effects, prolonged life, and that maintained their QoL.

Patient values, experience on or expectations for treatment: Better disease control, less toxic treatment options, and maintenance of QoL
Seventeen respondents had direct experience with apalutamide plus ADT; six patients received apalutamide for up to one month and 11 patients received apalutamide for two or three months. Most respondents indicated that apalutamide was better able to control their symptoms than other treatments. Respondents indicated that apalutamide had reduced side effects and was easier to take compared to their previous medications or treatments. In addition, respondents commented that apalutamide better managed their disease progression. Fatigue and hot flashes were the most commonly reported side effects. Weight gain, loss of muscle mass, erectile dysfunction, hormonal changes, dizziness, feelings of anxiety, nausea and vomiting, decreased appetite, diarrhea, and weight loss were other side effects reported by respondents. Respondents also indicated that side effects experienced while receiving apalutamide were generally tolerable. Bowel incontinence, loss of bone mass, and feelings of depression were indicated as being the least tolerable side effects. In general, respondents considered the benefits of apalutamide to outweigh the side effects.

ECONOMIC EVALUATION

Apalutamide is available as a 60 mg tablet, at a submitted price of $28.35 per tablet. The recommended starting dosage in combination with ADT is 240 mg daily, at a 28-day cycle treatment cost of $3,175 and an annual treatment cost of $41,384 per patient (apalutamide costs only).

The sponsor submitted a partitioned survival analysis considering apalutamide plus ADT as first-line treatment for patients with mCSPC. The proportion of patients who were progression-free, who experienced progressive disease, or who were dead at any time over the model horizon was derived from non-mutually exclusive survival curves. Patients transitioning to the mCRPC state could receive one or more subsequent treatments, represented as a market basket of Health Canada–approved treatments. An HR approach was applied for both rPFS and OS in the model using ADT as the reference curve given that this represents the common control group between clinical trials included in the sponsor-submitted indirect treatment comparison. Historical studies with long-term follow-up using ADT were used to validate OS projections. Comparators included ADT, docetaxel plus ADT, and abiraterone acetate with prednisone plus ADT. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a 20-year time horizon.

In the sponsor's base case, apalutamide plus ADT was associated with an expected cost of $260,274 and 5.05 quality-adjusted life-years over a 20-year time horizon. Based on a full sequential analysis, apalutamide plus ADT was extendedly dominated by abiraterone acetate with prednisone plus ADT and abiraterone acetate with prednisone plus ADT, indicating this treatment has a higher incremental cost-effectiveness ratio when compared to docetaxel plus ADT and the next more effective treatment (i.e., apalutamide plus ADT).

The following key limitations were identified:

- Uncertainty exists regarding the duration of treatment effect and the long-term extrapolation of OS. The approach taken by the sponsor appeared to overestimate patient survival in the model.
- The sponsor inappropriately applied treatment-dependent utilities, which should be captured by the model structure, independent of assigned treatment. Further, AE disutilities that were considered clinically meaningful were excluded from the base-case analyses.
- A short time horizon was utilized; however, with interventions that have differential effects on mortality, a lifetime time horizon is more appropriate.
- The adjustment of drug costs according to dose intensity underestimated treatment costs.
- Subsequent treatment sequencing was not fully captured in the model, limiting generalizability to clinical practice.
- Docetaxel drug costs were overestimated as only the highest available strength was included.

The CADTH base case reflected changes to the following parameters: using health state utilities independent of treatment assignment and including AE utility decrements, correcting docetaxel cost calculations, revising dose intensity, adjusting mortality to include non-cancer death, and extending the time horizon.

The CADTH reanalysis results aligned with the sponsor's base-case results, indicating that apalutamide plus ADT is extendedly dominated by docetaxel plus ADT and abiraterone acetate with prednisone plus ADT. Price reductions can improve the cost-effectiveness of apalutamide plus ADT in patients with mCSPC, if a decision-maker's willingness to pay is $100,000 and $50,000 per quality-adjusted life-year, approximate price reductions between 60% to 70% and 80%, respectively, are required.
Several limitations were identified that could not be addressed by CADTH; most notably, the model structure precluded CADTH from exploring the downstream impact of subsequent treatment and the impact of treatment effect waning.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact underestimated
To assess the feasibility of implementing a reimbursement recommendation for apalutamide plus ADT for patients with mCSPC, the sponsor provided a Canada-wide budget impact analysis spanning three years. pERC and the CADTH Economic Guidance Panel noted that assumed market shares of apalutamide provided by the sponsor, prostate cancer incidence data, and drug costs were key factors influencing the budget impact. Based on the CADTH base-case reanalyses, the budget impact is expected to be $28,574,855 over three years, with scenario analyses ranging between $30,727,343 and $37,246,547. However, the CADTH budget impact utilized the market share assumptions provided by the sponsor and as these projections were considered low by pERC, an increase in the market share of apalutamide will substantially increase the budget impact.

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)
Daryl Bell, Patient Member
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. W. Dominika Wranik, Health Economist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Dr. Avram Denburg, who was not present for the meeting
- Dr. Christopher Longo, who was not present for the discussion and deliberation for this review
- Dr. Maureen Trudeau, who did not vote due to their role as the pERC Chair.

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

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 (Erleada) for mCSPC, through their declarations, one member had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were 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*. Janssen Inc., as the primary data owner, did not agree to the disclosure of clinical and economic information, therefore, this information has been redacted in publicly available guidance reports.

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.

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is seeking clarity on whether or not the following patients would be eligible for treatment with apalutamide plus ADT: ○ patients with an ECOG PS of 2 or greater ○ patients who had more than six months of ADT in the past.	• TITAN required study participants to have an ECOG PS of 0 or 1. The CGP noted that the benefit for patients with an ECOG status of 2 or greater cannot be formally concluded from this study. However, pERC agreed with the CGP that it would be reasonable to offer apalutamide plus ADT to patients with a good PS, based on clinical experience and the manageable side-effect profile. • TITAN allowed study participants to have received up to six months of ADT in the adjuvant or neoadjuvant setting as long as it was completed more than one year prior to randomization. pERC agreed with CGP that providing patients, who received more than six months of ADT with prior local therapy, with apalutamide was acceptable, so long as treatment with ADT had been completed more than one year from the timing of initiating apalutamide.
• PAG is seeking guidance on whether there is a specific high-risk subgroup (e.g., Gleason score of 8 to 10, high PSA at diagnosis) that is more likely to benefit from the addition of apalutamide to ADT for the treatment of mCSPC.	• The TITAN trial included patients with a Gleason of score greater than 7 and higher PSA at diagnosis. pERC agreed with the CGP and registered clinicians that there is no specific high-risk subgroup of patients that is more likely to benefit from apalutamide plus ADT.
• PAG noted that patients who are currently treated with other treatments (e.g., ADT alone for more than six months) and who have not progressed would need to be addressed on a time-limited basis.	• pERC agreed with the CGP that patients who are currently being treated for mCSPC with other treatments (e.g., ADT alone for more than six months) but who have not progressed should not be considered eligible for apalutamide.
• PAG noted that patients who are recently treated (e.g., docetaxel for six cycles) and who have not progressed would need to be addressed on a time-limited basis.	• pERC agreed with the CGP that patients who were recently treated (e.g., docetaxel for six cycles) but who have not progressed may be considered eligible for apalutamide plus ADT and would need to be addressed on a time-limited basis.
• PAG is seeking guidance on preference for treatment with: ○ apalutamide or docetaxel in this mCSPC setting ○ apalutamide or abiraterone for high-risk patients.	• TITAN randomized patients to receive apalutamide plus ADT or ADT monotherapy. pERC agreed with the CGP that there is a lack of direct comparative evidence between apalutamide and other comparators, including docetaxel or abiraterone. pERC acknowledged the limitations of the NMA noted by the CADTH Methods Team and agreed with its concerns regarding heterogeneity across the study designs and populations. pERC agreed with the CGP and CADTH Methods Team and cautioned against drawing conclusions from the NMA on the magnitude of effect of apalutamide plus ADT compared to other treatments in the absence of more robust direct evidence from randomized trials. pERC agreed with CGP that treatment choice would be based on patient preferences, side-effect profile, and treatment schedule.
PAG is seeking information on the appropriate treatment for castration-resistant metastatic disease after treatment with apalutamide plus ADT in the castration-sensitive metastatic disease setting. Treatments available for castration-resistant metastatic	• pERC was unable to make an informed recommendation on the optimal sequencing of treatments for castration-resistant prostate cancer after treatment with apalutamide plus ADT in the castration-sensitive setting, noting that there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon

disease include abiraterone, enzalutamide, and chemotherapy.	implementation of reimbursement of apalutamide plus ADT and noted that a national approach to developing clinical practice guidelines addressing sequencing of treatments would be of value.

PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; ADT = androgen deprivation therapy; CGP = Clinical Guidance Panel; ECOG = Eastern Cooperative Oncology Group; mCSPC = metastatic castration-sensitive prostate cancer; NMA = network meta-analysis; PS = performance status; PSA = prostate-specific antigen.