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: Enzalutamide (XTANDI)

Submitted Reimbursement Request:
In combination with androgen deprivation therapy, for the treatment of patients with metastatic castration-sensitive prostate cancer

Submitted by:
Astellas Pharma Canada, Inc.

Manufactured by:
Astellas Pharma Canada, Inc.

NOC Date:
June 2, 2020

Submission Date:
February 24, 2020

Initial Recommendation Issued:
September 3, 2020

Approximate per patient drug costs	At the recommended dose of 160 mg (four 40 mg capsules) as a single oral daily dose, enzalutamide costs $3,270 per 28-day cycle.

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 reimbursement of enzalutamide in combination with androgen deprivation therapy (ADT) for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC), if the following condition is met:

- cost-effectiveness being improved to an acceptable level.

Patients must be castration sensitive (i.e., no prior ADT in the metastatic setting or within six months of beginning ADT), with good performance status and no risk factors for seizures. Treatment should be continued until unacceptable toxicity or disease progression.

pERC made this recommendation because it was satisfied that enzalutamide in combination with ADT has a net clinical benefit compared with ADT alone or ADT in combination with a nonsteroidal antiandrogen (NSAA) based on statistically significant and clinically meaningful improvements in radiographic progression-free survival (rPFS) and overall survival (OS), a manageable toxicity profile, and no detriment to quality of life (QoL).

pERC also concluded that enzalutamide in combination with ADT aligns with the following patient values: no detriment to QoL, delay in disease progression, delay in the onset of symptoms, delay of the need for chemotherapy, manageable side effects, and additional treatment choice.

pERC concluded that enzalutamide plus ADT was not cost-effective at the submitted price versus currently relevant comparators and that a reduction in 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 ARCHES and ENZAMET trials would help to decrease the uncertainty associated with rPFS and OS extrapolations and further inform the true cost-effectiveness of enzalutamide plus ADT. pERC noted that the budget impact of enzalutamide plus ADT is underestimated given the sponsor's low expected market share uptake from inexpensive treatment alternatives (i.e., docetaxel plus ADT and ADT alone).
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 enzalutamide in combination with ADT, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of enzalutamide plus ADT. pERC noted that a substantial reduction in the price of enzalutamide would be required in order to improve cost-effectiveness and to decrease the predicted budget impact. **Preferred Treatment Between Androgen Receptor-Targeted Drugs** pERC discussed that there is currently insufficient evidence to make an informed decision on the use of enzalutamide in combination with ADT compared to other androgen receptor-targeted drugs (e.g., apalutamide, abiraterone plus prednisone). 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 androgen receptor-targeted drugs. **Sequencing of Treatments following Treatment with enzalutamide 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 enzalutamide in combination with ADT for mCSPC and enter the metastatic castration-resistant prostate cancer (mCRPC) setting. pERC noted that there is insufficient evidence to inform this clinical situation. However, pERC agreed with the pCODR Clinical Guidance Panel (CGP) that there is currently no high-level evidence to support the sequencing of androgen receptor axis-targeted therapies (ARATs) which have the same mechanism of action. pERC recognized that provinces will need to address this issue upon implementation of reimbursement of enzalutamide in combination with 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, with a five-year survival rate of 29.8%. It is estimated that there will be 22,900 new cases of prostate cancer (one in five cancers in men) and 4,100 deaths related to this type of cancer in Canada in 2020. Approximately 2,000 to 3,000 men in Canada will be diagnosed with mCSPC. While first-line ADT has traditionally been the backbone of therapy for patients with mCSPC, the addition of docetaxel for patients with a higher disease burden has improved outcomes and is now standard of care for those able to tolerate chemotherapy. Nearly all patients with mCSPC will initially respond to first-line therapy; however, patients will eventually progress to castration-resistant prostate cancer (CRPC). pERC noted that apalutamide received a conditional positive final pERC recommendation for mCSPC in April 2020; however, apalutamide is currently not funded for this indication in Canadian jurisdictions. Abiraterone plus prednisone is presently under review at CADTH (though at the time of this publication, the abiraterone Initial Recommendation is suspended). pERC agreed with the pCODR Clinical Guidance Panel (CGP) and the registered clinicians providing input that new therapies that extend the period during which patients remain in the metastatic castration-sensitive setting with manageable toxicity profiles are a continued need for these patients.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated the results of two randomized, multinational, phase III trials (ARCHES and ENZAMET) that evaluated the efficacy and safety of enzalutamide in combination with ADT compared with ADT alone (ARCHES) and with ADT plus an NSAA (ENZAMET) among adult men with mCSPC. pERC noted that overall, both trials were well-designed randomized controlled trials and the patient populations aligned with the requested reimbursement criteria. pERC considered that rPFS, the primary outcome in the ARCHES trial, and OS, the primary outcome in the ENZAMET trial, were statistically significant and clinically meaningful in favour of enzalutamide in combination with ADT. Key secondary outcomes in ARCHES (including time to prostate-specific antigen [PSA] progression, time to start of new antineoplastic therapy, and time to deterioration in urinary symptoms) and ENZAMET (clinical progression-free survival [PFS] and PSA PFS) were also statistically significant in favour of enzalutamide. pERC noted that the OS data in both trials were immature (median OS was not reached in either group) but the analysis results were statically significant in favour of enzalutamide in the ENZAMET trial. Overall, pERC agreed with the CGP and the registered clinicians proving input that the improvements in rPFS and OS observed in the trials are of clinical importance for patients with this incurable disease. Extending the period patients remain in the metastatic castration-sensitive setting is important as the transition from mCSPC to metastatic CRPC is a clinically relevant event that is associated with a higher burden of symptoms, decrease in QoL, and shorter survival times.

pERC discussed the toxicity profile of enzalutamide in combination with ADT based on the results of the ARCHES and ENZAMET studies and noted that the incidence and severity of adverse reactions were broadly similar between the two groups and were consistent with the safety profile of enzalutamide in the metastatic castration-resistant setting. In the ARCHES trial, the most reported grade 3 or greater adverse events (AEs), occurring more frequently in the ADT alone group, included hypertension, asthenia, and fatigue. In the ENZAMET trial, the most reported grade 3 to 5 AEs, occurring more frequently in the enzalutamide group, included febrile neutropenia, hypertension, neutrophil count decease, and fatigue. Most of the febrile neutropenia events occurred during early docetaxel treatment. pERC noted that a very small number of patients in the trials suffered a seizure during treatment (seizures occurred only in the enzalutamide group in the ENZAMET trial while a similar incidence of seizures occurred across groups in the ARCHES trial) and felt that enzalutamide was contraindicated in patients with risk factors for seizures. pERC discussed that a small but increased fracture risk was observed with the use of enzalutamide and agreed with the CGP that increased osteopenia can potentially be mitigated with the use of bone-conserving therapies. Overall, pERC agreed with the CGP and the registered clinicians providing input that enzalutamide has a manageable safety profile.

pERC discussed the available patient-reported outcomes data from the ARCHES and ENZAMET trials and noted that overall QoL was similar between study groups and did not show a negative effect from enzalutamide plus ADT compared with ADT plus placebo (ARCHES) or ADT plus a NSAA (ENZAMET). pERC considered this to be reasonable in the mCSPC setting, where patients' QoL is expected to be relatively high and stable.

pERC deliberated a sponsor-provided network meta-analysis (NMA) comparing the efficacy of enzalutamide plus ADT with other relevant treatments (i.e., abiraterone plus prednisone, docetaxel, apalutamide, NSAA, placebo (all of which were combined with ADT), and ADT alone). pERC noted that the results of the NMA favoured enzalutamide plus ADT for OS in the comparison with ADT plus placebo and ADT plus a NSAA, and favoured enzalutamide for rPFS in the comparison with ADT plus placebo and docetaxel plus ADT. When compared with abiraterone plus prednisone plus ADT and apalutamide plus ADT, enzalutamide plus ADT demonstrated no statistically significant benefit for rPFS or OS. pERC acknowledged the limitations of the NMA noted by the CADTH Methods team and agreed with the Method team's concerns regarding heterogeneity across the study designs and populations. pERC agreed with the CGP and CADTH Methods team to caution against drawing conclusions from the NMA on the magnitude of effect of enzalutamide plus ADT compared to other treatments in the absence of more robust direct evidence from randomized trials.

pERC concluded that enzalutamide in combination with ADT has a net clinical benefit compared with ADT alone or ADT in combination with a NSAA based on statistically significant and clinically meaningful improvements in rPFS and OS, a manageable toxicity profile, and no detriment to QoL.

pERC deliberated the patient advocacy group input from the Canadian Cancer Society, and noted that, according to patients, key symptoms with mCSPC include bladder and/or bowel problems, fatigue, and sexual dysfunction. A few patients who had direct experience using enzalutamide indicated that diarrhea, weight gain, fatigue, hot flashes, and muscle loss were the side effects associated with the use of this drug. Most patients taking enzalutamide reported improvements with their cancer. pERC agreed that the benefits of enzalutamide outweighed the potential risk of side effects, and concluded that the use of enzalutamide aligned with the following patient values: no detriment to QoL; delay in disease progression; delay in onset of symptoms, delay of the need for chemotherapy; manageable side effects; and additional treatment choices.

pERC deliberated the cost-effectiveness of enzalutamide plus ADT compared with ADT alone, docetaxel plus ADT, apalutamide plus ADT, and abiraterone plus prednisone plus ADT for patients with mCSPC. pERC noted the lack of data informing the duration of treatment effect and long-term extrapolation of OS, which increased the uncertainty regarding the magnitude of benefit associated with enzalutamide. pERC concluded that enzalutamide plus ADT was not cost-effective at the submitted price versus currently relevant comparators and that a reduction in 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 ARCHES and ENZAMET trials would help to decrease the uncertainty associated with rPFS and OS extrapolations and further inform the true cost-effectiveness of enzalutamide plus ADT.

pERC discussed the feasibility of implementing a reimbursement recommendation for enzalutamide plus ADT for patients with mCSPC, and noted that the budget impact of enzalutamide plus ADT may be underestimated given the sponsor's low expected market share uptake from inexpensive treatment alternatives (i.e., docetaxel plus ADT and ADT alone).

The Committee deliberated the input from PAG regarding factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

EVIDENCE IN BRIEF

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

- 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 (the Canadian Cancer Society)
- input from registered clinicians: one joint clinician input from the Cancer Care Ontario Genitourinary Drug Advisory Council, one individual clinician input from Sunnybrook Hospital's Odette Cancer Centre in Ontario, and one individual clinician input from a clinician practising in Ontario
- input from PAG.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the efficacy and safety of enzalutamide in combination with ADT compared with ADT alone or ADT plus a NSAA in men with mCSPC.

Studies included: Two ongoing, multinational, randomized phase III trials (ARCHES and ENZAMET)

The CADTH systematic review included two randomized controlled trials (ARCHES and ENZAMET) that assessed the efficacy and safety of enzalutamide for patients with mCSPC.

ARCHES Trial

A total of 1,150 patients were randomized on a 1:1 ratio to receive either enzalutamide (160 mg per day) with ADT (N = 574) or placebo with ADT (N = 576). Randomization was stratified by disease volume (low versus high) and prior docetaxel chemotherapy for prostate cancer (no cycles, one to five cycles, or six cycles). Two patients in the enzalutamide group and two in the placebo group did not receive their assigned therapies. At the October 14, 2018, data cut-off, 76.1% of patients (N = 437) were still receiving enzalutamide and 57.6% of patients (N = 332) were still receiving placebo. The median duration of therapy was 12.8 months (range = 0.2 to 26.6) in the enzalutamide group and 11.6 months (range = 0.2 to 24.6) in the placebo group.

Patients were included in the trial if they met the following criteria: adult men with pathologically confirmed prostate adenocarcinoma without neuroendocrine differentiation, signet-cell or small-cell features; metastatic prostate cancer documented by positive bone scan or metastatic lesions on CT or MRI scan; able to maintain ADT with a luteinizing hormone-releasing hormone analogue agonist or antagonist during study treatment, or have a history of bilateral orchiectomy after day 1 of randomization; and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. ARCHES allowed patients into the trial who had up to six cycles of prior docetaxel therapy completed within two months of randomization and no disease progression.

ENZAMET Trial

A total of 1,125 patients were centrally randomized on a 1:1 ratio to receive either enzalutamide (160 mg per day) with ADT (N = 563) or NSAA with ADT (N = 562). The type of NSAA was at the discretion of the treating clinician, and it could include bicalutamide (50 mg per day), nilutamide (150 mg per day), or flutamide (250 mg three times a day). Randomization was stratified by disease volume (low versus high), study site, anti-resorptive therapy (yes versus no), comorbidities according to the Adult Comorbidity Evaluation 27 (ACE-27; 0 to 1 versus 2 to 3), and early planned use of docetaxel (yes versus no).

Four patients in the NSAA group did not receive their assigned therapies. At the database cut-off, 64.3% of patients (N = 362) were still receiving enzalutamide and 35.9% of patients were still receiving NSAA (N = 202). [redacted]

Patients were included in the trial if they met the following criteria: adult men with prostatic adenocarcinoma with metastases on computed tomography, bone scanning with technetium 99m, or both; and an ECOG performance status of 0 to 2. Patients were eligible for the trial if they had testosterone suppression that was initiated up to 12 weeks before randomization, or if they had previous adjuvant testosterone suppression for up to 24 months that was completed at least 12 months earlier. In addition, patients who started docetaxel prior to study entry were still eligible if they were tolerating full doses of docetaxel (75 mg/m^2) with ADT, met all the eligibility criteria for the trial while receiving docetaxel, and had no more than two cycles prior to randomization. Patients who had not already started docetaxel were allowed to commence docetaxel at least four weeks after starting enzalutamide, and no more than six weeks after randomization.

Patient populations: Median age: 70 (ARCHES), median age: 69 (ENZAMET), baseline characteristics well balanced

ARCHES Trial
Overall, the baseline characteristics were well balanced. The median age in the trial was 70 years (enzalutamide = 70.0 [range = 46 to 92] versus placebo = 70.0 [range = 42 to 92]) and the majority of patients in both groups were White (enzalutamide: 81.2% versus placebo: 79.9%) or Asian (enzalutamide = 13.1% versus placebo = 13.9%) and had an ECOG performance status of 0 (enzalutamide = 78% versus placebo = 76.9%). A large proportion of patients had a Gleason score of eight or greater (enzalutamide = 67.2% versus placebo = 64.8%) and more than half of the patients in the trial had a high volume of disease (enzalutamide = 61.7% versus placebo = 64.8%). The majority of patients in the trial had bone only (44.6% for all) or bone and soft tissue (39.8%) metastasis, as assessed by independent central review. The majority of patients did not receive prior docetaxel (enzalutamide = 82.1% versus placebo = 82.3%).

ENZAMET Trial
Overall, the baseline characteristics were well balanced. The median age in the trial was 69 years (enzalutamide = 69.2 [interquartile range = 63.2 to 74.5] versus NSAA = 69.0 [interquartile range = 63.6 to 74.5]) and a large proportion of patients had a Gleason score of eight to 10 (enzalutamide = 60% and NSAA = 57%). ECOG performance status was balanced between the two groups with 72.1% and 71.9% of patients having an ECOG score of 0 and 26.9% and 26.6% of patients having an ECOG score of 1 in the enzalutamide and NSAA groups, respectively. Eleven percent of patients in the enzalutamide group and 12% in the NSAA group had visceral metastases. More than half of the patients in the trial had a high volume of disease (enzalutamide = 52% and NSAA = 53%). Almost 10% of patients in the enzalutamide group (10.3%) and 9.8% in the NSAA group received bone anti-resorptive therapy and most of the patients had 0 to 1 ACE-27 stratum (enzalutamide = 74.6% and NSAA = 75.0%).

Overall, 44.6% of patients had early use of docetaxel (enzalutamide = 45.1% and NSAA = 44.1%), and 42.8% in the enzalutamide group and 42.1% in the NSAA group had at least one dose of docetaxel after randomization. Approximately one-third of the patients received six cycles of docetaxel (enzalutamide = 27.9% and NSAA = 32.3%).

Key efficacy results: Clinically meaningful improvement in rPFS and OS in favour of enzalutamide plus ADT

ARCHES Trial
The primary end point was rPFS as assessed by independent central review. Secondary outcomes included OS, time to first symptomatic skeletal related events, time to castration resistance, time to deterioration of QoL, time to deterioration in urinary symptoms, time to start of new antineoplastic therapy, time to PSA progression, PSA undetectable rate (< 0.2 ng/mL), objective response rate (ORR), and time to pain progression. Exploratory outcomes were combined response (soft tissue lesions and bone lesions), PSA reduction, health-related quality of life (HRQoL), and safety.

The database cut-off for the ARCHES trial was October 14, 2018, and this represents a median follow-up time of 14.4 months.

The median rPFS was not reached (95% confidence interval [CI], not reached to not reached) in the enzalutamide group and was 19.0 months (95% CI, 16.6 to 22.2 months) in the placebo group. Enzalutamide was associated with a longer rPFS as compared to placebo (hazard ratio [HR] = 0.39; 95% CI, 0.30 to 0.50; P ≤ 0.0001). Pre-specified subgroup analysis results, including subgroups of disease volume

and prior docetaxel chemotherapy, were consistent with the overall estimates of rPFS. However, the subgroup analyses were not adjusted for stratification factors or multiplicity and should be interpreted with caution.

The median time to PSA progression was not reached for both treatment groups. Enzalutamide was associated with a significant improvement in the time to PSA progression as compared to placebo (HR = 0.19; 95% CI, 0.13 to 0.26; P < 0.0001). The median time to initiating a new antineoplastic therapy was 30.2 months (95% CI, not reached) for enzalutamide and was not reached for placebo (HR = 0.28; 95% CI, 0.20 to 0.40; P < 0. 0001. Patients in the enzalutamide group had a higher PSA undetectable rate when compared to those in the placebo group (68.1% [N = 348] versus 17.6% [N = 89]; P < 0.001). The absolute difference between the two groups was 50.5% (95% CI, 45.3 to 55.7; P < 0.0001).

ORR was significantly higher for enzalutamide (ORR = 83.1% [N = 147]) as compared to placebo (ORR = 63.7% [N = 116]) (P value for difference ≤ 0.001).

The median time to deterioration of urinary symptoms was not reached (19.35, not reached) in the enzalutamide group and was 16.8 months (95% CI, 14.06 to not reached) in the placebo group (HR = 0.88; 95% CI, 0.72 to 1.08; P = 0.2162).

The median OS was not reached for both treatment groups (HR = 0.81; 95% CI, 0.53 to 1.25; P = 0.3361). The results of OS are immature and should be interpreted with caution.

ENZAMET Trial
The primary end point was OS and the secondary outcomes included PSA PFS and clinical PFS. Exploratory outcomes were HRQoL and safety.

The database cut-off for the ENZAMET trial was February 28, 2019; this represents a median follow-up of 34.4 months.

Treatment with enzalutamide was associated with a significant improvement in OS compared to the NSAA group (HR = 0.67; 95% CI, 0.52 to 0.86; P = 0.002). The survival rate at three years was 80% (N = 94) in the enzalutamide group and 72% (N = 130) in the NSAA group.

Overall, the subgroup analysis results were consistent with the intention-to-treat results. However, after adjusting for multiple testing, there were no significant differences among the pre-specified subgroups based on age, ECOG performance status, Gleason score at initial diagnosis, volume of disease, planned early use of docetaxel, and ACE-27 scores.

[redacted] Treatment with enzalutamide was associated with a significant improvement in clinical PFS compared to the NSAA group (HR = 0.40; 95% CI = 0.33 to 0.49; P < 0.001). The effect of enzalutamide on clinical PFS remained significant after adjusting for multiple testing.

The median PSA PFS was not reached for the enzalutamide group and was [redacted] in the placebo group. Treatment with enzalutamide was associated with a significant improvement in PSA PFS compared to the NSAA group (HR = 0.39; 95% CI, 0.33 to 0.47; P < 0.001).

Patient-reported outcomes: No difference between treatment groups

ARCHES Trial
In the ARCHES trial, HRQoL was measured using the Brief Pain Inventory – Short Form (BPI-SF), Functional Assessment of Cancer Therapy – Prostate Cancer (FACT-P), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer 25 (QLQ-PR25), and the EuroQoL 5-Dimensions 5-Levels Visual Analogue Scale (EQ-5D-5L VAS). Patient-reported outcome (PRO) instruments were measured at baseline, week 13, and every 12 weeks during the study until disease progression. Longitudinal changes from baseline to week 73 were assessed using mean scores and mixed-model repeated measures and were adjusted for baseline PRO score, volume of disease, and prior docetaxel therapy.

The BPI-SF item 3 (pain at its worst in the last 24 hours) and FACT-P total scores remained stable over time. In addition, the mean scores for pain severity and pain interference, as measured by the BPI-SF, remained stable during the study. The authors also commented that there were no statistical differences from baseline to week 73 for the BPI-SF score, any of the FACT-P subscales, or the EQ-5D-5L VAS. However, there was a significant difference for the FACT-P personal well-being score, which favoured placebo over enzalutamide (difference = –1.02; 95% CI, –1.90 to –0.13) but there was no clinically meaningful difference.

ENZAMET Trial
In the ENZAMET trial, HRQoL was assessed using the European Organization for Research and Treatment of Cancer quality of life questionnaire (QLQ-C30), the QLQ-PR25, and the EQ-5D-5L instruments. Only data from the QLQ-C30 instrument were summarized by the CADTH Methods team, as the sponsor noted that the results for the QLQ-PR25 and the EQ-5D-5L instruments have not yet been reported. PRO instruments were measured at baseline, week 4, and week 12, and every 12 weeks during the study until clinical progression. Longitudinal changes from baseline to year 3 were assessed using differences in least squares means with mixed-model repeated measures. There was no significant difference between the two treatment groups for the QLQ-C30 Global Health domain, and the minimal important difference was not met.

Safety: Manageable toxicity profile, similar between treatment groups

The side effect profile was consistent with the previous experience with enzalutamide in the metastatic castration resistant setting. The incidence and severity of AEs were broadly similar between groups in both trials.

ARCHES Trial
In the ARCHES trial treatment-emergent adverse events (TEAEs) of any grade were reported in most patients (enzalutamide = 85.1% and Placebo = 85.9%) and were balanced across groups. Grade 3 and 4 TEAEs were also similar for both treatment groups (enzalutamide = 23.6% and placebo = 24.7%), while slightly more patients in the placebo group had a serious TEAE as compared to the enzalutamide group (19.5% versus 18.2%, respectively). Overall, 2.4% of patients in the enzalutamide group and 1.7% in the placebo group died. None of the deaths in the enzalutamide group were related to the therapy (as assessed by the investigator); however, one death in the placebo group (i.e., general physical health deterioration) was reported to be related to the therapy. Fractures of all grades occurred in 6.5% and 4.2% of patients in the enzalutamide and placebo groups, respectively. Convulsion (i.e., seizure) occurred in 0.3% of patients in each group. Grade 3 and 4 TEAEs were similar for both treatment groups (enzalutamide = 23.6% and placebo = 24.7%).

Overall, 7.2% of patients in the enzalutamide group and 5.2% in the placebo group discontinued their assigned therapies due to an AE. Only 4.4% of patients in the enzalutamide group had an AE that led to a dose reduction, compared to 1.9% of patients in the placebo group.

ENZAMET Trial
In the ENZAMET trial, more patients in the NSAA group had grade 1 and grade 2 AEs (7% and 14% [grade 1] and 36% and 41% [grade 2] in the enzalutamide and NSAA groups, respectively), while more patients in the enzalutamide group had a grade 3 or higher AE (57% in the enzalutamide group versus 43% in the NSAA group). Slightly more patients in the enzalutamide group had a serious AE compared to the NSAA group (42% versus 34%, respectively). Overall, six grade 5 AEs occurred in the enzalutamide group (two patients died from an unknow cause, and one patient each had a stroke, myocardial infarction, aspiration pneumonia, or acidosis). In the NSAA group, seven grade 5 AEs occurred (sepsis in two patients and one patient each had cardiac arrest, sudden death from an unknown cause, gastric hemorrhage, urinary tract infection, or symptomatic progression of prostate cancer). Seizures of any grade occurred in seven patients in the enzalutamide group and no events occurred in the NSAA group. [redacted]

More patients in the enzalutamide group discontinued study treatment due to an AE than in the NSAA group (N = 33 versus N = 14). It was noted that six patients in the enzalutamide group discontinued treatment due to a seizure while one patient discontinued enzalutamide because of clinical progression before the seizure event.

Limitations: No direct comparative data to relevant treatment options

The CADTH Methods team critically appraised and summarized three NMAs (one provided by the sponsor and two published NMAs). The sponsor-provided NMA compared the efficacy of enzalutamide plus ADT with abiraterone plus prednisone, docetaxel, apalutamide, NSAA, placebo (all of which were combined with ADT), and ADT alone. The results of the NMA favoured enzalutamide plus ADT for OS in the comparison with ADT plus placebo and ADT plus an NSAA, and favoured enzalutamide for rPFS in the comparison with ADT plus placebo and docetaxel plus ADT. When compared with abiraterone plus prednisone plus ADT and apalutamide plus ADT, enzalutamide plus ADT demonstrated no statistically significant benefit for rPFS or OS. Several limitations of the NMA were noted by the CADTH Methods team; notably, heterogeneity across the study designs and populations. The CADTH Methods team and the CGP cautioned against drawing conclusions from the NMA on the magnitude of effect of enzalutamide plus ADT compared to other treatments in the absence of more robust direct evidence from randomized trials.

The CADTH Methods team also identified two additional relevant published NMAs comparing enzalutamide to additional comparators, including abiraterone plus prednisone, apalutamide, 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. The uncertainty related to the direct and indirect comparisons warrants caution when interpreting the results.

Need and burden of illness: Most common cancer diagnosed among Canadian men, newer therapies (i.e., androgen receptor axis-targeted therapies) have not been funded yet

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, with a five-year survival rate of 29.8%. It is estimated that there will be 22,900 new cases of prostate cancer (one in five cancers in men) and 4,100 deaths related to this type of cancer in Canada in 2020. Approximately 2,000 to 3,000 men in Canada will be diagnosed with mCSPC. While first-line ADT has traditionally been the backbone of therapy for patients with mCSPC, the addition of docetaxel for patients with a higher disease burden has improved outcomes and is standard of care for those able to tolerate chemotherapy. Nearly all patients with mCSPC will initially respond to first-line therapy; however, patients will eventually progress to CRPC. pERC noted that apalutamide received a conditional positive final pERC recommendation for mCSPC in April 2020; however, apalutamide is currently not funded in Canadian jurisdictions. Abiraterone plus prednisone is presently under review at CADTH (though at the time of this publication, the abiraterone Initial Recommendation is suspended). The CGP and registered clinicians providing input agreed that new therapies that extend the period during which patients remain in the metastatic castration-sensitive setting with manageable toxicity profiles are a continued need for these patients.

Registered clinician input: Enzalutamide can be prescribed to all patient subgroups, some patients may prefer enzalutamide over other options

A total of three clinician inputs were provided for the review of enzalutamide for mCSPC: one joint clinician input from the Cancer Care Ontario Genitourinary Drug Advisory Council, one individual clinician input from Sunnybrook Hospital's Odette Cancer Centre in Ontario, and one individual clinician input from a clinician practising in Ontario. Overall, the clinicians agreed that enzalutamide can generally be prescribed to all patient subgroups with mCSPC; however, there are certain subgroups of patients for whom enzalutamide would be preferred over other options, such as patients who don't qualify for docetaxel and/or abiraterone plus prednisone, patients with node-predominant mCSPC, and patients who have hypertension. All three clinician groups had experience with prescribing enzalutamide, which is also commonly prescribed to patients with mCRPC. The clinicians reported that the majority of patients prefer enzalutamide over docetaxel and/or chemotherapy due to the fact that it has less toxicity. No major contraindications to enzalutamide were mentioned by the clinicians. The choice between enzalutamide and other androgen receptors is usually based on comorbidities, contraindications, patient preferences, and toxicity profiles. For sequencing and priority of treatments, the clinicians advised that enzalutamide would be used in the first-line setting. Other options upon progression are docetaxel chemotherapy, radium-223 (for bone-limited metastatic disease), or clinical trial participation. An unmet need for mCSPC patients was asserted by one clinician due to limited access to other oral androgen receptor antagonists.

PATIENT-BASED VALUES

Experience of patients with prostate cancer: Concerning symptoms include urinary and sexual dysfunction; diagnosis can have significant emotional and mental health impact

One patient advocacy group, the Canadian Cancer Society, provided input on enzalutamide for mCSPC. Some common symptoms and challenges of living with prostate cancer experienced by patients included bladder and/or bowel problems; living with uncertainty, anxiety, panic attacks, and/or depression; and sexual dysfunction. Some previous treatments used by patients included surgery, chemotherapy, hormone therapy, second-line hormone therapy, radiation therapy, radium-223, and active surveillance/monitoring. Patients identified the following key side effects from prostate cancer treatments: sexual dysfunction, fatigue, anxiety, panic attacks, and/or depression. The Canadian Cancer Society highlighted the significant emotional and mental health impact that the cancer diagnosis can have on patients.

Patient values, experience on or expectations for treatment: No detriment to QoL; delay in disease progression, onset of symptoms, and the need for chemotherapy; manageable side effects; and additional treatment choices

Six patients had experience with enzalutamide, the majority of whom reported that the drug had been effective in improving their cancer. All six patients reported that enzalutamide has lowered their PSA level. Patients identified some negative side effects of enzalutamide treatments, including diarrhea, weight gain, fatigue, hot flashes, muscle loss, and loss of energy. The survey respondents were asked to indicate how important they think a drug like enzalutamide would be for patients with mCSPC, and most respondents reported that the drug would be an important treatment option for patients. Overall, patients value having alternative treatment options that focus on maintaining QoL, delaying the need for chemotherapy or palliative care, and delaying the onset of symptoms with a particular emphasis on controlling side effects, such as urinary and sexual dysfunction, which could impact patient's QoL. Few patients also noted that cost-effectiveness would be of value for new treatments.

ECONOMIC EVALUATION

Enzalutamide is available as a 40 mg tablet at a submitted price of $29.20 per tablet. The recommended starting dose is 160 mg daily alongside ADT. The per patient 28-day cycle treatment cost is $3,270 for enzalutamide and between $68 and $625 for ADT for a total regimen cost between $3,338 and $3,895.

The sponsor submitted a Markov model based on a standard three-state partitioned survival structure considering enzalutamide as first-line treatment for patients with mCSPC. The proportion of patients who were progression-free, experienced progressive disease, or were dead at any time over the model horizon was derived from non-mutually exclusive survival curves. Patients transitioning to mCRPC could receive upwards of three lines of treatment, with specific sequencing of Health Canada–approved treatments according to the prior therapy used for mCSPC. The clinical efficacy of enzalutamide plus ADT was informed from a pooled analysis of the ARCHES and ENZAMET trials for OS and ARCHES for rPFS, where a within-trial direct comparison between enzalutamide plus ADT and ADT was conducted. The efficacy (measured in terms of rPFS and OS) for docetaxel plus ADT, apalutamide plus ADT, and abiraterone plus prednisone plus ADT were obtained from an unpublished NMA commissioned by the sponsor. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a 15-year time horizon.

The following key limitations were identified:

- Based on the limited duration of the clinical trials and immaturity of the OS data, there was substantial uncertainty regarding the duration of treatment effect and the long-term extrapolation of OS. The rPFS extrapolations selected by the sponsor were not considered to be clinically plausible as projected rPFS was greater than OS at specified time points.
- The sponsor used direct trial data rather than the NMA results to inform the efficacy for enzalutamide plus ADT, which biased the cost-effectiveness results in favour of enzalutamide plus ADT. Given that comparator treatments were informed using NMA results, there is further uncertainty when incorporating clinical effects from separate data sources.
- The sponsor utilized a 15-year time horizon; however, with interventions that have differential effects on mortality, a lifetime time horizon of 20 years was considered more appropriate.

- Drug dose intensity was assumed to be equal for all treatments; however, this assumption may be overly optimistic for treatments with increased toxicity and where compliance may not be comparable to oral treatments.
- Non-cancer mortality was not included, and the sponsor assumed general population mortality was representative of patients with mCSPC. However, compared with the general population, patients with mCSPC have an increased risk of mortality due to comorbidities.

The CADTH base case reflected changes to the following parameters: a revised dose intensity for docetaxel plus ADT, extending the time horizon, using NMA results for enzalutamide plus ADT, applying non-cancer mortality, modifying rPFS extrapolations, and applying a treatment waning effect.

The CADTH reanalysis results indicated that enzalutamide plus ADT was not cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY), with an incremental cost-effectiveness ratio of $294,805 per QALY at the current price. Based on current list prices, at a willingness-to-pay threshold of $50,000 per QALY, a price reduction of approximately 75% is required.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact underestimated

CADTH reanalyses suggest that the budget impact of introducing enzalutamide to the market was underestimated [redacted]. CADTH's revised results estimated an increase to budgets of $3,139,045 over the first 3 years. This budget impact estimate is based on the assumption of apalutamide being funded.

Factors related to currently funded treatments, the eligible patient population, implementation, and the sequencing and priority of treatments are described in Appendix 1.

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. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
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
Dr. W. Dominika Wranik, Health Economist

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

- Dr. Maureen Trudeau, who did not vote due to her role as pERC Chair
- Dr. Avram Denburg, who was absent from the deliberations on enzalutamide (Xtandi) for mCSPC.

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 enzalutamide (Xtandi) for mCSPC, through their declarations, no members had a real, potential, or perceived conflict and, based on 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*. Astellas Pharma Canada, Inc., as the primary data owner, did not agree to the disclosure of certain clinical and economic information, therefore, this information has been redacted in this recommendation and 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.

Disclaimer

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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
Current funded treatments	
The standard of care for newly diagnosed mCSPC is docetaxel plus ADT or ADT alone for those unable to tolerate chemotherapy (i.e., docetaxel).	
• PAG noted that in the ENZAMET trial, the comparator group received a testosterone-lowering drug or surgical castration and a first-generation nonsteroidal antiandrogen (bicalutamide, nilutamide, or flutamide). Patients in the enzalutamide arm also received a testosterone-lowering drug or surgical castration but did not receive another first-generation antiandrogen. PAG noted that first-generation antiandrogens are not used frequently in Canadian practice.	• pERC agreed with the CGP that the trials' results can be generalized to patients who do not routinely receive first-generation antiandrogens with an LHRH agonist or surgical castration. The CGP noted that there is currently insufficient evidence to determine if first-generation NSAAs in combination with ADT have a clinically meaningful benefit.
• PAG is seeking information on the comparative efficacy of enzalutamide plus ADT versus apalutamide plus ADT, abiraterone plus ADT, and docetaxel plus ADT.	• Currently, only indirect comparisons can be made between enzalutamide plus ADT, apalutamide plus ADT, abiraterone plus prednisone and ADT, and docetaxel plus ADT as no trial to date has directly compared these drugs. Network meta-analyses suggest similar overall survival benefit of enzalutamide compared to docetaxel, abiraterone plus prednisone, or apalutamide and suggest less high-grade toxicity of ARAT drugs compared with docetaxel. However, pERC agreed with the CGP and the CADTH Methods team, that due to several limitations identified in the network meta-analyses, caution must be used in interpreting the comparative efficacy and safety estimates. Given the absence of direct comparison, there is no robust evidence to ascertain which of the drugs (i.e., enzalutamide, other androgen receptor-targeted drugs, or docetaxel) has superior efficacy. Therefore, the CGP concluded that patient values and preferences, comorbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection.
Eligible patient population	
PAG is seeking guidance on whether the following patients would be eligible for treatment with enzalutamide plus ADT:	
• Patients having experienced at least one course of radiation therapy or surgery to treat symptoms related to metastatic disease	• pERC agreed with the CGP that the trials' results are generalizable to patients who have had at least one course of radiation therapy or surgical intervention for metastatic prostate cancer.
• Patients with an ECOG performance status score greater than 2	• pERC agreed with the CGP that the benefit for patients with an ECOG status of 2 or greater cannot be formally concluded from the ARCHES and ENZAMET trials. However, it would be reasonable to offer enzalutamide plus ADT in some situations where it is believed that the disease may have a negative impact on patients' performance status, based on clinical

	experience and the manageable side-effect profile of this oral drug.
• Patients having started ADT (12 or more weeks prior to enzalutamide). What would be the maximum duration of prior ADT before adding enzalutamide in practice?	• For patients who have already started ADT, pERC agreed with the CGP that up to six months is the maximum duration of prior ADT before adding enzalutamide in practice. There is insufficient evidence to generalize the trial results to patients who have started ADT more than six months ago.
• Patients having received more than two cycles of docetaxel	• pERC agreed with the CGP that despite the fact that ARCHES allowed sequential docetaxel and enzalutamide; and ENZAMET allowed concurrent docetaxel and enzalutamide, there is no adequate data to support this approach in the Canadian context. Enzalutamide should not be routinely combined with or sequenced right after docetaxel therapy. However, as stated subsequently, pERC agreed with the CGP that patients currently treated with ADT plus docetaxel for up to six months and who have not progressed would need to be addressed on a time-limited basis.
• Patients having received ADT in the adjuvant setting where the time since completion of adjuvant hormonal therapy is 12 months or longer	• For patients who have received prior adjuvant ADT, pERC agreed with the CGP that it would be reasonable to provide these patients with enzalutamide as long as adjuvant therapy with ADT has been completed more than one year prior to the initiation of enzalutamide.
• Patients with non-metastatic CSPC	• As patients with non-metastatic CSPC were excluded from the trial, pERC noted that there are no data to support generalizing the treatment benefit with enzalutamide plus ADT to this patient population.
• Patients intolerant to one of the alternative drugs	• pERC noted that there is currently no evidence on switching patients who are intolerant to an alternative drug to enzalutamide plus ADT. However, pERC agreed with the CGP that switching therapies in this context would appear reasonable and beneficial to patients who generally do better with treatment than without treatment.
• Patients with high risk factors	• pERC agreed with the CGP that the trials' results can be generalized to patients who have high-risk factors. pERC noted that based on the evidence (ARCHES and ENZAMET trials), it is reasonable to expect that enzalutamide plus ADT will be equally beneficial in high- and low-risk or -volume patients.
Is there any evidence or recommendations to support using ADT plus enzalutamide only in specific high-risk subgroups rather than for all patients with mCSPC? Given that abiraterone has evidence for use in high-risk mCSPC, are there specific high-risk patient populations where abiraterone versus enzalutamide would be preferred due to clinical reasons?	pERC agreed with the CGP that in the absence of evidence to guide this decision, there is inter-clinician variability in the identification of the optimal patient.
If recommended for reimbursement, PAG noted that patients currently treated with	pERC agreed with the CGP that patients currently treated with ADT alone or with docetaxel for up to six months and who have

ADT with or without docetaxel for more than 12 weeks would need to be addressed on a time-limited basis.	not progressed would need to be addressed on a time-limited basis. However, patients who have been treated for mCSPC with ADT alone or with docetaxel for more than six months and who have not progressed should not be considered eligible for enzalutamide.
Implementation factors	
PAG noted that the ENZAMET trial defined progression either by a PSA increase or radiographically. A clear definition of progression would be needed to identify discontinuation criteria.	pERC agreed with the CGP that clinicians will commonly seek confirmation of progression in all possible areas; i.e., PSA progression, clinical progression (i.e., well-being of patient), and radiographic progression. PSA progression and radiographic progression tend to align with each other. However, pERC noted that if a patient has PSA progression alone (no radiographic progression or development of symptoms attributable to cancer progression), then a patient may continue treatment.
Early/prior docetaxel use (ENZAMET: early docetaxel up to two cycles prior to randomization; ARCHES: prior docetaxel up to six cycles with final treatment administration completed within two months of day 1 was permitted). PAG is seeking clarity on docetaxel dosage, timing, and optimal target population.	pERC agreed with the CGP that in patients with mCSPC, there are two main approaches: ADT and six cycles of docetaxel or ADT and an ARAT (abiraterone, apalutamide, or enzalutamide). Despite the fact that ARCHES allowed sequential docetaxel and enzalutamide; and ENZAMET allowed concurrent docetaxel and enzalutamide, there is no adequate data to support this approach in the Canadian context. However, as previously mentioned, pERC agreed that patients who have been treated with docetaxel for up to six months and who have not progressed would be eligible to receive enzalutamide on a time-limited basis. If a patient is found to have developed mCRPC after completion of docetaxel chemotherapy, then that patient will be managed according to the treatment options available for the metastatic castration-resistant setting.
If androgen deprivation therapy is started in the metastatic hormone sensitive setting with an LHRH agonist, does the LHRH agonist continue for this phase of treatment and onwards with all treatments the patient would receive upon progression in the mCRPC setting?	pERC agreed with the CGP that the LHRH agonist continues to be administered indefinitely with current treatment and with all treatments the patients would receive upon progression in the mCRPC setting.
Sequencing and priority of treatment	
PAG is seeking guidance on the appropriate place in therapy of enzalutamide plus ADT and overall sequencing of all treatments available for non-metastatic, metastatic, castration-resistant, and castration-sensitive prostate cancer settings.	pERC was unable to make an informed recommendation on the optimal sequencing of treatments for castration-resistant prostate cancer after treatment with enzalutamide plus ADT in the castration-sensitive setting, noting that there is insufficient evidence to inform this clinical situation.

ADT = androgen deprivation therapy; ARAT = androgen receptor axis-targeted; CGP = Clinical Guidance Panel; CSPC = castration-sensitive prostate cancer; ECOG = Eastern Cooperative Oncology Group; LHRH = luteinizing hormone-releasing hormone; mCRPC = castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; NSAA = nonsteroidal antiandrogen; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; PSA = prostate-specific antigen.