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: Fulvestrant (Faslodex) **Submitted Reimbursement Request:** For hormonal treatment of non-visceral locally advanced or metastatic HER2– breast cancer in postmenopausal women, regardless of age, who have not been previously treated with endocrine therapy	
Submitted By: AstraZeneca Canada Inc.	**Manufactured By:** AstraZeneca Canada Inc.
NOC Date: November 09, 2017	**Submission Date:** July 17, 2017
Initial Recommendation: November 30, 2017	**Final Recommendation:** February 1, 2018

Drug Costs:	
Approximate per Patient Drug Costs, per Month (28 Days)	Fulvestrant costs $582.90 per 250 mg/5 mL injection Cycle 1: $124.91 per day and $3,497.37 per 28-day course Subsequent cycles: $41.64 per day and $1,165.79 per 28-day course

pERC RECOMMENDATION

pERC recommends the reimbursement of fulvestrant (Faslodex) conditional on its cost-effectiveness being improved to an acceptable level.

Reimbursement should be for fulvestrant monotherapy in the treatment of postmenopausal women with non-visceral locally advanced or metastatic human epidermal growth factor receptor 2-negative (HER2−) breast cancer, regardless of age, who have not been previously treated with endocrine therapy (including in the adjuvant setting) and who have a good performance status. Treatment should continue until unacceptable toxicity or disease progression.

pERC made this recommendation because the Committee was satisfied that there may be a net clinical benefit of fulvestrant monotherapy compared with anastrozole in this patient population based on a clinically meaningful improvement in progression-free survival (PFS). pERC also concluded that the therapy aligns with patient values, in that it is an additional treatment option that offers an improvement in PFS that does not adversely affect quality of life.

pERC concluded that fulvestrant monotherapy is not likely to be cost-effective because there is considerable uncertainty in the clinical effect estimates (immature and likely overestimated OS benefits in the model; subgroup analyses).

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that there may be a net clinical benefit of fulvestrant, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of fulvestrant to an acceptable level. pERC noted that a reduction in the price of fulvestrant would be required to improve the cost-effectiveness to an acceptable level.

Collecting Evidence to Reduce Uncertainty in the Magnitude of Clinical Benefit and the Cost-Effectiveness of Fulvestrant
Given the uncertainty in the magnitude of the OS benefit of fulvestrant in postmenopausal women with non-visceral locally advanced or metastatic HER2− breast cancer who have not been previously treated with endocrine therapy, pERC concluded that additional prospective evidence should be collected by jurisdictions to decrease the uncertainty in the incremental effect and to provide a greater understanding of the true cost-effectiveness of fulvestrant.

Fulvestrant Relative to Current Treatment Landscape
pERC acknowledged a continued need for new and effective therapies for patients with advanced or metastatic breast cancer that provide improvements in patient survival, have more favourable toxicity profiles, and improve quality of life. Based on the available evidence, the Committee agreed that there is no urgent unmet need that can be filled by fulvestrant in this patient population; however, patients do value the choice of alternative treatment options with reduced symptoms. Furthermore, pERC anticipates that only a small number of patients would qualify for treatment with fulvestrant, as the majority of patients in the clinical setting would have received adjuvant hormonal therapy.

SUMMARY OF pERC DELIBERATIONS

Breast cancer is the most common cancer in women in Canada and the second most common cause of cancer mortality in Canadian women. Estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2−) breast cancer represents approximately 65% to 70% of all breast cancers. The goals of treatment for patients with advanced or metastatic breast cancer are primarily palliative; namely, maintaining or improving patients' length of life and quality of life by controlling progression of the disease. Traditionally, the first-line treatment for postmenopausal women with ER+/HER2− advanced or metastatic breast cancer has included hormonal therapies (letrozole, anastrozole, exemestane, and tamoxifen). More recently, the CDK4/6 inhibitor palbociclib, in combination with letrozole, was recommended for reimbursement in this setting, having demonstrated improvements in PFS and objective response rates and having a manageable, but not insignificant, toxicity profile. pERC acknowledged a continued need for new and effective therapies for patients with advanced or metastatic breast cancer that provide improvements in patient survival, have more favourable toxicity profiles, and improve quality of life. However, the Committee agreed that the availability of palbociclib plus letrozole demonstrates that there is no urgent unmet need that can be filled by fulvestrant in this setting. This was in alignment with feedback received from Registered Clinicians on the initial pERC Recommendation.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of two randomized controlled trials, FALCON and FIRST, which compared fulvestrant against anastrozole alone in postmenopausal women with ER+/HER2− locally advanced or metastatic breast cancer not previously treated with endocrine therapy. pERC noted that the submitted reimbursement request was narrower than the Health Canada indication and focused on a subgroup of patients with non-visceral disease (nearly half of the patients in both trials).

Progression-free survival: The Committee noted that the overall trial results for the FALCON trial reported a modest and statistically significant 2.8 months' improvement in median PFS in favour of fulvestrant compared with anastrozole alone. Notably, although the clinical benefit rate was the primary outcome in FIRST, PFS was also improved in the FIRST trial in favour of the fulvestrant group. pERC noted that subgroup analysis based on non-visceral disease indicated a larger magnitude of benefit in both trials with regard to PFS. However, pERC further noted that the subgroup analysis in non-visceral disease was not reported to be pre-planned, and therefore the results cannot be considered robust.

Overall survival: pERC noted a lack of mature OS data in the FALCON trial, which increased the Committee's uncertainty regarding the clinical benefit of fulvestrant. Although there appeared to be an OS benefit in the overall results of the FIRST trial, the Committee agreed that the limitations of the trial, namely the open-label design, the lack of power to detect a true difference for OS, and multiple data-driven amendments to the trial made interpretation of the data difficult.

Quality of FALCON and FIRST trials: A global interaction test, conducted only in the FALCON trial, indicated that there were no statistically significant effect modifiers of fulvestrant identified. In a post-hoc interaction test to assess for consistency of treatment effects across visceral involvement subgroups (visceral and non-visceral) the p-value was 0.0092, however, these results should be considered hypothesis generating as they were not pre-planned. Therefore, pERC agreed that until more robust data become available, treatment effect in the subgroup of patients with non-visceral disease is at worst similar to results observed in the full trial. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the submitter related to the subgroup analysis in patients with non-visceral disease. The submitter indicated that this subgroup was pre-specified after the finalization of the protocol and included in the statistical analysis plan. pERC noted that the pCODR Methods Team indicated that although the non-visceral subgroup analysis was reported to be pre-specified by the submitter, it was not pre-specified at the trial onset and thus not included in the original study protocol. Furthermore, with regard to the non-visceral subgroup analysis, no

information was available on the following: pre-specification of the analysis a priori, sample size calculation and power estimation, stratification to ensure balance across treatment groups, and formal adjustment for multiple comparisons to control for the risk of type I error (i.e., incorrectly concluding that a difference exists). pERC also agreed with the Methods Team's assessment that subgroup analyses are exploratory in nature, indicative only of possible subgroup effects (i.e., they are hypothesis-generating) and lacking the statistical strength to support strong conclusions on treatment effect. pERC reiterated that there is uncertainty in the interpretation that can be made from this subgroup analysis and agreed that the treatment effect in patients with non-visceral disease is, at worst, similar to results observed in the overall trial results.

Overall, pERC discussed the clinical significance of a modest improvement in PFS in advanced or metastatic breast cancer in the absence of an OS benefit. Although multiple opinions were expressed, the majority of pERC members agreed that a modest delay in progression of disease is clinically meaningful to patients in this setting. pERC also discussed the available quality-of-life data from the FALCON trial and noted that overall mean Functional Assessment of Cancer Therapy–Breast Cancer (FACT-B) and Trial Outcome Index were maintained and similar in both treatment groups. Notably, one-third of patients in both treatment groups experienced a clinically meaningful improvement. pERC also discussed the toxicity profile of fulvestrant and noted that grade 3 or 4 adverse events, serious adverse events, withdrawals due to adverse events, and deaths on treatment were similar between the two treatment groups. pERC agreed that rates of these adverse events were low (< 25% of patients) and similar between the two studies.

Overall, based on a modest improvement in PFS, maintenance of quality of life, and low incidence of toxicity of fulvestrant, pERC concluded that there may be a net clinical benefit of fulvestrant compared with anastrozole in patients with previously untreated ER+/HER2– metastatic breast cancer who have not received prior endocrine therapy and who have non-visceral disease. In reaching this conclusion, the Committee's deliberations were tempered by the modest improvement in PFS and, as yet, the unavailability of evidence demonstrating an improvement in OS. pERC concluded that additional prospective evidence should be collected to decrease the uncertainty in the incremental effect of fulvestrant.

pERC further discussed the fact that palbociclib plus letrozole, although not yet funded at this time, will be the most relevant treatment option in this setting. The results of a submitted network meta-analysis making a comparison between palbociclib plus letrozole and fulvestrant were not conclusive, as a number of limitations were identified in that analysis. In the absence of sufficient data to guide treatment choice between these two treatments, pERC considered that the decision to use one treatment over the other may be guided by a variety of considerations. pERC agreed with the Clinical Guidance Panel (CGP) that fulvestrant may be a more desirable treatment for patients for whom adherence to oral therapy may be a concern, who would prefer not to undergo regular phlebotomies, and who place a greater value on the maintenance of quality of life, as fulvestrant has a low incidence of toxicity. This may be especially true for more marginalized oncologic populations, including older patients or patients averse to additional pills.

pERC deliberated upon patient advocacy group input indicating that patients value having additional treatment options that provide disease control and maintain or improve quality of life. Based on modest improvements in PFS, maintenance of quality of life, and a low incidence of toxicity, pERC agreed that fulvestrant aligned with patient values. Patient with direct experiences of fulvestrant indicated that fulvestrant had a low incidence of toxicity and had a positive effect on quality of life. Patients further indicated that improvements in survival and disease progression are valued more than reducing side effects or managing symptoms. pERC noted that there is uncertainty about the impact of fulvestrant on OS.

pERC deliberated upon the cost-effectiveness of fulvestrant and concluded that it is not cost-effective when compared with anastrozole monotherapy. pERC observed that the lack of mature OS data from the FALCON trial created the largest uncertainty in the incremental cost-effectiveness ratio (ICER). pERC discussed the Economic Guidance Panel's (EGP's) analysis where the OS for each treatment group is set to be equal beyond three years (i.e., after the trial follow-up period, no difference in OS is assumed). Although acknowledging that such a sudden change in the relative OS is not a clinically plausible scenario, the Committee noted that this was the only way EGP was able to demonstrate, using the submitted model, the impact that OS has on the ICER and the resulting uncertainty in the estimates. The Committee noted that the trial did not demonstrate a difference in OS for the subgroup of patients with non-visceral

disease. Therefore, pERC agreed that the true ICER is likely closer to EGP's highest estimate and potentially higher. pERC noted that other inputs had minimal impact on the ICER. Furthermore, pERC noted that the clinical effect estimates used in the economic model were based on the subgroup analysis in non-visceral disease. However, pERC concluded that treatment effect in the subgroup of patients with non-visceral disease is at worst similar to results observed in the overall trial. Therefore it is unclear how the ICER may be impacted if the clinical effect estimates used in the model were altered to match the lower magnitude of effect observed in the overall trial results. Given these uncertainties, pERC concluded that fulvestrant is not cost-effective and that a substantial price reduction would be required to improve the cost-effectiveness of fulvestrant to an acceptable level. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the submitter related to EGP's reanalysis estimates. pERC reiterated that the treatment effect in the subgroup of patients with non-visceral disease is, at worst, similar to results observed in the overall trial, which reported no OS advantage. Despite the uncertainty in the clinical evidence, a long-term OS benefit in favour of fulvestrant was modelled in the submitted base case. pERC recognized that the only way the EGP was able to explore uncertainty in the modelled OS benefit was by setting OS to be equal between the two treatment groups beyond three years. As previously indicated, such a drastic drop in OS is not a clinically plausible scenario as it means patients are dying exactly at the three-year mark. In the absence of updated OS data to provide a full picture of the treatment's long-term effects, the Committee accepted that this was a reasonable way to demonstrate the impact of OS on the ICER. pERC also reiterated that the model used data from the subgroup analysis, which reported improvements in OS and a larger magnitude of PFS benefit in favour of fulvestrant. Based on further input from the EGP, pERC agreed that had the overall trial results been used in the model, the ICER is likely to be higher.

pERC also considered the feasibility of implementing a reimbursement recommendation for fulvestrant. The pCODR Provincial Advisory Group (PAG) noted that palbociclib plus letrozole is not yet funded at the time of this review but is a relevant comparator in this setting. pERC noted that there is insufficient direct or indirect clinical evidence to determine the comparative effectiveness between palbociclib plus letrozole and fulvestrant at this time. pERC agreed with CGP that patient values and preferences and clinical factors should guide treatment selection. pERC further noted that there is no evidence to support sequencing of one treatment after the other. PAG also requested input on the patient population that would qualify for treatment with fulvestrant. pERC agreed that the reimbursement population should be limited to patients with non-visceral disease, as indicated in the reimbursement request. Patients who had previously received adjuvant hormonal therapy were also excluded from the FIRST trial and pERC noted CGP's input indicating that previous trials have demonstrated a lack of efficacy in treating these patients with fulvestrant in combination with a hormonal therapy. Therefore, the results of the FALCON and FIRST trials should not be generalized to patients who have received adjuvant hormonal therapy. If fulvestrant is reimbursed, pERC noted that the uptake in first-line therapy for the prevalent population of patients with advanced or metastatic breast cancer is expected to be low, as many patients in the clinical setting would have received adjuvant hormonal therapy. Therefore, pERC anticipates that a small number of patients would qualify for treatment with fulvestrant. pERC further noted that there are data comparing the use of fulvestrant and palbociclib as a combination therapy against fulvestrant alone. Given the scope of the current review, pERC agreed that this evidence would need to be submitted for full review before a decision on reimbursement could be made.

EVIDENCE IN BRIEF

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

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget-impact analysis
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy groups: Rethink Breast Cancer and Canadian Breast Cancer Network
- input from registered clinicians [Cancer Care Ontario (CCO) Breast Site Group]
- input from pCODR's Provincial Advisory Group (PAG)

Feedback on the pERC Initial Recommendation was also provided by:

- Two patient advocacy group, [Rethink Breast Cancer and Canadian Breast Cancer Network]
- One clinician group, [Cancer Care Ontario (CCO) Breast Site Group]
- The PAG
- The submitter [AstraZeneca Canada Inc.]

The pERC Initial Recommendation was to recommend reimbursement of fulvestrant (Faslodex) conditional on its cost-effectiveness being improved to an acceptable level. Feedback on the pERC Initial Recommendation indicated that the registered clinician group and patient groups agreed in part while the submitter and PAG agreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of fulvestrant (Faslodex) for the treatment of postmenopausal women with non-visceral locally advanced or metastatic human epidermal growth factor receptor 2–negative (HER2–) breast cancer, regardless of age, and who have not been previously treated with endocrine therapy.

Studies included: Two randomized controlled trials, indirect comparison to palbociclib uncertain

The pCODR systematic review included two randomized controlled trials, FALCON and FIRST. FALCON (n = 462) was a phase III, double-blind, superiority, international, multi-centred randomized controlled trial comparing the efficacy and safety of fulvestrant against anastrozole among postmenopausal patients who had not received previous endocrine therapy. FIRST (n = 205) was a phase II, open-label, non-inferiority, international, multi-centred randomized controlled trial that preceded FALCON and also compared fulvestrant with anastrozole as first-line endocrine therapy for advanced hormone receptor–positive breast cancer in postmenopausal women. Both studies randomized patients in a 1:1 ratio to either fulvestrant or anastrozole. Key inclusion criteria for both studies required that patients have positive hormone receptor status, locally advanced or metastatic breast cancer that was not amenable to therapy of curative intent, and World Health Organization performance status 0 to 2. Patients were excluded if they received prior endocrine therapy for advanced disease. In the FIRST trial, patients could have received adjuvant endocrine therapy for early disease, provided it was completed more than 12 months before random assignment.

The pCODR review also provided contextual information on a manufacturer submitted network meta-analysis (NMA) comparing fulvestrant against palbociclib plus letrozole. The results of the NMA in the subgroup with non-visceral disease indicated that treatment with fulvestrant compared with palbociclib plus letrozole was not statistically significant for progression-free survival (PFS) and overall survival (OS). Key limitations identified included limited reporting on the methodology for the NMA in the subgroup of patients with non-visceral disease. Due to this, critical appraisal of the submitted NMA was limited by the lack of information. The assumption of proportional hazards was also not tested for PALOMA-1 (trial evaluating palbociclib plus letrozole). Overall, given these assumptions and the limited

reporting on the methodology for the subgroup NMA, the comparative efficacy of fulvestrant to palbociclib plus letrozole is uncertain.

Patient populations: Visceral disease not reported as a pre-planned analysis

In FALCON, patients were stratified based on disease (locally advanced or metastatic), prior chemotherapy (yes/no), and measurable (or non-measurable) disease. Although patient characteristics were mostly well balanced, a greater number of patients had visceral disease in the fulvestrant group (8% proportional difference) and were aged ≥ 65 years (8% proportional difference). The median age of patients was 64 years and 62 years in the fulvestrant and anastrozole groups, respectively. Most patients were white (76%), had a World Health Organization performance status of 0 to 1 (96%), receptor status (estrogen receptor–positive and progesterone receptor–positive [ER+PgR+]) (77%), metastatic disease (87%), and visceral disease (55%). All patients were HER– except for one patient in the anastrozole group. More patients in the fulvestrant group had at least one important protocol deviation compared with the anastrozole group (45.2% versus 33.6%).

In FIRST, there were more patients with visceral disease in the anastrozole group (9.2% proportional difference), more with previous hormonal treatment in the fulvestrant group (5.2% proportional difference), and more with no previous endocrine treatment in the anastrozole group (6.1% proportional difference). The median age of patients was 66 years and 68 years in the fulvestrant and anastrozole groups, respectively. Most patients had receptor status ER+PgR+ (76%), metastatic disease (82%), and visceral disease (52%). Human epidermal growth receptor status was negative for approximately 47% of patients in the FIRST study; however, the status for 34% of patients was unknown.

pERC considered the generalizability of the trial results and noted that few patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 2 were included in the trial; however, input from the Clinical Guidance Panel (CGP) indicated that the results of the trial can be generalized into patients with ECOG PS 0 to 3. pERC agreed that the decision for treatment should be based on the treating oncologist and whether a patient is deemed to be appropriate for therapy. Patients who have received adjuvant hormonal therapy were excluded from the FALCON trial. pERC also noted CGP's input indicating that previous trials have demonstrated a lack of efficacy in treating patients previously treated with hormonal therapy with fulvestrant in combination with a hormonal therapy. Therefore, the reimbursement population should be limited to patients who have not had hormonal therapy in any setting, including in the adjuvant setting. pERC also agreed that the reimbursement population should be limited to patients with non-visceral disease, in alignment with the submitted reimbursement request.

Key efficacy results: Modest improvement in PFS

The key efficacy outcome deliberated on by pERC was investigator-assessed PFS, the primary outcome from the FALCON study. PFS in the FIRST trial was a secondary end point.

In the overall trial population, fulvestrant was associated with a statistically significant improvement in PFS compared with anastrozole, with median PFS of 16.6 versus 13.8 months, respectively. This translated to an absolute difference in medians of 2.8 months (hazard ratio 0.797; 95% CI, 0.637 to 0.999; $P = 0.0486$). Median OS could not be calculated, as only 31% maturity had been achieved at a median follow-up of 25.0 months. The magnitude of PFS benefit in the subgroup of patients with non-visceral disease was larger (22.3 versus 13.8 months in the fulvestrant and anastrozole groups, respectively; hazard ratio 0.59; 95% CI, 0.42 to 0.84; $P = 0.0030$), translating into an absolute difference of 8.5 months. Similar to the total population, the median OS could not be calculated for the visceral disease subgroups.

The primary end point in the FIRST trial was clinical benefit rate, defined as the proportion of all randomly assigned patients who had a best overall response of a complete response, a partial response, or stable disease for at least 24 weeks. Fulvestrant was at least as effective as anastrozole, with clinical benefit rates of 72.5% and 67.0%, respectively. There was a statistically significant difference in PFS for fulvestrant compared with anastrozole (23.4 and 13.1 months, respectively; hazard ratio 0.58; 95% CI, 0.34 to 0.99; $P = 0.05$). Median OS in the overall trial also indicated statistical significance (hazard ratio 0.70; 95% CI, 0.50 to 0.98; $P = 0.04$). In the non-visceral subgroup, the clinical benefit rates were lower than those observed in the overall trial in both treatment groups. Median PFSs in the non-visceral subgroup of patients were 34.0 and 21.3 months in the fulvestrant and anastrozole groups, respectively (hazard ratio 0.58; 95% CI, 0.34 to 0.99; $P = 0.05$); this corresponds to a difference in medians of 12.7 months. OS was not statistically improved with fulvestrant among patients with non-visceral compared with visceral disease.

pERC considered the results of the FALCON trial and agreed that a modest and statistically significant improvement in PFS is clinically meaningful for patients. Given that the subgroup analysis based on non-visceral disease was not reported to be pre-planned, there is uncertainty in the interpretation that can be made from this analysis. Furthermore, a global test for interaction did not indicate the presence of any effect modifiers. In a post-hoc interaction test to assess for consistency of treatment effects across visceral involvement subgroups (visceral and non-visceral) the p-value was 0.0092, however, these results should be considered hypothesis generating as they were not pre-planned. Based on the Clinical Guidance Report, the test for interaction was likely not adequately powered, suggesting that the results on the test for interaction do not necessarily mean that there are no effect modifiers. pERC noted that PFS is not an established surrogate for OS in breast cancer; therefore, uncertainty remains about the impact of fulvestrant and anastrozole on OS. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the submitter related to the subgroup analysis in patients with non-visceral disease. The submitter indicated that this subgroup was pre-specified after the finalization of the protocol and included in the statistical analysis plan. pERC noted that the pCODR Methods Team indicated that although the non-visceral subgroup analysis was reported to be pre-specified by the submitter, it was not pre-specified at the trial onset and thus not included in the original study protocol. Furthermore, with regard to the non-visceral subgroup analysis, no information was available on the following: pre-specification of the analysis a priori, sample size calculation and power estimation, stratification to ensure balance across treatment groups, and formal adjustment for multiple comparisons to control for the risk of type I error (i.e., incorrectly concluding that a difference exists). pERC also agreed with the Methods Team's assessment that subgroup analyses are exploratory in nature, indicative only of possible subgroup effects (i.e., they are hypothesis-generating) and lacking the statistical strength to support strong conclusions on treatment effect. pERC reiterated that there is uncertainty in the interpretation that can be made from this subgroup analysis and agreed that the treatment effect in patients with non-visceral disease is, at worst, similar to results observed in the overall trial results.

Patient-reported outcomes: Maintained quality of life

pERC deliberated upon the available quality-of-life data from the FALCON trial, measured using the FACT-B and Trial Outcome Index (TOI) scales. Compliance to the FACT-B questionnaire was high in both groups. Overall, mean FACT-B and TOI scores were reported to be maintained and similar in both treatment groups. The mean change from baseline in TOI and FACT-B total scores remained stable (approximately ± 3 points to week 132); similar results were maintained in the FACT-B subscales. There was no clinically meaningful difference in the proportion of patients who had improved FACT-B total score and TOI with fulvestrant compared with anastrozole. Approximately one-third of patients had clinically meaningful improved TOI total scores from baseline up to week 144 with fulvestrant treatment and anastrozole treatment. pERC noted that these results were in alignment with input from patient advocacy groups, who indicated that fulvestrant had a mild toxicity profile and moderately improved quality of life.

Safety: Low incidence of toxicity

pERC discussed the toxicity profile of fulvestrant and noted that grade 3 or 4 adverse events (AEs), serious adverse events (SAEs), withdrawals due to AEs, and deaths on treatment were similar between the two treatment groups. In FALCON, there were grade 3 or higher AEs in 51 (22%) and 41 (18%) patients in the fulvestrant and anastrozole groups, respectively. SAEs occurred in 30 (13%) and 31 (13%) patients in the fulvestrant and anastrozole groups, respectively. Any AE leading to discontinuation occurred in 16 (7%) and 11 (4.7%) patients in the fulvestrant and anastrozole groups, respectively. Deaths due to AEs occurred in 6 (2.6%) and 7 (3%) patients in the fulvestrant and anastrozole groups, respectively. In the FIRST trial, SAEs were identified in 11.9% and 9.7% of patients in the fulvestrant and anastrozole groups, respectively. Three patients in each treatment group discontinued treatment because of an AE. One death due to an AE was reported in the FIRST trial. pERC discussed the available safety data on fulvestrant and agreed that the toxicity profile was low and similar between the two treatment groups in both studies.

Need and burden of illness: Treatment options available

Breast cancer is the most common cancer in women in Canada and the second most common cause of cancer mortality in Canadian women. Metastatic breast cancer is considered incurable but treatable, with 70% of women dying of their disease within five years and a median life expectancy of 31 months. ER+/HER2− breast cancer represents approximately 65% to 70% of all breast cancers. The goals of treatment for patients with advanced or metastatic breast cancer are primarily palliative; namely, maintaining or improving patients' length of life and quality of life by controlling progression of the disease. Traditionally, the first-line treatment for postmenopausal women with ER+/HER2− advanced or

metastatic breast cancer has included hormonal therapies (letrozole, anastrozole, exemestane, and tamoxifen). The selection and sequencing of hormone therapies are dependent factors that include patient's preference, comorbidities of the patient, performance status involvement of vital organs, pace of the disease, and previous history of exposure to treatments in the adjuvant (curative) setting. More recently, the CDK4/6 inhibitor palbociclib, in combination with letrozole, received a positive recommendation for reimbursement in this setting, having demonstrated improvements in PFS, objective response rates, and a manageable but not insignificant toxicity profile. Notably, this combination treatment is expected to be available to patients soon. The most effective treatment tends to be the one first employed, making the selection of such first-line therapy critical to a patient's cancer journey. pERC acknowledged a continued need for new and effective therapies for patients with advanced or metastatic breast cancer that provide improvements in patient survival, have more favourable toxicity profiles, and improve quality of life. However, the Committee agreed that the availability of palbociclib plus letrozole indicates that there is no urgent unmet need that can be filled by fulvestrant in this setting.

Registered clinician input: Fulvestrant as an alternative to palbociclib

According to registered clinician input, most clinicians would not prescribe fulvestrant in the first-line setting; rather, this drug may be regarded as an alternative to letrozole plus palbociclib in patients who do not want to be treated with a CDK4/6 inhibitor. Input also indicated that fulvestrant could be considered as a lower toxicity option for first-line therapy in patients with locally advanced or metastatic breast cancer. Fulvestrant was described as being favourable in patients who have a low-risk or intermediate-risk disease with good prognosis (e.g., non-visceral disease), patients with high-risk disease who have comorbidities limiting the use of combination targeted therapies, patients who cannot afford a CDK4 or CDK6 inhibitor, or patients in countries where CDK4 or CDK6 inhibitors have not been approved by regulatory authorities. pERC considered this input and reiterated that, in the absence of robust direct or indirect evidence comparing fulvestrant against palbociclib plus letrozole, the choice of treatment used will be guided by a variety of considerations. pERC agreed with CGP and registered clinician input that fulvestrant may be a more desirable treatment for patients for whom adherence to oral therapy may be a concern, who would prefer not to undergo regular phlebotomies, and who place a greater value on the maintenance of quality of life, as fulvestrant has a mild toxicity profile.

PATIENT-BASED VALUES

Values of patients with metastatic breast cancer: Quality of life and symptom management

pERC deliberated upon patient advocacy group input for palbociclib for advanced or metastatic breast cancer and discussed the values of patients with advanced or metastatic breast cancer. Patients with a diagnosis of metastatic breast cancer understand the limitations of current treatment options and seek to live their remaining months and years with the best possible quality of life that they can achieve. Input indicates that the diagnosis of advanced breast cancer, as well as the treatments that are used, impact both the social and physical well-being of a patient, thus impacting their quality of life. Fatigue was rated as having a significant or debilitating impact by most patients, followed by insomnia and pain.

Among 46 respondents, the most common symptoms experienced as a result of breast cancer include bone pain (76%), muscle weakness (50%), shortness of breath (41%), nausea (37%), and loss of appetite (33%). Based on the FIRST trial, pERC noted that any grade of bone pain occurred in less than 15% of patients and was reported in a similar proportion of patients in the two treatment groups. These symptoms most affected patients' ability to work, followed by ability to exercise, ability to perform household chores, and ability to travel. Patients also described how the social impact of their disease spreads across all aspects of their life, restricting their employment and career, ability to care for children and dependents, and ability to be social and meaningfully participate in their community. The financial burden associated with living with breast cancer also extends far beyond any loss of income during a temporary or permanent absence from employment, as patients can also incur substantial costs associated with treatment and disease management. Patients reported that they experience significant barriers and challenges around the availability of health care services and quality child care in their community.

pERC acknowledged that patients value having access to therapies that delay the progression of disease, relieve cancer-related symptoms, and improve quality of life. Therefore, pERC agreed that fulvestrant aligned with patient values.

Patient values on treatment: Treatment options, improved quality of life, improved survival

Patient input indicated that the goals of current treatment options for metastatic breast cancer include controlling the progression of the disease (extending life) and reducing cancer-related symptoms (extending or stabilizing quality of life). Patients gave varying responses when asked about the level of side effects and impact on quality of life they would be willing to accept to extend progression-free disease by six months. Input indicated that patients had previously taken a variety of treatments, with palbociclib, letrozole, and capecitabine listed as the top three. pERC noted that the majority of patients providing input had been previously treated and were not the population representative of the current reimbursement request. Among 48 respondents, the most commonly reported side effect from these treatments were fatigue (92%), followed by joint pain (69%), muscle pain (52%), back pain (48%), insomnia (48%), diarrhea (42%), constipation (42%), and nausea (38%).

Patients have an expectation that fulvestrant will extend PFS and allow them to live a better quality of life than if they were to receive chemotherapy or other hormonal therapies with more significant toxicity profiles. By delaying the progression of disease, treatments can relieve cancer-related symptoms and improve patients' quality of life. Patients placed greater emphasis on controlling disease and ensuring longer survival compared with reducing symptoms and managing side effects. Patients also stressed the importance of having a variety of treatment options available to them to avoid having to turn to chemotherapy as a treatment option. pERC noted that 31 patients who provided input had direct experience with fulvestrant, either as monotherapy or in combination therapy. Patients indicated that fulvestrant was moderately effective in reducing disease progression and drug side effects and improving quality of life. Patients indicated that side effects associated with fulvestrant ranged from non-existent to tolerable. Patients also indicated that quality of life, including productivity and ability to regain mobility and perform daily functioning, had improved on fulvestrant. Furthermore, patients described the ease of the injection and appreciated being able to schedule treatment in their lives. Overall, patients with ER+/HER2– advanced breast cancer who provided input value treatment options that improve survival, provide disease control, and improve quality of life.

ECONOMIC EVALUATION

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

The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness and cost-utility analysis for the hormonal treatment of non-visceral locally advanced or metastatic HER2– breast cancer in postmenopausal women, regardless of age, who have not been previously treated with endocrine therapy. Fulvestrant was compared with anastrozole monotherapy. An NMA was also conducted to compare fulvestrant against palbociclib plus letrozole; however, the results were not considered to be robust. pERC agreed with EGP's decision to not use the results of the NMA to provide reanalysis estimates.

Basis of the economic model: Clinical and economic inputs

Costs considered in the model provided by the submitter included drug costs, routine monitoring costs, and end-of-life care costs. The factors that most influence cost are the cost of fulvestrant and the duration and cost of active treatment in the post-progression state.

The key clinical outcomes considered in the model provided by the submitter were PFS, OS, and utilities. The factors that most influence the clinical effect estimates are the estimated long-term OS benefit gained with fulvestrant.

Drug costs: Fulvestrant costs more than anastrozole

At the list price, fulvestrant costs $582.90 per 250 mg/5 mL injection. At the recommended dosage of 500 mg on days 0, 14, and 28 in cycle 1, and then every 28 days thereafter, fulvestrant costs $124.91 per day and $3,497.37 per 28-day cycle 1. For subsequent cycles, fulvestrant costs $41.64 per day and $1,165.79 per 28-day cycle.

At the list price, anastrozole costs $1.27 per 1 mg tablet. At the recommended dose of 1 mg daily, anastrozole costs $1.27 per day and $35.64 per 28-day cycle.

Clinical effect estimates: Immature overall survival data have biggest impact on incremental cost-effectiveness ratio

pERC deliberated upon the cost-effectiveness of fulvestrant and concluded that it is not cost-effective as first-line therapy when compared with anastrozole monotherapy in postmenopausal women with ER+/HER2– advanced or metastatic breast cancer. pERC observed that the lack of mature OS data from FALCON trial created the largest uncertainty in the incremental cost-effectiveness ratio (ICER). EGP explored a number of model inputs and noted that only OS had the largest impact on the ICER. Based on three years of follow-up from the FALCON trial, which did not demonstrate statistically significant improvements in OS, the submitter modelled an OS advantage over a 15-year time horizon. To explore the impact of reducing this benefit, EGP made the OS beyond three years identical between the two treatment groups. This would, in effect, result in a sudden change of the OS curve from the fulvestrant group down to the anastrozole curve at the 3-year mark. Although acknowledging that such a sudden change in the relative OS is not a clinically plausible scenario, the Committee noted that this was the only way EGP was able to demonstrate the impact that OS has on the ICER and the resulting uncertainty in the estimates. Furthermore, pERC noted that the clinical effect estimates used in the economic model were based on the subgroup analysis in non-visceral disease. Given pERC's conclusion that the treatment effect in the subgroup of patients with non-visceral disease is at worst similar to results observed in the overall trial, it is unclear how the ICER may be impacted if the clinical effect estimates used in the model were altered to match those more modest results observed in the overall trial. Given these uncertainties, pERC concluded that fulvestrant is not cost-effective, and a substantial price reduction would be required to improve the cost-effectiveness to an acceptable level. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the submitter related to the EGP's reanalysis estimates. pERC reiterated that the treatment effect in the subgroup of patients with non-visceral disease is, at worst, similar to results observed in the overall trial, which reported no OS advantage. Despite the uncertainty in the clinical evidence, a long-term OS benefit in favour of fulvestrant was modelled in the submitted base case. pERC recognized that the only way the EGP was able to explore uncertainty in the modelled OS benefit was by setting OS to be equal between the two treatment groups beyond three years. As previously indicated, such a drastic drop in OS is not a clinically plausible scenario as it means patients are dying at exactly the three-year mark. In the absence of updated OS data to provide a full picture of the treatment's long-term effects, the Committee accepted that this was a reasonable way to demonstrate the impact of OS on the ICER. pERC also reiterated that the model used data from the subgroup analysis, which reported improvements in OS and a larger magnitude of PFS benefit in favour of fulvestrant. Based on further input from the EGP, pERC agreed that had the overall trial results been used in the model, the ICER is likely to be higher.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Few patients will qualify for treatment with fulvestrant

pERC discussed the feasibility of implementing a reimbursement recommendation for fulvestrant. The pCODR PAG noted that palbociclib plus letrozole is not yet funded at the time of this review but is a relevant comparator in this setting. pERC noted that there is insufficient direct or indirect clinical evidence to determine the comparative effectiveness between palbociclib plus letrozole and fulvestrant at this time. pERC agreed with CGP that patient values and preferences and clinical factors should guide treatment selection. pERC noted that there is no evidence to support sequencing of one treatment after the other.

PAG also requested input on the patient population that should qualify for treatment with fulvestrant. pERC agreed that the reimbursement population should be limited to patients with non-visceral disease, as indicated in the reimbursement request. Patients who had previously received adjuvant hormonal therapy were excluded from the trials; therefore, the results of the FALCON and FIRST trials should not be generalized into these patients. If fulvestrant is reimbursed, pERC noted that the uptake in first-line therapy for the prevalent population of patients with advanced or metastatic breast cancer is expected to be low, as many patients in the clinical setting would have received adjuvant hormonal therapy. Therefore, pERC anticipates that a small number of patients would qualify for treatment with fulvestrant. pERC further noted that the assumptions for market share were based on Ontario Public Drug coverage, which does not provide coverage to all patients under 65 years of age. pERC recognized that this assumption is not true for all jurisdictions, as 100% of patients in this age category may be covered in other jurisdictions.

pERC further noted that there are data comparing the use of fulvestrant and palbociclib as a combination therapy against fulvestrant alone. Given the scope of the current review, pERC agreed that this evidence would need to be submitted for full review before a decision on reimbursement could be made on this combination therapy. pERC also agreed that there is no evidence available on the use of fulvestrant as maintenance therapy after chemotherapy. At the time of implementing a reimbursement recommendation for fulvestrant, jurisdictions may consider addressing the short-term, time-limited need to offer fulvestrant to patients currently receiving anastrozole monotherapy for the treatment of postmenopausal women with non-visceral locally advanced or metastatic HER2– breast cancer, regardless of age, who have not been previously treated with endocrine therapy (including in the adjuvant setting).

DRUG AND CONDITION INFORMATION

Drug Information	• Selective estrogen receptor antagonist • 500 mg administered intramuscularly as two 5 mL (250 mg/5 mL) injections, one in each buttock, administered on days 0, 14, and 28 and then every 28 days thereafter
Cancer Treated	• Non-visceral locally advanced or metastatic HER2− breast cancer
Burden of Illness	• The median life expectancy is 31 months, with 70% of women dying of their disease within 5 years
Current Standard Treatment	• Palbociclib plus letrozole (not yet funded but anticipated to be most relevant comparator) • Anastrozole • Tamoxifen • Letrozole
Limitations of Current Therapy	• Frequent diagnostic phlebotomy, neutropenia, anemia, and fatigue with CDK4/6 inhibitors (i.e., palbociclib)

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:

pERC Membership During Deliberation of the Initial Recommendation

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

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

- Lauren Flay Charbonneau and Dr. Craig Earle, who were not present for the meeting
- Dr. Maureen Trudeau, who was excluded from chairing and voting due to a conflict of interest
- Dr. Anil Abraham Joy and Carole McMahon, who were excluded from voting due to a conflict of interest

pERC Membership During Deliberation of the Final Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Dr. Kelvin Chan, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician

Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Craig Earle, Oncologist
Cameron Lane, Patient Member Alternate
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

For the final recommendation Dr. Marianne Taylor acted as Chair. All members participated in deliberations and voting on the Final Recommendation, except:

- Drs. Craig Earle, Winson Cheung, Kelvin Chan and Catherine Moltzan, who were not present for the meeting
- Dr. Maureen Trudeau, who was excluded from chairing and voting due to a conflict of interest
- Carole McMahon, who was excluded from voting due to a conflict of interest

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 fulvestrant (Faslodex) for metastatic breast cancer, through their declarations, six members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, two 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 pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines.* There was no non-disclosable information in this Recommendation document.

Use of this Recommendation

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

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