

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:
Palbociclib (Ibrance)

Submitted Funding Request:
In combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease

Submitted By:
Pfizer Canada Inc.

Manufactured By:
Pfizer Canada Inc.

NOC Date:
March 16, 2016

Submission Date:
June 10, 2016

Initial Recommendation Issued:
November 3, 2016

pERC RECOMMENDATION

pERC recommends reimbursement of palbociclib (Ibrance) conditional on the cost-effectiveness being improved to an acceptable level. Reimbursement should be in combination with letrozole, for the treatment of post-menopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received any prior treatment for metastatic disease. Treatment should continue until unacceptable toxicity or disease progression. Patients should have good performance status and not be resistant to prior (neo)adjuvant aromatase inhibitor therapy, nor have active or uncontrolled metastases to the central nervous system.

pERC made this recommendation because it was satisfied that compared with letrozole monotherapy, there is a moderate net clinical benefit of palbociclib plus letrozole, based on statistically significant and clinically meaningful improvements in progression-free survival (PFS), objective response rates, and a manageable, but not insignificant toxicity profile. However, the Committee's assessment of net clinical benefit was tempered by the lack of a demonstrated improvement in quality of life (QoL) and a lack of evidence, at this time, demonstrating an improvement in overall survival (OS). pERC agreed that palbociclib plus letrozole partially aligns with patient values because of the delay in disease progression; however, the Committee agreed that, given the available evidence at this time, it was unclear whether cancer-related symptoms and QoL are improved with palbociclib plus letrozole.

pERC concluded that, at the submitted price, palbociclib plus letrozole is not cost-effective compared with letrozole monotherapy. pERC also

highlighted that the submitted potential budget impact of palbociclib plus letrozole is likely underestimated and would be substantial.

**POTENTIAL NEXT STEPS
FOR STAKEHOLDERS**

Pricing Arrangements to Improve Cost-Effectiveness and Decrease Budget Impact

Given that there is a moderate net clinical benefit of palbociclib plus letrozole, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of palbociclib plus letrozole to an acceptable level. pERC noted that a substantial reduction in the price of palbociclib would be required in order to improve the cost-effectiveness to an acceptable level and to decrease the predicted substantial budget impact.

Time-Limited Need for Palbociclib Plus Letrozole in Patients Currently Receiving First-Line Letrozole Monotherapy

At the time of implementing a funding recommendation for palbociclib plus letrozole, jurisdictions may consider addressing the short-term, time-limited need to offer palbociclib plus letrozole to patients currently receiving letrozole monotherapy for the treatment of post-menopausal women with ER-positive, HER2-negative (ER+/HER2-) advanced breast cancer who have not received any prior treatment for metastatic disease and who are not resistant to (neo)adjuvant aromatase inhibitor therapy.

Choice of Aromatase Inhibitor in Combination With Palbociclib

pERC agreed that palbociclib should be used in combination with letrozole, based on the available randomized controlled trial (RCT) evidence. However, the Committee felt that, in patients with intolerance to letrozole, it would be reasonable to use another aromatase inhibitor in combination with palbociclib if no disease progression had occurred during letrozole plus palbociclib.

Second-Line Use of Palbociclib Plus Fulvestrant Out of Scope

Although pERC acknowledged that data for the use of palbociclib in combination with fulvestrant for metastatic breast cancer patients who have progressed on prior endocrine therapy have been published (i.e., the PALOMA-3 trial), this was not the funding request from the submitter, and therefore it was considered to be out of scope for this review. pERC noted that a recommendation for palbociclib plus fulvestrant in the second-line setting would require that a submission with the appropriate clinical and economic information be made to pCODR.

Sequencing of Treatments in ER-Positive, HER2-Negative Advanced Breast Cancer

pERC was unable to make an informed recommendation on the optimal sequencing of everolimus plus exemestane and palbociclib plus letrozole, as the Committee noted that, as yet, there is no evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of palbociclib plus letrozole and noted that a national approach to develop evidence-based clinical practice guidelines would be of value.

Need for Appropriate Monitoring Due to Toxicity Concerns With Palbociclib

Given the risks of toxicity with palbociclib, pERC noted that jurisdictions should consider developing guidelines or processes to monitor and manage toxicity in patients who receive palbociclib.

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. pERC noted that the goals of treatment for patients with advanced or metastatic breast cancer are primarily palliative; namely, to prolong life while maintaining or improving QoL. pERC noted that in the treatment of first-line post-menopausal women with ER+/HER2- advanced or metastatic breast cancer, a number of endocrine therapies are available, including letrozole, anastrozole, exemestane, and tamoxifen. pERC acknowledged and agreed with the pCODR Clinical Guidance Panel that these endocrine therapies are standard treatment options in the first-line setting. Overall, pERC considered there to be a 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 QoL.

[pERC's Deliberative Framework](#) for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

The present review is a resubmission based on new clinical information. pERC deliberated upon the results of two RCTs, PALOMA-1 and PALOMA-2, that both compared palbociclib plus letrozole to letrozole monotherapy. pERC considered letrozole monotherapy to be a reasonable comparator. The Committee noted that the PALOMA-1 trial was the basis of the original submission to pCODR for palbociclib plus letrozole, and as such the Committee had previously deliberated upon it. The PALOMA-2 trial was a phase 3 double-blind RCT that, while not yet fully published, provided new evidence on the use of palbociclib plus letrozole for the requested reimbursement population. The Committee noted that PALOMA-2, similar to PALOMA-1, reported a statistically significant improvement in PFS and higher overall response rates in favour of palbociclib plus letrozole compared with letrozole plus placebo. pERC also noted a lack of OS data available at this time for the PALOMA-2 trial, which increased the Committee's uncertainty regarding the clinical benefit of palbociclib plus letrozole. In the absence of OS data, pERC discussed the clinical significance of PFS in advanced or metastatic breast cancer. While multiple opinions were expressed, the majority of pERC members agreed that the delay in progression of disease is a meaningful end point in this clinical setting, and therefore, a majority of the Committee members agreed that the PFS benefit observed in PALOMA-2 is clinically meaningful. pERC also discussed the available QoL data from the PALOMA-2 trial and noted that the QoL for palbociclib plus letrozole did not decline more than for letrozole plus placebo. However, pERC also noted that the QoL for palbociclib plus letrozole was not improved compared with letrozole plus placebo and that the number of patients who contributed to the assessments substantially decreased over time, which increases the uncertainty in the QoL results.

pERC discussed the toxicity profile of palbociclib plus letrozole and noted that there were more frequent toxicities compared with letrozole monotherapy, including adverse events such as neutropenia, fatigue, anemia, nausea, and alopecia. In particular, the Committee noted that neutropenia occurred in a much higher proportion of patients who received palbociclib plus letrozole compared with letrozole monotherapy, and that a small proportion of patients who received palbociclib plus letrozole experienced neutropenic fever. pERC recognized that the toxicity profile of palbociclib is different from standard endocrine therapies and that patients on palbociclib would require more frequent clinic visits and health care resources to monitor for and treat adverse events. pERC noted that the adverse events could be managed in clinical practice through dose adjustments.

pERC concluded that there is a moderate net clinical benefit of palbociclib plus letrozole compared with letrozole monotherapy, based on the clinically meaningful results in PFS and overall response, no observed detriment in QoL and a manageable, but not insignificant, toxicity profile. In making this conclusion, the Committee's deliberations were tempered by the lack of a demonstrated improvement in QoL and as yet, the unavailability of evidence demonstrating an improvement in OS.

pERC noted that the submitter provided a network meta-analysis that compared palbociclib plus letrozole with other first-line therapies. pERC acknowledged and agreed with the pCODR Clinical Guidance Panel's inability to confidently draw conclusions on palbociclib plus letrozole compared with other aromatase inhibitors (AIs) given the limitations in the submitted network meta-analysis.

pERC reviewed patient advocacy group input indicating that patients value treatments that delay progression, relieve cancer-related symptoms, and improve QoL. Input indicated that patients with ER+/HER2- advanced or metastatic breast cancer were willing to accept adverse effects if there was a clinical benefit. pERC acknowledged that in the patient advocacy group input, patients who had direct experience with palbociclib indicated that the side effects of palbociclib were tolerable. pERC noted that in PALOMA-2, despite the toxicities of palbociclib plus letrozole, QoL did not decline more than for letrozole plus placebo; however, there was no improvement in QoL for patients who received palbociclib plus letrozole compared with those who received letrozole plus placebo. On balance, therefore, pERC considered palbociclib plus letrozole to only partially align with patient values.

pERC deliberated upon the cost-effectiveness of palbociclib plus letrozole and concluded that it is not cost-effective when compared with letrozole monotherapy in post-menopausal women with ER+/HER2- advanced or metastatic breast cancer as first-line therapy. pERC discussed that the lack of OS data from PALOMA-2 increased the uncertainty in the estimates of incremental cost-effectiveness. Furthermore, the Committee discussed the available QoL data from PALOMA-2 that were used in the submitted model and noted that the limitations in the available data increased the uncertainty in the incremental cost-effectiveness estimates. pERC noted that the main drivers of the incremental cost in the analysis were the cost of the palbociclib and the cost of treatments in the post-progression state. pERC noted that neither the submitter's nor the pCODR Economic Guidance Panel's best estimates of the incremental cost-effectiveness of palbociclib plus letrozole could be considered cost-effective compared with letrozole monotherapy. The Committee discussed the lack of OS data from PALOMA-2 and the uncertainty in the QoL benefit that patients would derive from palbociclib, and that this increased the uncertainty in the incremental cost-effectiveness estimates for palbociclib plus letrozole compared with letrozole monotherapy. Given these limitations, pERC concluded that a substantial price reduction would be required in order to improve the cost-effectiveness of palbociclib to an acceptable level.

pERC also considered the feasibility of implementing a reimbursement recommendation for palbociclib plus letrozole. The pCODR Provincial Advisory Group (PAG) noted the high cost of palbociclib, large patient population, and additional health care resources as being key challenges. pERC noted that palbociclib is to be added on to existing therapy, and overall treatment costs could be expected to increase if it were reimbursed. pERC noted that the submitted budget impact analysis likely underestimates the market share that palbociclib would capture if reimbursed. If palbociclib were reimbursed, the uptake in first-line therapy for the prevalent population of advanced or metastatic breast cancer would be high, and there would exist a short-term, time-limited need to offer palbociclib plus letrozole to patients currently receiving letrozole monotherapy for the treatment of post-menopausal women with ER+/HER2- metastatic breast cancer. pERC concluded that a substantial reduction in the price of palbociclib would be required to decrease the budget impact. PAG also requested input on the use of palbociclib plus letrozole in patients who have failed other AIs. pERC noted that the PALOMA-2 trial excluded patients who were resistant to prior (neo)adjuvant AI therapy and that these patients should not receive therapy with palbociclib plus letrozole. The Committee also discussed the fact that patients with active or uncontrolled metastases to the central nervous system were excluded from the trial and, therefore, should not receive treatment with the combination. pERC noted that, although palbociclib is an oral therapy, frequent monitoring of adverse events and dose adjustments may limit its accessibility. pERC also agreed that, given the toxicity concerns with palbociclib (e.g., neutropenia), jurisdictions should consider developing guidelines or processes to monitor and manage patients who receive palbociclib.

Input from the PAG indicated that various AIs are available for the initial treatment of ER+/HER2- metastatic breast cancer, including anastrozole, letrozole, and exemestane. pERC discussed the generalizability of the combination of palbociclib with letrozole to other AIs and noted that, based on the available evidence, palbociclib should be used in combination with letrozole. However, the Committee agreed that, in patients with intolerance to letrozole, it would be reasonable to offer palbociclib in combination with another AI. Lastly, pERC discussed the sequencing of treatments in ER+/HER2- metastatic breast cancer. Specifically, the Committee was unable to draw any conclusions on the optimal sequencing of everolimus plus exemestane with palbociclib plus letrozole, as there is no evidence, to

date, to inform this clinical situation. pERC agreed that, upon implementation of reimbursement of palbociclib plus letrozole, provinces should collaborate to develop national evidence-based clinical practice guidelines to inform this clinical situation.

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 provides clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from pCODR clinical and economic review panels
- Input from two patient advocacy groups: Rethink Breast Cancer and Canadian Breast Cancer Network
- Input from two individual oncologists
- Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the efficacy and safety of palbociclib (Ibrance) in combination with letrozole for the treatment of post-menopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative (ER+/HER2-) advanced breast cancer who have not received previous systemic treatment for their advanced disease.

Studies included: Two randomized trials

The pCODR systematic review included two trials: PALOMA-1 and PALOMA-2. Both trials were international, multi-centre randomized controlled trials (RCTs) and both compared palbociclib plus letrozole to letrozole monotherapy. PALOMA-1 was a phase 2, open-label trial evaluating the initial efficacy and safety of palbociclib-letrozole compared with letrozole alone. PALOMA-2 was a double-blinded, placebo-controlled phase 3 trial to confirm the results of PALOMA-1. pERC noted that the PALOMA-2 trial was published in abstract form only and that additional trial data was provided in a top line clinical summary report by the Submitter. In both trials, patients received palbociclib at a dose of 125 mg once daily for 21 days, with seven days off. Letrozole was given at a continuous dose of 2.5 mg once daily in both treatment groups, and in PALOMA-2 a matched placebo was administered in addition to letrozole monotherapy to patients randomized to the control arm (letrozole plus placebo). Treatment was continued until disease progression, unacceptable toxicity, study withdrawal, or death. Crossover was not permitted in either trial.

Patient populations: Stage IV de novo or metastatic disease, ECOG performance status 0 to 1

The PALOMA-1 trial randomized 165 patients 1:1 to receive palbociclib plus letrozole or letrozole alone. The PALOMA-2 trial randomized 666 patients 2:1 to receive palbociclib plus letrozole or letrozole plus placebo. Overall, the distribution of patient characteristics appeared similar in both trials. PALOMA-2 had higher proportions of patients with non-visceral sites of disease and prior receipt of hormonal therapy, whereas in PALOMA-1, more patients had shorter disease-free interval (≤ 12 months) from completion of (neo)adjuvant therapy to recurrence. PALOMA-1 enrolled patients with Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1, whereas PALOMA-2 allowed enrolment of patients with ECOG performance status 0-2, although the number of patients with ECOG performance status 2 was very small (1.8%).

Key efficacy results: Progression-free survival

Results from PALOMA-2, presented in an abstract, confirmed that the primary end point of progression-free survival (PFS) was improved with the addition of palbociclib to letrozole compared with letrozole monotherapy in the treatment of first-line ER+/HER2- post-menopausal patients with advanced or metastatic breast cancer. The median investigator-assessed PFS was 24.8 months in the palbociclib plus letrozole group, compared with 14.5 months in the letrozole monotherapy group (hazard ratio [HR] 0.58; 95% confidence interval [CI], 0.46-0.72; one-sided $P < 0.000001$). This 10-month incremental PFS benefit was also seen in the PALOMA-1 trial. All secondary outcomes examined in each trial, including objective response rate (ORR), duration of response, and disease control/clinical benefit, also favoured palbociclib

plus letrozole. Overall survival (OS) data were deemed immature at the time of data collection. pERC noted that the pCODR Clinical Guidance Panel (CGP) felt that PFS is a clinically meaningful end point for first-line ER+/HER2- post-menopausal advanced or metastatic breast cancer. The Committee discussed whether, in the absence of OS data, PFS is a meaningful end point in this clinical setting. Differing opinions were expressed regarding the interpretation of a PFS benefit where there is a lack of a demonstrated improvement, or detriment, in quality of life (QoL) (see Quality of Life section, below).

Quality of life: No demonstrated improvement or detriment, but caution required

Quality-of-life outcomes were not collected in PALOMA-1 but were measured in PALOMA-2. The addition of palbociclib to letrozole did not appear to lead to an improvement, or a detriment, in health-related QoL or pain outcomes as measured by Functional Assessment of Cancer Therapy scale for patients with breast cancer (FACT-B), EuroQoL 5-Dimensions (EQ-5D), and modified Brief Pain Inventory-Short Form (BPI-sf) instruments, although these analyses have limitations, such as the substantial decline in the number of patients completing assessments over the course of the trial and the lack of adjustment for testing multiple comparisons of the QoL data. pERC acknowledged that the pCODR Methods Team stated that the assessments of QoL need to be interpreted with caution.

Safety: Moderate toxicities requiring more frequent monitoring

The most common serious adverse events (AEs), of any grade, include neutropenia, alopecia, fatigue, nausea, and anemia. The most common grade 3 or 4 adverse event in both the PALOMA-1 and PALOMA-2 trials was neutropenia: 54% and 55% in the palbociclib plus letrozole group, in PALOMA-1 and PALOMA-2, respectively, versus 1% and < 1% in the letrozole monotherapy group. In the PALOMA-2 confirmatory trial, pERC noted that febrile neutropenia occurred in 1.6% of patients on palbociclib plus letrozole, compared with no patients on letrozole monotherapy. pERC also noted that permanent discontinuation of treatment and deaths due to AEs were higher in the palbociclib plus letrozole group compared with the letrozole monotherapy group. Although most of the AEs could be managed in clinical practice through dose adjustments, pERC noted that patients on palbociclib plus letrozole would require more frequent clinic visits and health care resources to monitor for and treat AEs than patients on letrozole monotherapy, and based on the CGP, these visits may be monthly for palbociclib plus letrozole, whereas they would be once every three months (or more) for letrozole monotherapy.

Comparator information: Other aromatase inhibitors, such as anastrozole and exemestane

PALOMA-1 and PALOMA-2 compared palbociclib plus letrozole to letrozole monotherapy in post-menopausal women with ER+/HER2- advanced breast cancer. pERC noted that the submitter conducted a network meta-analysis comparing palbociclib plus letrozole to anastrozole, tamoxifen, and exemestane to inform the cost-effectiveness analyses. Contextual information provided in the pCODR Clinical Guidance Report discussed the limitations of the indirect comparison, and included the omission of other combination therapies from the Submitter's primary analysis (versus only single-agent regimens), failure to include other important outcomes (i.e., AEs), significant heterogeneity across the included trials, and the inability to adjust for the influence of heterogeneity due to constraints in the structure of the evidence networks (e.g., single trial connections or small number of trials). pERC noted that the pCODR Clinical Guidance Report concluded that the results of the network meta-analysis should be interpreted with caution. pERC acknowledged that the CGP felt that, based on the available RCT evidence, palbociclib should be used in combination with letrozole.

Need and burden of illness: Treatment with improved survival, quality of life, and reduced toxicity

Breast cancer is the most common cancer in women in Canada and the second most common cause of cancer mortality in Canadian women. ER+/HER2- breast cancer represents approximately 65% to 70% of all breast cancers. For the treatment of first-line post-menopausal women with ER+/HER2- advanced or metastatic breast cancer, a number of endocrine therapies are available including letrozole, anastrozole, exemestane, and tamoxifen. pERC noted that the main goal of treatment is to extend survival while maintaining or improving QoL. pERC noted that there is a need for new and more effective treatments that improve OS, have fewer toxicities, and improve QoL.

Registered clinician input: Large potential budget impact, concern with toxicities

According to registered clinician input, ER+/HER2- advanced or metastatic breast cancer is a common disease with a high incidence, which has the potential for a large budget impact. pERC noted that one of

the registered clinicians had concerns about using palbociclib plus letrozole in the absence of OS data and long-term safety data. The clinician noted that with exemestane plus everolimus, the initial trial data were promising, but later publications indicated that the benefit was not as large as initially reported and no OS benefit was demonstrated. pERC also noted that the other registered clinician who provided input expressed that the PFS benefit of palbociclib plus letrozole observed in the available evidence is large and would lead to longer-term disease control and delay of progression. That clinician also noted that the toxicities of palbociclib plus letrozole are predictable, manageable, and limited in duration if therapy is discontinued.

PATIENT-BASED VALUES

Values of patients with metastatic breast cancer: Improved disease control and quality of life

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. pERC acknowledged that patients indicated that it is important to have access to therapies that delay the progression of disease, relieve cancer-related symptoms, and improve QoL.

Patient values on treatment: Disease control with acceptable toxicities

pERC noted that seven patients who provided input had direct experience with palbociclib. These patients reported that palbociclib stabilized and controlled their disease and provided the ability to live a productive life with excellent QoL. AEs, such as neutropenia and fatigue, were reported to be tolerable and manageable through dose adjustments and supportive medications. pERC noted that there was limited information available on the seven patients who had experience with palbociclib which made it difficult for the Committee to draw conclusions.

Overall, patients with ER+/HER2- advanced breast cancer and who provided input were willing to accept AEs for longer survival, improved disease control, or QoL.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis in the first-line setting for post-menopausal women with ER+/HER2- advanced or metastatic breast cancer. Palbociclib plus letrozole was compared with letrozole monotherapy. A network meta-analysis was also conducted to compare palbociclib plus letrozole to other aromatase inhibitors (AIs) (anastrozole or exemestane) or tamoxifen.

Basis of the economic model: Clinical and economic inputs

Costs considered in the model provided by the submitter included drug costs, monitoring costs, and post-progression treatment costs. The key clinical outcomes considered in the model provided by the submitter were PFS, OS, and utilities. The factors that most influence cost are the cost of palbociclib, and the duration and cost of active treatment in the post-progression state.

Drug costs: Cost of treatment

Palbociclib costs \$297.62 per 75 mg, 100 mg, and 125 mg capsule. At the recommended dose of 125 mg once daily for 21 days followed by seven days off treatment, palbociclib costs \$297.62 per day and \$6,250 per 28-day course.

Letrozole costs \$1.38 per 2.5 mg tablet. At the recommended dose of 2.5 mg once daily for 28 days, letrozole costs \$1.38 per day and \$38.58 per 28-day course.

The cost of palbociclib plus letrozole combination, at the recommended doses, is \$299.00 per day and \$6,288.58 per 28-day course.

Anastrozole costs \$1.28 per 1 mg tablet. At the recommended dose of 1 mg once daily for 28 days, anastrozole costs \$1.29 per day and \$35.64 per 28-day course. Exemestane costs \$1.33 per 25 mg tablet.

At the recommended dose of 25 mg once daily for 28 days, exemestane costs \$1.33 per day and \$37.14 per 28-day course. Tamoxifen costs \$0.35 per 20 mg tablet. At the recommended dose of 20 mg once daily for 28 days, tamoxifen costs \$0.35 per day and \$9.80 per 28-day course.

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

pERC deliberated upon the cost-effectiveness of palbociclib plus letrozole and noted that the EGP's estimate of the incremental cost-effectiveness ratio (ICER) was higher than the submitter's estimate. The factors that most influence cost are the survival benefits after trial period, assumptions regarding duration of post-progression active treatment, and different clinical pathways that may not be concordant with clinical practice. pERC reviewed the ICERs provided by both the submitter and the EGP and determined that palbociclib plus letrozole was not cost-effective, at the submitted price, when compared with letrozole monotherapy in either analysis. pERC noted that a substantial reduction in the price of palbociclib would be required to improve the cost-effectiveness to an acceptable level.

pERC agreed with the EGP's approach to not provide reanalysis estimates for the comparison of palbociclib plus letrozole versus anastrozole, tamoxifen, and exemestane, given limitations in the submitted network meta-analysis (see the Comparator Information section).

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Large population and high drug cost

pERC discussed the feasibility of implementing a reimbursement recommendation for palbociclib plus letrozole. pERC noted that the key challenges to implementation are the high cost of palbociclib, large patient population, and additional health care resources required for monitoring AEs. pERC noted that palbociclib is added on to an existing therapy and overall treatment costs would be expected to increase, if it were reimbursed. pERC also noted that the submitted budget impact analysis is likely underestimated, as it probably underestimated the market share that palbociclib would capture if reimbursed. The Committee noted that, if palbociclib were reimbursed, the uptake in first-line therapy for the prevalent population of advanced or metastatic ER+/HER2- breast cancer would be high, and that there would exist a short-term, time-limited need to offer palbociclib plus letrozole to patients currently receiving letrozole monotherapy. pERC recognized that, at the current price, the affordability of palbociclib would be unmanageable for most (if not all) jurisdictions and that a substantial price reduction would be required to decrease the budget impact.

pERC noted that PAG requested input on the use of palbociclib plus letrozole in patients who have failed other AIs. pERC noted that the PALOMA-2 trial excluded patients who were resistant to prior (neo)adjuvant AI therapy and that these patients should not receive therapy with palbociclib plus letrozole. pERC also discussed patients with active or uncontrolled metastases to the central nervous system and that they were excluded from the trial, and that these patients should not receive treatment with palbociclib plus letrozole. pERC also noted that, although palbociclib is an oral therapy, it has significant toxicities that require frequent monitoring and dose adjustments, which may limit its accessibility. In discussion, pERC noted that, given those toxicity concerns (e.g., neutropenia), jurisdictions should consider developing guidelines or processes to monitor and manage patients who receive palbociclib.

PAG indicated that various aromatase inhibitors are available for initial treatment of ER+/HER2- advanced or metastatic breast cancer. pERC was unable to draw conclusions on the clinical benefit of palbociclib plus letrozole compared with other AIs, given limitations in the network meta-analysis provided. However, the Committee discussed that, in patients with intolerance to letrozole, it may be reasonable to offer palbociclib in combination with another AI. Lastly, pERC discussed the sequencing of treatments for ER+/HER2- metastatic breast cancer and noted that there is a lack of evidence to inform the optimal sequencing of the available treatments. pERC noted that, upon implementation of a reimbursement recommendation for palbociclib plus letrozole, the provinces should collaborate to develop national evidence-based clinical practice guidelines to inform this clinical situation.

DRUG AND CONDITION INFORMATION

Drug Information	<ul style="list-style-type: none"> • Potent and highly selective reversible inhibitor of cyclin dependent protein kinase 4 and 6 • 75 mg, 100 mg, and 125 mg capsules • 125 mg orally once daily for 21 consecutive days, followed by seven days off treatment
Cancer Treated	<ul style="list-style-type: none"> • Estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-) advanced or metastatic breast cancer • First-line setting
Burden of Illness	<ul style="list-style-type: none"> • Breast cancer is the most common cancer in women in Canada and the second most common cause of cancer mortality in Canadian women • Patients with breast cancer may present with or develop advanced or metastatic disease
Current Standard Treatment	<ul style="list-style-type: none"> • Letrozole • Anastrozole • Exemestane • Tamoxifen • Fulvestrant
Limitations of Current Therapy	<ul style="list-style-type: none"> • Estrogen-driven breast cancers with an initial response to endocrine therapy eventually become resistant

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. Paul Hoskins, Oncologist (Vice-Chair)
 Dr. Scott Berry, Oncologist
 Dr. Kelvin Chan, Oncologist
 Dr. Matthew Cheung, Oncologist
 Dr. Craig Earle, Oncologist
 Dr. Allan Grill, Family Physician
 Don Husereau, Health Economist

Dr. Anil Abraham Joy, Oncologist
 Karen MacCurdy Thompson, Pharmacist
 Valerie McDonald, Patient Member Alternate
 Carole McMahon, Patient Member
 Dr. Catherine Moltzan, Oncologist
 Jo Nanson, Patient Member
 Dr. Marianne Taylor, Oncologist
 Danica Wasney, Pharmacist

Dr. Paul Hoskins chaired the meeting in his capacity as Vice-Chair of pERC. All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Maureen Trudeau, Dr. Anil Abraham Joy, and Don Husereau, who were excluded from deliberations and voting due to a conflict of interest
- Carole McMahon and Jo Nanson, who were excluded from voting due to a conflict of interest
- Dr. Allan Grill, who was not present for the meeting.

Avoidance of conflicts of interest

All members of pERC 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 palbociclib (Ibrance) for advanced breast cancer, through their declarations, five members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, the five 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, clinician, and Provincial Advisory Group input, as well as original patient advocacy group and clinician 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*.

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