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Reimbursement Recommendation

Abemaciclib (Verzenio)

Indication: For the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative, advanced or metastatic breast cancer, in combination with fulvestrant in women with disease progression following endocrine therapy

Sponsor: Eli Lilly Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Verzenio Plus Fulvestrant?

Canada's Drug Agency (CDA-AMC) recommends that Verzenio plus fulvestrant be reimbursed by public drug plans for the treatment of hormone receptor (HR)–positive, HER2-negative advanced or metastatic breast cancer in combination with fulvestrant for patients with disease progression following endocrine therapy if certain conditions are met.

Which Patients Are Eligible for Coverage?

Verzenio plus fulvestrant should only be covered to treat adults with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. Verzenio plus fulvestrant should not be covered for patients who have previously received cyclin-dependent kinase (CDK) 4 or CDK6 inhibitors in the metastatic setting, more than 1 line of chemotherapy or more than 1 line of endocrine therapy, or treatment with fulvestrant.

What Are the Conditions for Reimbursement?

Verzenio plus fulvestrant should only be reimbursed if prescribed under the care of clinicians with expertise in the treatment of advanced breast cancer, and if the cost of Verzenio for the indicated population does not exceed the drug program cost of treatment with ribociclib, both in combination with fulvestrant.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical trial (MONARCH 2) demonstrated that Verzenio plus fulvestrant improved overall survival (OS) and progression-free survival (PFS) with a manageable safety profile compared to placebo plus fulvestrant.
- Based on the CDA-AMC assessment of the health economic evidence, Verzenio plus fulvestrant does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Verzenio than for ribociclib, both in combination with fulvestrant, which was deemed to be the most relevant comparator for abemaciclib in this reimbursement decision.
- Verzenio plus fulvestrant was considered to meet important patient and clinician needs by providing clinically meaningful improvements in OS and disease control, delaying disease progression, and offering a manageable safety profile in a convenient oral formulation.

Summary

- Based on public list prices, Verzenio plus fulvestrant is estimated to cost the public drug plans approximately $29.3 million over the next 3 years. However, the actual budget impact is uncertain and will depend on the remaining number of people eligible for treatment with abemaciclib in the second line due to previous exposure to abemaciclib, as well as the uptake of generics for palbociclib.

Additional Information

What is HR-Positive, HER2-Negative Advanced or Metastatic Breast Cancer?

Breast cancer is the most common cancer, and the second leading cause of cancer deaths, among women in Canada. When it spreads beyond the breast or cannot be removed surgically, it is considered locally advanced or metastatic. The most common subtype in Canada is HR-positive, HER2-negative breast cancer, representing about 66% to 75% of cases.

Unmet Needs in HR-Positive, HER2-Negative Advanced or Metastatic Breast Cancer

For patients with HR-positive, HER2-negative advanced or metastatic breast cancer that has progressed after endocrine therapy, treatment options are limited. Major gaps include resistance to available therapies, treatment-related side effects, and lack of curative options.

How Much Does Verzenio Plus Fulvestrant Cost?

Treatment with Verzenio as an add-on to fulvestrant is expected to cost $6,508 per patient for a 28-day cycle. The 28-day per patient cost of abemaciclib plus fulvestrant for the indicated population is expected to be $7,324 for the first cycle and $6,916 for subsequent cycles.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that abemaciclib be reimbursed for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer, in combination with fulvestrant for patients with disease progression following endocrine therapy only if the conditions listed in Table 1 are met.

This recommendation supersedes the pERC recommendation for this drug and indication dated July 5, 2019.

Rationale for the Recommendation

One phase III, randomized, double-blind, placebo-controlled trial (MONARCH 2; N = 669) demonstrated that abemaciclib plus fulvestrant provides added clinical benefit in patients with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease has progressed following endocrine therapy. The final analysis after a median follow-up of 79.7 months showed that, compared to placebo, abemaciclib plus fulvestrant significantly improved OS (median OS = 45.8 months versus 37.3 months; hazard ratio = 0.78; 95% confidence interval [CI], 0.64 to 0.96) and PFS (median PFS = 16.9 months versus 9.3 months; hazard ratio = 0.54; 95% CI, 0.45 to 0.65). These benefits were consistent across prespecified subgroups and confirmed by sensitivity analyses. Diarrhea and neutropenia were the most common adverse events (AEs). However, harms were generally considered manageable in clinical practice.

Results from the sponsor-submitted indirect treatment comparisons (ITCs) suggested favourable effects of abemaciclib plus fulvestrant relative to everolimus-based regimens, fulvestrant monotherapy, and exemestane. However, comparisons with ribociclib plus fulvestrant, palbociclib plus fulvestrant, and exemestane plus everolimus were associated with substantial uncertainty due to imprecise effect estimates, heterogeneity across studies, and methodological limitations in the indirect comparisons. As a result, definitive conclusions regarding the comparative clinical efficacy of abemaciclib plus fulvestrant versus these regimens could not be drawn.

pERC acknowledged the needs identified by patients and clinicians for therapy options that prolong survival, delay progression, maintain health-related quality of life (HRQoL), and defer the need for chemotherapy. Based on the evidence reviewed, pERC determined that abemaciclib plus fulvestrant met some of these needs, such as offering a meaningful clinical benefit in survival and disease control with a manageable safety profile, and the oral route of administration will be convenient to many patients. Overall, pERC concluded that abemaciclib plus fulvestrant represents a useful treatment option for patients with HR-positive, HER2-negative advanced or metastatic breast cancer.

At the sponsor-submitted price for abemaciclib and publicly listed prices for all other drugs, abemaciclib plus fulvestrant was more costly than other CDK4 or CDK6 inhibitor combinations and exemestane plus everolimus. As abemaciclib plus fulvestrant is considered likely similarly effective as ribociclib plus fulvestrant, the total drug cost of abemaciclib plus fulvestrant should not exceed the total drug cost of ribociclib plus fulvestrant.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Reimbursement of abemaciclib plus fulvestrant should be limited to adults with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.	Based on the eligibility criteria from the MONARCH 2 trial, abemaciclib plus fulvestrant improved OS and PFS in patients with these characteristics.	There is insufficient evidence that abemaciclib is clinically superior or inferior to other CDK4 or CDK6 inhibitors currently reimbursed for the same indication. Therefore, the eligibility criteria for abemaciclib should align with those used by each of the public drug plans for reimbursement of CDK4 or CDK6 inhibitors for the same indication.
2. Patients should not be eligible if they: 2.1. were previously treated with a CDK4 or CDK6 inhibitor in the metastatic setting 2.2. received more than 1 line of chemotherapy or more than 1 line of endocrine therapy 2.3. received prior treatment with fulvestrant.	Patients previously exposed to CDK4 or CDK6 inhibitors were excluded from the MONARCH 2 trial. No evidence was submitted to demonstrate benefit in this subgroup.	pERC noted that while this exclusion criterion of the MONARCH 2 trial was appropriate for its purpose, in clinical practice, patients who are intolerant to palbociclib or ribociclib (given in combination with fulvestrant) would be permitted to switch to abemaciclib as long as they had not had progressive disease while on these therapies.
Discontinuation		
3. Reimbursement of abemaciclib should be discontinued upon the occurrence of any of the following: 3.1. disease progression 3.2. intolerable side effects.	These discontinuation criteria are consistent with the protocol of the MONARCH 2 trial and routine clinical practice. In the MONARCH 2 trial, treatment was continued until disease progression or unacceptable toxicity.	According to the clinical experts, treatment response and tolerability should be assessed at regular intervals based on clinical evaluation and imaging every 8 to 12 weeks. In the Monarch 2 trial, monitoring was based on tumour response assessment, and RECIST 1.1 criteria (e.g., imaging) every 6 to 8 weeks. pERC noted that evaluation of response to treatment should be based on standard institutional guidelines for metastatic breast cancer.
Prescribing		
4. Abemaciclib plus fulvestrant should be prescribed under the care of clinicians with expertise in the treatment of advanced breast cancer.	This condition ensures appropriate patient selection, monitoring, and management of treatment-related adverse events.	—
Pricing		
5. Abemaciclib should be negotiated so that abemaciclib plus fulvestrant does not exceed the drug program cost of treatment with ribociclib plus fulvestrant reimbursed for the treatment of HR-positive, HER2--	pERC and the clinical experts considered ribociclib to be the most relevant comparator for abemaciclib. The sponsor-submitted indirect treatment comparisons had limitations that prevented a definitive conclusion about the comparative efficacy	—

Reimbursement condition	Reason	Implementation guidance
negative advanced or metastatic breast cancer for patients with disease progression following endocrine therapy.	of abemaciclib vs. other CDK4 or CDK6 inhibitors. As such, there is insufficient evidence to justify a cost premium for abemaciclib plus fulvestrant over ribociclib plus fulvestrant reimbursed for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer for patients with disease progression following endocrine therapy.	
Feasibility of adoption		
6. The feasibility of adoption of abemaciclib plus fulvestrant must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimates.	—

CDK = cyclin-dependent kinase; HR = hormone receptor; OS = overall survival; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1; vs. = versus.

Discussion Points

- **New data supporting reassessment**: pERC discussed that in 2019 abemaciclib plus fulvestrant was given a conditional recommendation for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer that noted a lack of evidence demonstrating a statistically significant improvement in OS based on the data available at the time (after a median follow-up of 47.7 months). The committee acknowledged that the sponsor's objective for this resubmission, based on mature long-term OS data after a median follow-up of 79.7 months, was to address the uncertainty regarding the OS benefit of abemaciclib plus fulvestrant for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer expressed in the previous recommendation. pERC observed that the updated data from the MONARCH 2 trial showed statistically significant and clinically meaningful OS and PFS benefits. pERC also noted that the results of the prespecified subgroups, confirmed by sensitivity analyses, indicated consistent clinically meaningful OS and PFS benefits, suggesting robustness of the findings.
- **Unmet needs**: Patients and clinicians identified key unmet needs, including improved survival, delayed disease progression, maintenance of quality of life, and treatment options that could defer the need for chemotherapy. pERC acknowledged the continued need for effective treatment options for patients whose disease has progressed following endocrine therapy. The committee determined that abemaciclib plus fulvestrant meets several of the identified needs, as demonstrated in the reported clinically meaningful OS and PFS benefits.
- **AEs**: pERC noted that the most common AEs were diarrhea and neutropenia, which were generally low grade and manageable with dose modifications. Although a high proportion of patients required

dose reductions, the clinical experts indicated that these were known and manageable AEs. The committee acknowledged that the safety profile of abemaciclib plus fulvestrant was generally consistent with other CDK4 and CDK6 inhibitors.

- **HRQoL:** pERC noted that the oral route of administration will increase convenience and abemaciclib plus fulvestrant offers delayed need for IV chemotherapy, which is beneficial to patients. However, pERC observed that the HRQoL analyses in the MONARCH 2 trial were exploratory and limited by missing data and unspecified minimally important differences. Therefore, the committee could not draw a firm conclusion regarding the HRQoL benefit of abemaciclib plus fulvestrant for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer.
- **Indirect evidence:** The committee reviewed ITCs submitted by the sponsor that compared the effectiveness of abemaciclib plus fulvestrant with other CDK4 or CDK6 inhibitor-based regimens (e.g., ribociclib and palbociclib), everolimus-based regimens, endocrine monotherapies such as exemestane and fulvestrant, and capecitabine. The results showed that abemaciclib plus fulvestrant was more favourable than everolimus, exemestane, and fulvestrant monotherapy. However, the indirect comparisons with other CDK4 and CDK6 inhibitors and comparators were limited by clinical heterogeneity, lack of common comparators, and imprecision in effect estimates, resulting in uncertainty that prevented a definitive conclusion about the comparative efficacy of abemaciclib versus the other CDK4 and CDK6 inhibitors currently reimbursed in Canada for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer.
- **Place in therapy:** pERC discussed the place in therapy of abemaciclib plus fulvestrant for the treatment of hormone receptor–positive, HER2-negative advanced or metastatic breast cancer, given that other CDK4 and CDK6 inhibitors are currently reimbursed for this indication. The committee acknowledged that, without any evidence showing that abemaciclib is superior or inferior to ribociclib and palbociclib, these 3 CDK4 and CDK6 inhibitors fit in a similar place in therapy for this indication. pERC acknowledged the clinical experts' input that ribociclib is often preferred in clinical practice, supported by individual trial data and experience. However, the literature suggests that the OS benefit of palbociclib is less certain. Based on this, ribociclib plus fulvestrant was considered the most relevant comparator to abemaciclib plus fulvestrant for this reimbursement decision. pERC noted that treatment choices should be individualized based on patient-specific factors and preferences.
- **Economic considerations**: pERC discussed the sponsor-submitted economic analysis, in which limitations with the ITCs could not be adequately addressed. Consequently, the added clinical value of abemaciclib plus fulvestrant relative to other CDK4 or CDK6 combination therapies in clinical practice in Canada remains too uncertain to be determined. As pERC and the clinical experts considered ribociclib to be the most relevant comparator, the total drug cost of abemaciclib plus fulvestrant should not exceed the total drug cost of ribociclib plus fulvestrant, while considering the differences in cycle lengths between these regimens (e.g., abemaciclib is continuous use while ribociclib is 21-day cycles with 7-day intervals between cycles).
- **Availability of generic ribociclib:** pERC discussed that, as of July 2025, ribociclib is only available as a brand-name product in Canada. However, there is 1 generic product under Health Canada

review. Should generic ribociclib become available in Canada, drug acquisition costs will likely be lower than estimated in this review. Upon approval of generic ribociclib in Canada, public drug programs could consider seeking a reduction in the price of abemaciclib to reflect the decrease in the price of ribociclib.

- **Budget impact considerations**: Given the uncertainty in uptake of treatment with abemaciclib in the second line due to previous exposure to abemaciclib in earlier lines of therapy and uptake of generic palbociclib, there is potential for a higher budget impact across jurisdictions than predicted by the sponsor. The sponsor estimated the 3-year incremental budget impact associated with reimbursing abemaciclib plus fulvestrant to be approximately $11.2 million. In contrast, CDA-AMC estimated an impact of approximately $29.3 million over the same period. While this difference may reflect a potential overestimation, particularly if a significant proportion of patients had prior exposure to abemaciclib in earlier lines of therapy, the CDA-AMC scenario analysis assuming a lower market uptake of abemaciclib in years 2 and 3 still projected a budget impact of approximately $24.6 million. This remains more than double the sponsor's estimate.

Background

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths among women in Canada. Approximately 75% of breast cancers are HR positive and 66% to 75% are HER2 negative. While early-stage breast cancer is often curable, metastatic breast cancer remains incurable, with a 5-year survival rate of approximately 23%. In HR-positive, HER2-negative advanced or metastatic breast cancer, treatment aims to prolong survival, delay progression, and maintain quality of life. The current standard of care includes endocrine therapy in combination with CDK4 and/or CDK6 inhibitors. However, resistance to therapy and treatment-related toxicity are ongoing challenges. Verzenio (abemaciclib) has been approved by Health Canada for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer for the following indications: "in combination with an aromatase inhibitor in postmenopausal women as initial endocrine-based therapy;" "in combination with fulvestrant in women with disease progression following endocrine therapy (pre- or perimenopausal women must also be treated with a gonadotropin-releasing hormone agonist);" and "as a single agent in women with disease progression following endocrine therapy and at least 2 prior chemotherapy regimens." Verzenio is a CDK4 and CDK6 inhibitor that is available as oral tablets in 50 mg, 100 mg, and 150 mg strengths. The recommended dosage in the product monograph is 150 mg taken orally twice daily in combination with endocrine therapy or 200 mg taken orally twice daily when used as a single drug.

Submission History

Abemaciclib was previously reviewed by CADTH and received a conditional recommendation to reimburse "for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with fulvestrant in women with disease progression following endocrine therapy." The recommendation was

issued by pERC in July 2019. The original review was based on evidence from 1 randomized, double-blind, placebo-controlled phase III trial (MONARCH 2), which demonstrated a significant improvement in PFS, but at the time, the OS data were immature and definitive conclusions regarding the long-term survival benefit could not be drawn.

This resubmission is based on the availability of updated evidence from the MONARCH 2 trial, including interim and final OS analyses with more than 5 years of follow-up, addressing the key evidence gap identified in the 2019 review. The submission also includes revised network meta-analyses (NMAs) and updated economic models that incorporate the new OS data.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 pivotal randomized controlled trial, MONARCH 2, a multicenter, double-blind, placebo-controlled phase III study comparing abemaciclib plus fulvestrant with placebo plus fulvestrant in 669 females with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease had progressed on endocrine therapy; 0 long-term extension studies were submitted; 1 ITC (the Monarch 2 trial ITC) using a Bayesian network meta-analysis that included 10 randomized controlled trials comparing abemaciclib plus fulvestrant with other relevant treatments (e.g., ribociclib, palbociclib, everolimus, capecitabine) and employed both Cox proportional hazards and fractional polynomial models; 4 observational real-world evidence studies: a US-based retrospective electronic health record database study, 2 single-institution retrospective cohort studies from Japan and Slovenia, and 1 prospective multicenter cohort study from Italy, all evaluating the safety, tolerability, and treatment patterns associated with abemaciclib in routine clinical practice
- patients' perspectives gathered by 3 patient groups: Breast Cancer Canada, the Canadian Breast Cancer Network, and Rethink Breast Cancer
- input from the public drug plans and cancer agencies that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with advanced or metastatic breast cancer
- input from 2 clinician groups: REAL Canadian Breast Cancer Alliance and Ontario Health (Cancer Care Ontario) Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Three patient groups — Breast Cancer Canada, the Canadian Breast Cancer Network, and Rethink Breast Cancer — provided input based on surveys, interviews, and patient networks. Patients highlighted the profound impact of HR-positive, HER2-negative advanced or metastatic breast cancer on their daily lives, describing significant emotional, physical, financial, and social burdens. The disease often disrupts employment, relationships, and overall quality of life, not only for patients but also for their families and caregivers.

Key outcomes identified as important by patients included extending OS, delaying disease progression, maintaining daily functioning and HRQoL, and having access to oral treatment options that postpone the need for IV chemotherapy. Patients emphasized a willingness to tolerate manageable side effects if the treatment provided meaningful clinical benefits. These perspectives align closely with the outcomes evaluated in the MONARCH 2 trial, reinforcing the relevance of improvements in PFS and OS observed with abemaciclib plus fulvestrant to patient priorities in the health care landscape in Canada.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted for this review emphasized that there remains an unmet need for effective therapies that prolong survival and delay disease progression in patients with HR-positive, HER2-negative advanced or metastatic breast cancer after endocrine therapy failure. They identified abemaciclib plus fulvestrant as an important treatment option that offers continuous CDK4 and CDK6 inhibition with a manageable safety profile. The experts noted that abemaciclib provides flexibility for patients who may not tolerate other CDK4 or CDK6 inhibitors, such as those with hematologic toxicity on palbociclib or ribociclib. They also highlighted the potential benefit of abemaciclib in patients with visceral disease, a subgroup often associated with poorer prognoses, and in those whose disease has previously demonstrated endocrine resistance.

According to the experts, the patients most likely to benefit from abemaciclib plus fulvestrant are those with good performance status, visceral involvement, or evidence of aggressive disease biology. The patients least likely to benefit include those with rapidly progressing disease unsuitable for endocrine-based therapy, poor performance status, or severe gastrointestinal comorbidities that could worsen treatment tolerability. Treatment initiation is recommended at the time of progression on endocrine therapy, with monitoring based on imaging, clinical assessment, and biomarkers when applicable. Discontinuation should occur on evidence of disease progression or if toxicity becomes unmanageable despite dose modifications.

Additional considerations noted by the experts included the importance of dose management strategies, patient education regarding early management of diarrhea, and the availability of oral administration as a patient-centred advantage compared with infusion-based therapies.

Clinician Group Input

Input was received from the REAL Canadian Breast Cancer Alliance (n = 16 participants) and the Ontario Health (Cancer Care Ontario) Drug Advisory Committee (n = 5 participants). Both groups emphasized that extending survival while maintaining quality of life is a key goal; they also identified a need for additional CDK4 or CDK6 inhibitor options, particularly for patients who experience toxicity with existing drugs.

The clinician groups anticipated that abemaciclib may have a role in delaying the need for chemotherapy and agreed it fits within current treatment approaches. Their input was consistent with that of the clinical experts consulted for this review, with no major disagreements identified and general agreement that abemaciclib addresses an important unmet need.

Drug Program Input

The clinical experts consulted for this review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Responses
Relevant comparators	
The comparator in the MONARCH 2 trial (fulvestrant) is placebo. However, the standard of care now is ribociclib or palbociclib. Is there any evidence comparing abemaciclib to either ribociclib or palbociclib (with fulvestrant)? In the second-line setting, capivasertib and fulvestrant may also be a comparator. Is there any evidence comparing capivasertib to abemaciclib?	In both settings, the experts considered that due to lack of head-to-head clinical trials directly comparing abemaciclib with ribociclib or palbociclib plus fulvestrant, the comparative effectiveness across these CDK4 and CDK6 inhibitors must be inferred indirectly through cross-trial comparisons or network meta-analyses and be interpreted accordingly with caution as the studies may have differences in design and patient populations. While all 3 drugs have demonstrated efficacy in combination with endocrine therapy, they differ in safety profiles, dosing schedules, and some subgroup outcomes, which may guide individual treatment decisions in clinical practice. pERC agreed with the clinical experts.
Considerations for prescribing of therapy	
Abemaciclib is an oral therapy: 150 mg orally twice daily when used in combination with endocrine therapy; 200 mg orally twice daily when used as a single drug with or without food. Consistency with the recommendations for ribociclib and palbociclib would be helpful.	The clinical experts agreed that the prescribing guidance should align with existing protocols for ribociclib and palbociclib, including clear criteria for patient selection, monitoring, and dose adjustments based on tolerability. pERC agreed with the clinical experts.
Generalizability	
In this specific indication, would it be reasonable to switch patients from ribociclib or palbociclib to abemaciclib?	While there is no direct clinical trial evidence evaluating switching from ribociclib or palbociclib to abemaciclib, the clinical experts considered it reasonable in certain scenarios — particularly for patients who are intolerant to 1 drug or have contraindications to others. Clinical experience and pharmacologic differences among CDK4 and CDK6 inhibitors support individualized switching, although efficacy following progression on a prior CDK4 or CDK6

Drug program implementation questions	Responses
	inhibitor remains an area of active investigation. pERC agreed with the clinical experts.
Funding algorithm	
It would be helpful to update the existing funding algorithm.	The clinical experts agreed that an update to the existing funding algorithm for CDK4 and CDK6 inhibitors would be beneficial. pERC agreed with the clinical experts.

CDK = cyclin-dependent kinase; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Clinical Evidence

Systematic Review

Description of Studies

The pivotal MONARCH 2 trial (N = 669) was a phase III, multicenter, double-blind, placebo-controlled study that compared abemaciclib plus fulvestrant to placebo plus fulvestrant in females with HR-positive, HER2-negative advanced or metastatic breast cancer who had experienced disease progression following endocrine therapy. The primary outcomes were PFS and OS. At the time of the original review, only interim PFS data and OS results were available. In the current submission, updated data have been provided, including an interim OS analysis (data cut-off: June 20, 2019) and a final OS analysis (data cut-off: March 18, 2022), offering an assessment of long-term outcomes with over 5 years of follow-up.

Baseline characteristics were well balanced across treatment arms. The median age of enrolled patients was 60 years, with the majority in the postmenopausal stage. Most patients had visceral metastases at baseline, and a high proportion has disease with prior resistance to endocrine therapy, reflecting a population with advanced disease and a poor prognosis.

Efficacy Results

At the interim analysis (data cut-off: June 20, 2019; median follow-up of 47.7 months), after 338 deaths had occurred, abemaciclib plus fulvestrant significantly improved OS compared to placebo plus fulvestrant, with a hazard ratio of 0.757 (95% CI, 0.606 to 0.945; P = 0.0137). The median OS was 46.72 months versus 37.25 months, representing a 9.47-month median survival gain (95% CI not reported).

At the final OS analysis (data cut-off: March 18, 2022), after a median follow-up of approximately 80 months for both arms and 440 deaths, the survival benefit was maintained. The hazard ratio was 0.784 (95% CI, 0.644 to 0.955; nominal P = 0.0157). Median OS was 45.80 months for the abemaciclib plus fulvestrant arm and 37.25 months for the placebo arm, corresponding to an 8.55-month improvement in median OS (95% CI not reported).

At the time of the primary PFS analysis (data cut-off: February 14, 2017, median follow-up of 19.5 months), abemaciclib plus fulvestrant significantly improved PFS compared to placebo plus fulvestrant, with a hazard ratio of 0.553 (95% CI, 0.449 to 0.681; P < 0.001). Median PFS was 16.4 months versus 9.3 months,

corresponding to a 7.2-month gain (95% CI was not reported). An updated PFS analysis at the interim OS data cut-off (June 20, 2019) confirmed consistent results, with a hazard ratio of 0.536 (95% CI, 0.445 to 0.645; P < 0.001). The median PFS was16.87 months in the abemaciclib arm versus 9.27 months in the placebo arm, maintaining a 7.59-month advantage (95% CI not reported). At the final analysis (data cut-off: March 18, 2022; median follow-up of 79.7 months), the PFS benefit remained sustained, with a hazard ratio of 0.539 (95% CI, 0.449 to 0.647). Median PFS was again 16.87 months for the abemaciclib arm versus 9.27 months for the placebo arm. Kaplan-Meier curves showed early separation at approximately 3 months, which was maintained over long-term follow-up, supporting the durability of the PFS benefit with abemaciclib plus fulvestrant.

Harms Results

In the MONARCH 2 trial, AEs were more frequently reported in the abemaciclib plus fulvestrant arm compared to the placebo plus fulvestrant arm. The most common AEs included diarrhea (patients; % versus patients); neutropenia (patients; % vs patients; %), and infections (patients; % versus patients); . Most events were low grade and manageable with dose adjustments and supportive care. Treatment discontinuations due to AEs were infrequent and the safety profile remained consistent with known effects of CDK4 and CDK6 inhibition. Serious AEs were reported more frequently in the abemaciclib arm (patients [as compared to placebo (patients %]), primarily related to infections and thromboembolic complications. Although the incidence of serious AEs was higher with abemaciclib, most events were effectively managed with supportive interventions.

AEs of special interest occurred more frequently with abemaciclib than placebo and included neutropenia reported in patients (%) receiving abemaciclib plus fulvestrant compared to patients with placebo. Diarrhea was reported in patients treated with abemaciclib and patients (%) treated with placebo; venous thromboembolic events were reported in patients in the abemaciclib group (%) versus patients in the placebo group (); infections occurred in patients (%) in the abemaciclib group and patients () in the placebo group; finally, interstitial lung disease and/or pneumonitis occurred in patients with abemaciclib (%) versus patient in the placebo arm (). Most events were low grade and manageable.

Critical Appraisal

The MONARCH 2 study demonstrated strong internal validity, with appropriate randomization (2:1 ratio; stratified), maintained allocation concealment, and double blinding. Although a higher incidence of diarrhea in the abemaciclib arm raised the potential for unblinding, this was unlikely to have impacted objectively measured outcomes like PFS and OS. Baseline characteristics were well balanced, adherence was high () and missing data were relatively limited. The study used hierarchical testing with appropriate control of type I error and prespecified subgroup and sensitivity analyses, supporting the robustness of the findings. While the final OS analysis was performed post hoc following a significant interim analysis, consistency between the interim and final results reduces concerns about bias.

The MONARCH 2 trial findings were overall generalizable to the population of patients in Canada with HR-positive, HER2-negative advanced breast cancer progressing after endocrine therapy. The study population, dosing regimens, and outcomes align well with clinical practice in Canada. However, it is unknown if generalizability of the findings would extend to patients with central nervous system metastases or visceral crisis, who were excluded from the study. The use of supportive medications was largely balanced across treatment arms, with higher loperamide use in the abemaciclib arm reflecting expected management of diarrhea. No major concerns regarding cointerventions or external applicability were identified by the clinical experts consulted for this review.

Long-Term Extension Studies

No other studies considered long-term were submitted.

Indirect Comparisons

Description of Studies

The sponsor submitted an ITC (the Monarch 2 trial ITC) using a Bayesian NMA to assess the relative efficacy of abemaciclib plus fulvestrant compared to other treatments for HR-positive, HER2-negative advanced or metastatic breast cancer. The network included 10 randomized controlled trials evaluating treatments including fulvestrant monotherapy (500 mg and 250 mg), exemestane, capecitabine, everolimus plus exemestane, palbociclib plus fulvestrant, ribociclib plus fulvestrant, and dalpiciclib plus fulvestrant. The analysis incorporated both fixed-effect and random-effects models, with model selection based on deviance information criterion. The report was divided into 2 sections according to the methods or models used — the Cox proportional hazards models and the fractional polynomial models that were applied as sensitivity analyses because violations of proportional hazards assumptions were detected. Consistency across the network was assumed rather than formally tested due to network sparsity.

Efficacy Results

The Monarch 2 trial ITC supports the results of the MONARCH 2 trial that abemaciclib plus fulvestrant had favourable PFS and OS compared with fulvestrant monotherapy. However, when comparing abemaciclib plus fulvestrant to other CDK4 and CDK6 inhibitors relevant to clinical practice in Canada, such as palbociclib or ribociclib combined with fulvestrant, the results were less certain.

Hazard ratios for OS from the Cox proportional hazards model suggested numerically favourable outcomes for abemaciclib plus fulvestrant when compared to fulvestrant monotherapy (both for the 500 mg and 250 mg doses) and exemestane monotherapy. When compared to all other interventions, the credible intervals were wide, reflecting imprecision. The same results were observed when assessing PFS, with the addition of a numerically favourable effect when compared to everolimus.

The fractional polynomial model results were overall aligned with the Cox proportional hazards models. The effect estimates, presented as the mean difference between treatments in expected OS, showed numerically favourable effects of abemaciclib when compared to exemestane and fulvestrant 250 mg. When compared to all other interventions the credible intervals were wide, reflecting imprecision. Similar results were

observed when assessing PFS (presented also as the mean difference between treatments in expected PFS), with favourable effects of abemaciclib plus fulvestrant when compared to fulvestrant (250 mg and 500 mg monotherapy), exemestane, and everolimus.

Harms Results

No harms data were provided with either the Cox proportional hazards or the fractional polynomial approaches.

Critical Appraisal

The Monarch 2 trial systematic literature review that informed the ITC was generally well-conducted, with appropriate prespecification of eligibility criteria, comprehensive database searches, duplicate review processes, and quality assessment using the Cochrane Risk of Bias tool. Four of the trials in the network were assessed as high risk of bias and several others were at unclear risk of bias. No trials were identified that enrolled the same population as the MONARCH 2 trial. Eligibility criteria were therefore broadened, which increased the heterogeneity across the trials in the network and may have resulted in a violation of the exchangeability assumption required to produce valid results. These included variations in patient characteristics, such as differences in visceral metastases, prior treatments, and follow-up durations. Due to network sparsity, consistency was assumed based on clinical judgment without performing formal checks; therefore, it is unknown whether consistency was upheld. Minor variations in patient characteristics, such as differences in visceral metastases, prior treatments, and follow-up durations, may have introduced potential effect modifiers, although the overall study designs and populations were deemed acceptable.

Clinical outcomes relevant to the patient population, namely PFS and OS, were appropriately selected, but harms outcomes were not included, limiting the ability to assess comparative safety. While sensitivity analyses supported the robustness of findings, small sample sizes for some treatments and wide credible intervals indicated imprecision, particularly when comparing the targeted therapy combinations to the chemotherapy-based regimens.

The limitation related to the violation of the proportional hazards assumption was addressed through sensitivity analysis using fractional polynomial models that do not require this assumption. The final models were selected from a choice of 88 possible models. None of the best-fitting models (by deviance information criterion) could be selected due to clinically implausible survival plateaus, particularly for OS. A limited number of models with poorer fit to the observed data were therefore considered. The poorer fit of the chosen models and limited transparency in the selection process may result in biased comparative effect estimates. The credible intervals produced do not account for the model selection procedures and may be overoptimistic. The clinical experts consulted by the review team felt that the comparative effectiveness results produced by these extrapolations might not all be plausible. The limitations included misalignment of the comparative effect of fulvestrant on PFS versus OS and lower than expected long-term projections at 5 and 10 years.

The included studies largely reflect the clinical context in Canada, although differences in disease severity and geographic variability may affect generalizability. Overall, the Monarch 2 trial ITC provides

useful comparative evidence for efficacy outcomes but should be interpreted cautiously given residual heterogeneity, untested consistency, and imprecision around some treatment effect estimates.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

To address gaps related to real-world harms and tolerability, the sponsor submitted 4 real-world evidence (RWE) studies evaluating the use of abemaciclib in broader clinical practice settings. These included 1 expanded access program (I3Y-MC-JPBK) and 3 observational cohort studies. Across these studies, patient populations were more heterogeneous than in the MONARCH 2 trial, often including individuals with a wider range of disease burdens, comorbidities, and prior treatments. These studies provided complementary information on the harms profile of abemaciclib outside of the controlled environment of randomized trials.

Efficacy Results

The primary focus of the RWE studies was on harms, with limited information on treatment outcomes. Nonetheless, PFS in these studies were generally consistent with the results observed in the MONARCH 2 trial. However, the absence of standardized follow-up protocols, variability in outcome definitions across studies, and lack of adjustment limit the ability to interpret the findings causally.

Harms Results

Across the RWE studies, the safety profile of abemaciclib was consistent with that observed in the MONARCH 2 trial. Diarrhea, neutropenia, and infections were the most frequently reported AEs, with diarrhea remaining the most common. Most AEs were manageable with dose reductions or delays, or supportive care measures such as anti-diarrheal medication. No new or unexpected harm signals were identified. The RWE studies suggested that AEs were manageable in clinical practice, although the rates of dose adjustments and treatment interruptions varied depending on patient characteristics and treatment settings.

Critical Appraisal

While the RWE studies provide useful supportive information on the safety and tolerability of abemaciclib, they are limited by their observational nature, small sample sizes, lack of standardized outcome reporting, and potential for selection bias. The studies were single arm or lacked adjustment, limiting the ability to interpret the findings causally. Differences in clinical practice patterns and follow-up intensity across studies also limit generalizability. Nevertheless, the findings broadly support the profile established in randomized controlled trials and provide information on the management strategies for AEs used in the MONARCH 2 trial that are applicable in routine clinical care.

Economic Evidence

- Abemaciclib is available as 50 mg, 100 mg, and 150 mg tablets. At the submitted price of $116.22 per 150 mg, the 28-day cycle of abemaciclib is predicted to cost $6,508 per patient, based on the

Health Canada–recommended dosage. The 28-day cost of abemaciclib plus fulvestrant is $7,324 in the first cycle and $6,916 in subsequent cycles per patient for HR-positive, HER2-negative advanced or metastatic breast cancer. Treatment should be continued until disease progression or unacceptable toxicity.

- Clinical efficacy in the economic analysis for abemaciclib plus fulvestrant in comparison to fulvestrant was derived from the MONARCH 2 trial. Evidence submitted by the sponsor indicates that abemaciclib plus fulvestrant is likely to improve PFS and OS compared with fulvestrant alone among patients with HR-positive, HER2-negative advanced or metastatic breast cancer. For abemaciclib plus fulvestrant compared to ribociclib plus fulvestrant, palbociclib plus fulvestrant, and exemestane plus everolimus, comparative clinical efficacy was informed by the sponsor-submitted NMA, which was subject to considerable uncertainty due to imprecise estimates and methodological limitations. This precluded CDA-AMC from drawing definitive conclusions about the comparative efficacy of abemaciclib plus fulvestrant versus palbociclib plus fulvestrant, ribociclib plus fulvestrant, and exemestane plus everolimus. The safety profile of abemaciclib remains consistent with that of other CDK4 and CDK6 inhibitors, with diarrhea, neutropenia, and infections being the most reported AEs, most of which are manageable with dose adjustments and supportive care. However, AEs were not assessed in the NMA, and long-term comparative safety data beyond the pivotal trial period and direct comparisons remain limited.
- The results of the CDA-AMC base case suggest:
  - The following treatments are on the cost-effectiveness frontier: fulvestrant alone, palbociclib plus fulvestrant, and ribociclib plus fulvestrant.
  - Abemaciclib plus fulvestrant was less effective and more costly than ribociclib plus fulvestrant (i.e., dominated). These results are driven by increased drug acquisition costs, lower survival (−0.16 life-years) and lower quality-adjusted life-years (incremental quality-adjusted life-years = −0.05).
- This finding is associated with uncertainty due to limitations with the comparative effectiveness estimates obtained from the sponsor-submitted NMA that are applicable regardless of the statistical methods (i.e., Cox proportional hazards models or fractional polynomial models). Although the Cox proportional hazards assumption is violated, applying the fractional polynomial model estimates into the economic evaluation produced implausible survival estimates that lacked face validity according to clinical expert input sought by CDA-AMC. Applying estimates from the Cox proportional hazards models, albeit not preferable given the violation of the Cox proportional hazards assumptions within the trials period, produced OS and PFS curves in the economic model that had better visual fit to the MONARCH 2 trial data and were more clinically plausible.
  - As noted in the CDA-AMC clinical review, comparisons of abemaciclib with other CDK4 and CDK6 inhibitors relevant to practice in Canada are limited as no definitive conclusions could be reached about comparative effect. There is therefore no robust evidence to support a price premium for abemaciclib plus fulvestrant over other relevant combination therapies to treat the

same patient population. Of note, generic palbociclib has recently become available and has a similar mechanism of action (i.e., CDK4 or CDK6 inhibitor).

- CDA-AMC estimates that the budget impact of reimbursing abemaciclib plus fulvestrant for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer will be approximately $29.3 million over the first 3 years of reimbursement compared to the amount currently spent on comparators. The expenditure on abemaciclib over this period is predicted to be $79.6 million (abemaciclib plus fulvestrant = $84.9 million). The actual budget impact of reimbursing abemaciclib plus fulvestrant will depend on the remaining number of people eligible for treatment with abemaciclib in the second line due to previous exposure to abemaciclib, as well as the uptake of generic palbociclib. At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption given the difference between the sponsor's estimate and the CDA-AMC estimate.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan (Vice Chair), Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: July 9, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.