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Reimbursement Recommendation

Abemaciclib (Verzenio)

Indication: For the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor (HER2)-negative advanced or metastatic breast cancer, in combination with an aromatase inhibitor (AI) in postmenopausal women as initial endocrine-based therapy.

Sponsor: Eli Lilly Canada Inc.

Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Verzenio?

Canada's Drug Agency (CDA-AMC) recommends that Verzenio should be reimbursed by public drug plans for the treatment of hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer in patients who were postmenopausal in combination with nonsteroidal aromatase inhibitors (NSAIs) as an initial endocrine-based therapy, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Verzenio plus NSAI should be covered to treat adults with HR-positive, HER2-negative advanced or metastatic breast cancer, with a good performance status. Verzenio plus NSAI should not be covered in patients who have previously received cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors or received more than 1 line of chemotherapy for advanced or metastatic breast cancer.

What Are the Conditions for Reimbursement?

Verzenio plus NSAI should only be reimbursed if prescribed by clinicians with expertise in managing advanced or metastatic breast cancer and if the cost of Verzenio does not exceed the drug program cost of treatment with ribociclib plus NSAI, reimbursed for the indicated population.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial (MONARCH 3) in patients who were postmenopausal with HR-positive, HER2-negative advanced or metastatic breast cancer demonstrated that treatment with abemaciclib plus NSAI delays cancer progression and may result in patients living longer compared to NSAI alone.
- Based on the CDA-AMC assessment of the health economic evidence, Verzenio plus NSAI does not represent good value to the health care system at the public list price. Indirect treatment comparisons presented no evidence of a benefit associated with Verzenio compared to ribociclib, deemed to be the most relevant comparator for abemaciclib in this reimbursement decision. As such, the committee determined that there is not enough evidence to justify a greater cost for Verzenio plus NSAI compared with ribociclib plus NSAI.
- Based on public list prices, Verzenio in combination with NSAI is estimated to cost the public drug plans approximately $83 million over the next 3 years. However, the actual budget impact is uncertain, and

Summary

it will depend on the remaining number of people eligible for treatment with abemaciclib due to previous exposure, and 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 death among females 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.

What Are the Unmet Needs in HR-Positive, HER2-Negative Advanced or Metastatic Breast Cancer?

HR-positive, HER2-negative advanced or metastatic breast cancer is generally considered to be incurable. Not all patients respond to current treatments, with some patients becoming resistant to some treatments over time. As such, patients are in need of other treatments that prevent or delay cancer progression, prolong life, and improve health-related quality of life (HRQoL).

How Much Does Verzenio Cost?

Treatment with Verzenio as an add-on to NSAI is expected to cost $6,508 per patient for a 28-day cycle. The 28-day per patient cost of abemaciclib plus NSAI for advanced or metastatic breast cancer as initial endocrine-based therapy is predicted to be $6,535 if using anastrozole and $6,547 if using letrozole as the NSAI component of the regimen.

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 patients who are postmenopausal in combination with NSAI as an initial endocrine-based 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 3, N = 493) of patients who were postmenopausal with HR-positive, HER2-negative advanced or metastatic breast cancer who had not received previous systemic therapy in the advanced or metastatic setting demonstrated that treatment with abemaciclib plus NSAI resulted in a statistically significant and clinically meaningful improvement in progression-free survival (PFS) (median PFS = 29.03 months; 95% confidence interval [CI], [redacted] to [redacted] months versus 14.76 months; 95% CI, [redacted] to [redacted] months) compared to placebo plus NSAI, and may improve overall survival (OS) (median OS = 66.81 months; 95% CI, [redacted] to [redacted] months versus 53.72 months, 95% CI, [redacted] to [redacted] months); however, there was some uncertainty in the magnitude of benefit as the results were not statistically significant (hazard ratio = 0.804; 95% CI, 0.637 to 1.015). Additional analyses of safety data at the final analysis were consistent with the conclusions drawn in the initial pERC recommendation, where treatment with abemaciclib was associated with more adverse events (AEs) and serious adverse events (SAEs) than NSAI alone, most notably diarrhea (83.5% versus 34.2%). However, the safety profile of abemaciclib plus NSAI was considered manageable by clinical experts, and as expected for CDK4/6 inhibitors.

In absence of head-to-head data comparing abemaciclib plus NSAI to other CDK4/6 inhibitors, indirect comparisons in the form of network meta-analyses (NMA) demonstrated no evidence of difference between abemaciclib plus NSAI and other CDK4/6 inhibitors plus NSAI for the outcomes of PFS or OS, and there was considerable uncertainty in the NMA results for grade 3 and/or grade 4 AEs.

HER2-negative advanced or metastatic breast cancer is generally considered to be incurable, and the patient and clinician input agreed that treatment goals therefore include prolongation of life, delaying disease progression, improving HRQoL, and delaying the need for IV chemotherapy. Based on the evidence reviewed, pERC concluded that abemaciclib meets some of these needs including delaying disease progression, delaying the need for IV chemotherapy (and providing access to an oral therapy), and may improve survival. However, pERC was unable to conclude that treatment with abemaciclib plus NSAI improves HRQoL relative to NSAI alone.

At the sponsor-submitted price for abemaciclib and publicly listed price for all other drugs, abemaciclib plus NSAI was more costly than other CDK4/6 inhibitor combinations. As abemaciclib plus NSAI is considered

likely to be similarly effective as ribociclib plus NSAI, the total drug cost of abemaciclib plus NSAI should not exceed the total drug cost of ribociclib plus NSAI.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with abemaciclib plus NSAI should be reimbursed when initiated in adult patients with previously untreated HR-positive, HER2-negative advanced or metastatic breast cancer.	Based on the eligibility criteria from the MONARCH 3 trial, abemaciclib plus NSAI improved OS and PFS in patients with these characteristics.	There is insufficient evidence that abemaciclib is clinically superior or inferior to other CDK4/6 inhibitors currently reimbursed for the same indication. Therefore, eligibility for abemaciclib should align with criteria used by each of the public drug plans for reimbursement of CDK4/6 inhibitors for the same indication.
2. Patients must have a good performance status.	Patients with an ECOG performance status of 0 or 1 were included in the MONARCH 3 trial.	Patients with an ECOG performance status of 2 may be treated at the discretion of the treating clinician.
3. Patients must not have any of the following: 3.1. Received prior endocrine therapy or more than 1 line of chemotherapy for advanced or metastatic breast cancer. 3.2. Previous treatment with a CDK4/6 inhibitor in the metastatic setting. 3.3. A disease-free interval of less than 12 months from completion of (neo)adjuvant endocrine therapy or received a CDK4/6 inhibitor in the adjuvant setting within 6 months.	The MONARCH 3 trial excluded patients with most of these characteristics. As such, the potential benefit of abemaciclib plus NSAI in these patients has not been demonstrated.	pERC noted that it would be appropriate to align with the funding conditions for other CDK4/6 inhibitors and allow funding for patients who have received 1 line of chemotherapy for advanced or metastatic breast cancer.
Discontinuation		
4. Reimbursement of abemaciclib should be discontinued upon the occurrence of any of the following: 4.1. disease progression 4.2. intolerable side effects.	These discontinuation criteria are consistent with the protocol of the MONARCH 3 trial and routine clinical practice.	—
Prescribing		
5. Abemaciclib should be prescribed by clinicians with expertise in managing advanced or metastatic breast cancer.	This is meant to ensure that abemaciclib is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. Abemaciclib should be negotiated so that abemaciclib plus NSAI does	pERC and the clinical experts considered ribociclib to be the most	—

Reimbursement condition	Reason	Implementation guidance
not exceed the drug program cost of treatment with ribociclib plus NSAI reimbursed for the indicated population.	relevant comparator for abemaciclib. The sponsor-submitted indirect treatment comparisons demonstrated no evidence of difference between abemaciclib plus NSAI and ribociclib plus NSAI for the outcomes of PFS or OS. As such, there is insufficient evidence to justify a cost premium for abemaciclib plus NSAI versus ribociclib plus NSAI reimbursed for HR-positive, HER2-negative advanced or metastatic breast cancer in patients who were postmenopausal as initial endocrine-based therapy.	
Feasibility of adoption		
7. The economic feasibility of adoption of abemaciclib plus NSAI must be addressed.	At the submitted price, the incremental budget impact of abemaciclib plus NSAI is expected to be greater than $40 million in year 3. 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(s).	—

CDA-AMC = Canada's Drug Agency; CDK4/6 = cyclin-dependent kinase 4 and 6; ECOG = Eastern Cooperative Oncology Group; HR = hormone receptor; NMA = network meta-analysis; NSAI = nonsteroidal aromatase inhibitor; OS = overall survival; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PFS = progression-free survival.

Discussion Points

- **Previous recommendation:** The initial recommendation by pERC for abemaciclib plus NSAI in the population who were endocrine-sensitive stated that it should be reimbursed only in patients who are unable to tolerate or have a contraindication to other available CDK4/6 inhibitors as a result of the immature and uncertain OS results, the side-effect profile, and the limitations of the indirect comparison conducted against other CDK4/6 inhibitors. This represented a narrower population than the reimbursement request and the Health Canada indication, which did not stipulate limiting abemaciclib to patients who could not receive other CDK4/6 inhibitors. pERC discussed the purpose of the current reassessment, which was to evaluate whether the updated evidence is sufficient to remove the limitation requiring patients to have intolerance or contraindication to other CDK4/6 inhibitors. pERC concluded that despite not being statistically significant, the clinically important improvement in OS at the most recent analysis, as well as the statistically significant PFS results were sufficient to reimburse abemaciclib plus NSAI despite the tolerability concerns or limitations of the indirect evidence.

- **New data supporting the reassessment:** pERC discussed the new clinical evidence provided as part of this reassessment which consisted of a phase III randomized controlled trial, MONARCH 3 (N = 493), for which additional follow-up data were available including the primary preplanned analysis of OS and an updated analysis of PFS and safety. Treatment with abemaciclib was associated with a clinically significant improvement in PFS when compared to placebo, which was aligned with the data reviewed in the previous recommendation. The results of the final OS analysis of the MONARCH 3 trial suggest an improvement in OS for patients treated with abemaciclib plus NSAI compared to placebo plus NSAI, but the results were not statistically significant. However, the clinical experts consulted for this review considered the 13.09-month (95% CI not reported) difference in median OS between abemaciclib and placebo to be clinically meaningful in the context of advanced or metastatic breast cancer. The safety profile of abemaciclib was as expected for CDK4/6 inhibitors, and treatment with abemaciclib as compared to placebo is associated with an increase in AEs and SAEs, most notably diarrhea. Real-world studies submitted by the sponsor provided supportive evidence on the management of diarrhea-related AEs associated with abemaciclib through dose reduction, proactive intervention plans, and concomitant medications, as done in clinical practice.
- **Indirect evidence:** The updated indirect treatment comparison submitted for this reassessment consisted of an NMA comparing abemaciclib plus NSAI to other therapies used in the treatment of advanced or metastatic breast cancer, most importantly palbociclib plus NSAI and ribociclib plus NSAI. There was no evidence of difference between abemaciclib plus NSAI and either of the CDK4/6-based combination therapies assessed for OS and PFS, suggesting that the efficacy of the CDK4/6-based regimens is expected to be roughly equivalent, which pERC noted aligns with the input from clinical experts. pERC discussed the harms results of the NMA, noting that there are differences in individual AE profiles of abemaciclib (diarrhea), ribociclib (QT prolongation), and palbociclib (neutropenia), which is not adequately captured in the sponsor-submitted NMA. Additionally, pERC noted the heterogeneity in the studies included, as well as the methodological limitations, and wide 95% credible intervals (CrIs) which increase the uncertainty and imprecision in the results for all outcomes.
- **AE profile:** pERC discussed the AE profile of abemaciclib plus NSAI and acknowledged that all of the available CDK4/6 inhibitors used in this patient population in combination with NSAI (i.e., abemaciclib, ribociclib, and palbociclib) are associated with more AEs and SAEs when compared to NSAI alone (e.g., abemaciclib associated with higher rates of diarrhea, palbociclib associated with higher rates of neutropenia, and ribociclib with higher incidence of prolonged QT interval). pERC and the clinical experts noted that the AEs associated with abemaciclib are not insignificant but are manageable with dose reductions and supportive care, and as expected for CDK4/6 inhibitors in this patient population, in the context of treating an incurable and life-limiting disease.
- **Place in therapy:** pERC discussed the place in therapy of abemaciclib plus NSAI in HR-positive, HER2-negative advanced or metastatic breast cancer, given other CDK4/6 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 CDK4/6 inhibitors fit in a similar place in therapy for this indication. The clinical experts indicated that ribociclib is typically the first choice CDK4/6 inhibitor in this population due to greater clinical benefits observed in both the literature and real-world practice, as well as the tolerability profiles of each drug. As such, pERC and the clinical experts considered ribociclib to be the most relevant comparator for abemaciclib in this reimbursement decision. pERC also highlighted that treatments would be chosen in consultation with the patient considering multiple factors including but not limited to the expected efficacy and the side-effect profiles of each drug in the context of individual patient-specific factors and preferences.

- **Economic considerations:** pERC discussed the sponsor-submitted economic analysis, in which the long-term efficacy was based on assumptions of durability of treatment effect with abemaciclib plus NSAI compared to ribociclib plus NSAI and palbociclib plus NSAI. CDA-AMC was unable to address several key limitations with the sponsor's economic submission. CDA-AMC was unable to validate the impact of extrapolations and long-term assumptions due to lack of available head-to-head trial data to inform comparative efficacy and methodological limitations with the NMA. Therefore, whether any predicted clinical results from the submitted model will be realized in clinical practice is highly uncertain. As pERC and the clinical experts considered ribociclib to be the most relevant comparator, the total drug cost of abemaciclib plus NSAI should not exceed the total drug cost of ribociclib plus NSAI, while considering the differences in cycle lengths between these regimens (e.g., abemaciclib used continuously while ribociclib used in 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 review at Health Canada. 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 due to previous exposure to abemaciclib in earlier lines of therapy and uptake of generic palbociclib, there is potential for a high budget impact across jurisdictions than predicted by the sponsor. The sponsor estimated the 3-year incremental budget impact associated with reimbursing abemaciclib plus NSAI to be approximately $34.2 million. In contrast, CDA-AMC estimated an impact of approximately $82.9 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, CDA-AMC scenario analysis assuming a lower market uptake of abemaciclib in years 2 and 3, still projected a budget impact of approximately $70.6 million. This remains more than double the sponsor's estimate.

Background

Breast cancer was the second leading cause of death in females in Canada in 2024 and accounted for 13% of cancer-related mortality. It was estimated that 30,500 new female cases and 5,500 deaths would occur as a result of breast cancer in Canada in 2024. Major molecular subtypes of breast cancer have been defined based on the expression of cell surface receptors HR and HER2. HR-positive and HER2-negative breast cancer is the most common molecular subtype, accounting for at least 66% to 75% of all breast cancer cases in North America and Europe. Metastatic cancer occurs when cancer spreads beyond the primary tumour site to other parts of the body, forming secondary metastatic tumours. Currently, first-line standard of care in patients with advanced or metastatic breast cancer is the combination of an aromatase inhibitor (AI) (in patients who were endocrine-sensitive) or fulvestrant (in patients who were endocrine-resistant) with a CDK4/6 inhibitor. Upon disease progression, patients may switch to an alternative endocrine drug alone or in combination with another targeted therapy, or to chemotherapy or antibody-drug conjugates. Abemaciclib is a CDK4/6 inhibitor approved by Health Canada for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer, in combination with an AI in patients who were postmenopausal as initial endocrine-based therapy (i.e., endocrine-sensitive disease), or in combination with fulvestrant in patients with recurrent disease while using adjuvant endocrine therapy, or after disease progression following endocrine therapy (i.e., endocrine-resistant disease). Other CDK4/6 inhibitors used in Canada in this patient population include palbociclib and ribociclib.

Abemaciclib (Verzenio) has been approved by Health Canada for multiple indications in early and advanced or metastatic breast cancer. In early breast cancer, abemaciclib is indicated in combination with endocrine therapy for the adjuvant treatment of adult patients with HR-positive, HER2-negative early breast cancer at high risk of disease recurrence based on clinicopathological features. In the advanced or metastatic setting, abemaciclib is approved by Health Canada for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer:

- in combination with an AI in patients who were postmenopausal as initial endocrine-based therapy
- in combination with fulvestrant in patients with disease progression following endocrine therapy (patients who were premenopausal or who were perimenopausal must also be treated with a gonadotropin-releasing hormone agonist)
- as a single drug for patients with disease progression following endocrine therapy and at least 2 prior chemotherapy regimens (at least 1 chemotherapy regimen should have been administered in the metastatic setting and at least 1 should have contained a taxane).

Abemaciclib is an inhibitor of CDK 4/6 preventing retinoblastoma protein phosphorylation, blocking progression from G1 into S phase of the cell cycle, leading to suppression of tumour growth in preclinical models following short duration target inhibition. In estrogen receptor–positive breast cancer cell lines, sustained target inhibition by abemaciclib prevents rebound of retinoblastoma phosphorylation and cell cycle re-entry, resulting in senescence and apoptosis. It is available as an oral tablet and the dosage recommended in the product monograph is 150 mg twice daily and taken orally until disease progression or unacceptable toxicity.

Submission History

Abemaciclib was previously reviewed by CDA-AMC and received a recommendation to reimburse with conditions in combination with NSAI for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in patients as initial endocrine-based therapy from pERC on July 5, 2019. The original review of abemaciclib included 1 phase III, randomized, placebo-controlled study (MONARCH 3), in patients who were postmenopausal with HR-positive, HER2-negative advanced breast cancer or metastatic breast cancer who had not received any previous systemic therapy in the advanced or metastatic setting.

This reassessment is based on the potential next steps identified by pERC. In the initial submission in 2019, for the population who were endocrine-sensitive, pERC recommended that abemaciclib should be reimbursed only in patients who are unable to tolerate or have a contraindication to other available CDK4/6 inhibitors as a result of the immature and uncertain OS results and the side-effect profile; this represents a narrower population than the reimbursement request and the Health Canada indication, which did not stipulate limiting abemaciclib to patients who could not receive other CDK4/6 inhibitors. As such, the sponsor has filed a reassessment of abemaciclib to lift the restriction for patients who are unable to tolerate or have a contraindication to other available CDK4/6 inhibitors, as mature OS data, representing an additional 5 years and 10 months of follow-up data since the first evaluation of the preplanned final OS analysis (data cut-off: September 29, 2023) has become available from the MONARCH 3 trial.

Sources of Information Used by the Committee

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

- a review of 1 phase III, randomized, placebo-controlled study (MONARCH 3) in patients who were postmenopausal with HR-positive, HER2-negative advanced breast cancer or metastatic breast cancer who had not received any previous systemic therapy in the advanced or metastatic setting; 2 indirect treatment comparisons; and 2 retrospective chart reviews included in the Studies Addressing Gaps in the Evidence From the Systematic Review section
- patients' perspectives gathered by 3 patient groups: Breast Cancer Canada (BCC), Canadian Breast Cancer Network (CBCN), and Rethink Breast Cancer
- input from public drug plans and cancer agencies that participate in the reimbursement review process
- two clinical specialists with expertise diagnosing and treating patients with advanced or metastatic breast cancer
- input from 2 clinician groups: the Research Excellence, Active Leadership (REAL) Canadian Breast Cancer Alliance and Ontario Health (Cancer Care Ontario) (OH [CCO]) Breast Cancer Drug Advisory Committee (DAC)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Three patient groups, BCC, CBCN, and Rethink Breast Cancer, provided their input for this submission. BCC is a national organization in Canada which encourages precision oncology research and awareness collaboration among physicians and researchers. Information for this submission was gathered via an electronic survey, distributed to 169 patients living with a first recurrence (i.e., first line) of HR-positive, HER2-negative metastatic breast cancer from February 15 to 23, 2025. The survey responses included 54 patients identified as the target group for this input submission; 64% in Ontario, 18% in Alberta, 11% in British Columbia, 3% in Quebec, and 2% in both Nova Scotia and New Brunswick. The CBCN is a leading, patient-directed, national health charity committed to ensuring the best quality of care for all people living in Canada affected by breast cancer through the promotion of information, education, and advocacy activities. Information for this submission was gathered via excerpts and key interviews from past submissions to CDA-AMC, including results from a 2012 survey of 71 patients with metastatic breast cancer and 16 caregivers, and a 2017 survey of 180 patients in Canada living with metastatic breast cancer. Additionally, information from a review of current studies and grey literature to highlight issues and experiences commonly shared among patients living with breast cancer, and relevant disease experience and treatment considerations from a 2022 survey of 30 patients in Canada who had HR-positive, HER2-negative metastatic breast cancer was submitted. Rethink Breast Cancer is a charity in Canada known for making positive change by educating, empowering, and advocating for system changes to improve the experience and outcomes of those with breast cancer. Information for this submission was gathered through observations and insights drawn through programs and meetings with 24 key patient advisors with lived experience of breast cancer, as well as an online survey documenting the lived experience with metastatic breast cancer from 78 patients and caregivers, conducted from September 2018 to April 2019. In addition, 4 people living with HR-positive, HER2-negative metastatic breast cancer, and had experience with abemaciclib, were interviewed from January to February 2025.

Results from the 2012 CBCN survey highlighted that fatigue, insomnia, and pain resulted in significant or a debilitating impact on quality of life. Patients who responded to the survey also stated moderate to significant restrictions in their ability to exercise, pursue hobbies and personal interests, participation in social events and activities, and their ability to spend time with loved ones. Patient groups noted that the disease further impacted mental health, with a physical and emotional toll associated with diagnosis, fear of recurrence, affecting caregivers and loved ones, and financial toxicity.

Patient groups highlighted the following barriers faced by patients who responded to the survey with existing treatments: AEs (e.g., fatigue, nausea, depression, problems with concentration, memory loss, diarrhea, and insomnia), financial impact (e.g., not qualifying for insurance, inability to change employers due to loss of insurance, and prohibitive cost of new treatment options), minimal or no access to appropriate care when experiencing debilitating symptoms, and challenges accessing quality care during cancer treatment. Patients emphasized the importance of having a choice of treatment options to determine a therapy that suited them.

The CBCN patient group specifically noted that efficacy, followed by quality of life, work, and cost were ranked as the most important to least important when considering treatment options.

All patient groups that provided input for this submission noted that extending cancer control and improved survival, combined with delayed progression (at least 6 to 9 months more than front-line treatments), a delay in IV chemotherapy, and improved quality of life were the most important outcomes of treatment. The CBCN also highlighted manageable AEs, although in the BCC survey, patients who responded noted that they were willing to accept higher rates of diarrhea as a trade-off for better recurrence-free survival outcomes. BCC also noted that patients were in favour of providing at-home, oral therapy that preserves quality of life. Rethink Breast Cancer suggested that patients valued long-term health outcomes compared to immediate concerns like reducing symptoms or managing side effects.

Of the 4 patients who were interviewed, 2 patients were taking abemaciclib and letrozole, 1 was taking abemaciclib and fulvestrant, and another was taking abemaciclib as their 11th line of treatment. Patients mentioned their condition was well managed, with no signs of progression, and tolerable side effects that could be managed with dose reductions or other medications, and that they had the ability to travel. One patient expressed comfort with frequent monitoring (scans every 6 months), a preference for oral treatment, and valued having multiple treatment options. The patient who received abemaciclib as their 11th line mentioned that even after being heavily pretreated, the treatment worked for a year.

Patient groups indicated that testing required for this treatment is already accessible and covered in jurisdictions across Canada but noted that this is only the case in early-stage breast cancer, and it is not relevant to the advanced or metastatic treatment setting. Rethink Breast Cancer and BCC agreed that expanding the range of available CDK4/6 inhibitor therapies with abemaciclib, without restriction to only unsuitable or intolerance to other CDK4/6 inhibitors, would ensure a more equitable approach to treatment across all provinces for patients while minimizing drug-related out-of-pocket costs for people who are financially vulnerable. Rethink Breast Cancer further added that since patient and physician choice was an important part of treatment, health care professionals should be able to tailor treatment plans to meet patient needs.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted for this review noted that treatment goals include prolonging life, delaying disease progression, and improving HRQoL. They also noted that not all patients respond to current treatments, and primary resistance to endocrine therapy in HR-positive disease remains a major challenge. Even among those who initially respond, resistance to CDK4/6 inhibitors often leads to disease progression, necessitating a transition to less effective and/or more toxic therapies. The clinical experts noted that there are currently 3 (including abemaciclib) CDK4/6 inhibitors that have demonstrated benefit in the first-line advanced or metastatic setting, and that clinicians generally perceive them to be approximately equivalent for the outcome of PFS. The experts agreed that choice of CDK4/6 inhibitor varies by patient and by clinician, and that a key decision-making factor was not just the prevalence of AEs, but also the particular type(s) of

AE associated with each CDK4/6 inhibitor, as different side-effect profiles will be more or less tolerable to different patients depending on their background health status and comorbid conditions. For instance, the clinical experts noted that ribociclib may not be the drug of choice if long-QT is an issue, and palbociclib may be avoided if neutropenia is an issue, while abemaciclib is generally associated with more diarrhea.

According to both clinical experts consulted by CDA-AMC, abemaciclib would not be the first drug in its class considered for this indication. However, it remains a valuable treatment option not only for patients with contraindications or intolerance to other CDK4/6 inhibitors, but also for other patients based on their individual health status, previous exposure to therapies in the adjuvant setting, duration between adjuvant therapy and diagnosis of metastatic disease, rate of disease progression, location and involvement of tumour sites, clinical status and comorbidities of the patients, and individual preferences. The clinicians noted that the best suited patients for treatment with abemaciclib are those with HR-positive, HER2-negative advanced or metastatic breast cancer. One expert noted that more significant benefit from the addition of abemaciclib may be observed in patients with high-risk features, such as visceral disease, PR-negative tumours, prior AI therapy, and high metastatic burden.

The clinicians noted that monitoring for treatment response involves a combination of clinical findings, bloodwork including tumour markers, and imaging, and should be assessed at every visit which typically occurs between once monthly (before each cycle) to once every 3 months. In some patients who have been deemed to be stable with treatment for several years, clinicians may extend the assessments longer than 3 months apart. Clinically meaningful outcomes, according to the experts, included improved survival, reduction in disease-related symptom frequency and severity, improved ability to perform daily activities, improvements in quality of life, and delaying chemotherapy. The clinicians stated that abemaciclib should be discontinued upon evidence of disease progression, whether clinically or radiographically (e.g., Response Evaluation Criteria in Solid Tumours Version 1.1 criteria), or in the event of intolerable side effects that cannot be managed supportively (e.g., dosage modification) and significantly impact the patient's quality of life. Patient preference is also considered. The experts noted that only a medical oncologist is qualified to initiate treatment with abemaciclib. Monitoring and continuing patients after initiation can be performed by other members of the health care team, including physicians in oncology, nurse practitioners, and oncology pharmacists.

Clinician Group Input

Two clinician groups, the REAL Canadian Breast Cancer Alliance, and OH (CCO) Breast Cancer DAC provided their input for this submission. REAL Canadian Breast Cancer Alliance is a standing committee of multidisciplinary clinical-academic oncologists across Canada who publishes national clinical consensus recommendations. Recommendations published by REAL Canadian Breast Cancer Alliance are routinely updated for timely health policy, funding, and consistent clinical adoption to ensure optimal outcomes for patients with breast cancer across all provinces and territories in Canada. A total of 16 clinicians provided their input, along with a literature review, clinical trial data, and recent data releases from international congresses, as well as collective clinical expertise of the members. The OH (CCO) DAC provides evidence-based clinical and health system guidance on drug-related issues including the Provincial Drug

Reimbursement Programs and the Systemic Treatment Program. Input from 5 clinicians was gathered via teleconference.

Both clinician groups indicated that CDK4/6 inhibitors plus endocrine therapy was the gold or current standard for the first-line treatment of HR-positive, HER2-negative advanced or metastatic breast cancer. The REAL Canadian Breast Cancer Alliance clinician group indicated that CDK4/6 inhibitors, when combined with endocrine therapy, were associated with significantly improved PFS in the first-line metastatic setting compared to endocrine therapy alone.

In line with the clinical experts consulted for this review, the REAL Canadian Breast Cancer Alliance clinician group noted that the goals of treatment were to extend life, maintain quality of life, delay the need for chemotherapy, and minimize treatment-related AEs. They highlighted that among currently publicly funded CDK4/6 inhibitors, ribociclib was the preferred first-line treatment option for HR-positive, HER2-negative advanced or metastatic breast cancer, given its proven OS benefit. They noted that the choice of therapy (i.e., ribociclib, palbociclib, and abemaciclib) was dependent not only on efficacy but also on the tolerability of side effects by patients and that expanding the range of available CDK4/6 inhibitor therapies would allow a more personalized approach to treatment, which aligned with the opinion of clinical experts consulted by CDA-AMC.

The REAL Canadian Breast Cancer Alliance clinician group noted that the population receiving CDK4/6 inhibitors would not be expected to expand; rather abemaciclib would be included as 1 of the treatment options for patients for whom CDK4/6 inhibitors are already considered standard of care. The REAL Canadian Breast Cancer Alliance clinician group noted that monitoring would mostly be required in the first 4 months of initiation with abemaciclib and would include bloodwork, assessing toxicities, and assessing treatment adherence. AEs were manageable with early interventions, including dose reduction and standard supportive care. Both clinician groups agreed that treatment discontinuation should be considered at the first sign of disease progression or due to persistent toxicity, as per the product monograph. The prescribing considerations noted by the group aligned with the opinion of clinical experts consulted by CDA-AMC. The REAL Canadian Breast Cancer Alliance clinician group noted that treatment initiation would be done by oncologists with experience in treating patients with breast cancer. OH (CCO) DAC noted that since abemaciclib and AI are oral therapies, an outpatient setting would be appropriate.

Drug Program Input

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

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
Should initiation criteria be consistent with CDA-AMC recommendations for ribociclib and palbociclib + AI in the same therapeutic space (e.g., have not received prior endocrine therapy for metastatic disease but may have received up to 1 line of chemotherapy for metastatic disease; are not resistant to [neo] adjuvant AI therapy; and do not have active or uncontrolled CNS metastases)?	Yes. The clinical experts consulted by CDA-AMC indicated that initiation criteria should be similar across CDK4/6 inhibitors in the treatment of this patient population, as they are considered broadly similar in efficacy and safety, albeit with differences in specific elements of the safety profiles that factors into clinician and patient decision-making. pERC agreed with the clinical experts.
Do the criteria from the previous CDA-AMC recommendation for abemaciclib + AI still apply? Specifically: • use of abemaciclib in combination with any AI (i.e., exemestane, anastrazole or letrozole) • including patients who were premenopausal, perimenopausal, and postmenopausal (surgically or chemically, be eligible)?	Yes. The clinical experts consulted by CDA-AMC did not indicate any need to change these criteria. pERC agreed with the clinical experts noting that eligibility for abemaciclib plus NSAI would apply to all adult patients independent of sex or ovarian function status.
Would it be reasonable to switch patients from ribociclib or palbociclib to abemaciclib (when there is toxicity to CDK4/6 inhibitor without progression)?	The clinical experts indicated that this scenario would be uncommon but would be an option for some patients having side effects from other CDK4/6 inhibitors but would only be done in the absence of disease progression. The experts noted that different CDK4/6 inhibitors may be tolerated differently in a given patient due to differences in side-effect profile. pERC agreed with the clinical experts.
Considerations for prescribing of therapy	
Note that the recommended dosing is twice daily for abemaciclib versus once daily for the other CDK4/6 inhibitors.	This is a comment from the drug programs to inform pERC deliberations.
System and economic issues	
Ribociclib and palbociclib have successfully gone through price negotiations for the same indication.	This is a comment from the drug programs to inform pERC deliberations.
Request an initiation of a rapid provisional funding algorithm. An update to the algorithm to incorporate the recommendation if positive.	This is a comment from the drug programs to inform pERC deliberations.

AI = aromatase inhibitor; CDA-AMC = Canada's Drug Agency; CDK4/6 = cyclin-dependent kinase 4 and 6; CNS = central nervous system; NSAI = nonsteroidal aromatase inhibitor; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Clinical Evidence

Systematic Review

Description of Studies

MONARCH 3 was a phase III, multicentre, randomized, double-blind, placebo-controlled study of abemaciclib or placebo plus an NSAI in patients who were postmenopausal with HR-positive, HER2-negative

advanced breast cancer or metastatic breast cancer who had not received any previous systemic therapy in the advanced or metastatic setting. The study was conducted in 158 centres in 22 countries.

The baseline demographic and disease characteristics were well balanced between the study arms. All enrolled patients were female and postmenopausal, with a mean age of 63 years (standard deviation = 9.92 years). Nearly all patients were white (56.7%, and 61.8% in the abemaciclib and placebo arms, respectively) or of Asian ethnicity (31.4%, and 27.3% in the abemaciclib and placebo arms, respectively), and had a measurable disease (81.4%, and 78.8% in the abemaciclib and placebo arms, respectively). Prior treatments were also well balanced between the 2 study arms. Approximately 40% of patients in each arm had received a prior adjuvant or neoadjuvant chemotherapy. At baseline, 25.9% of patients in the abemaciclib plus AI arm and 30.3% of patients in the placebo plus AI arm had received a prior AI.

Efficacy Results

Due to the nature of the reassessment, only OS and PFS are discussed as these outcomes have been updated since the prior review. Results are presented for both the November 3, 2017, data cut (i.e., the time of the final planned PFS analysis) and the September 29, 2023, data cut (i.e., the time of the final planned OS analysis). Results from the November 3, 2017, data cut are only provided for context as these results have previously been appraised by CDA-AMC and considered by pERC in 2019.

Overall Survival

The data for OS were immature at the time of the original review. At the January 3, 2017, data cut-off date, there were a total of 49 deaths (32 deaths [9.8%] in the abemaciclib plus AI arm and 16 deaths [9.9%] in the placebo plus AI arm). The median OS was not reached in either arm.

In the final OS analysis (data cut: September 29, 2023), 314 OS events (deaths) were observed in the intention-to-treat (ITT) population; 198 patients (60.4%) experienced OS events, and [redacted] were censored in the abemaciclib plus NSAI arm, and 116 patients (70.3%) experienced OS events, and [redacted] were censored in the placebo plus NSAI arm. The hazard ratio for OS in the ITT population was 0.804 (95% CI, 0.637 to 1.015; 2-sided stratified log-rank P = 0.0664). Based on the O'Brien-Fleming boundary, the 2-sided P value boundary for OS was 0.034 for the ITT population. Median OS was 66.81 months (95% CI, [redacted] to [redacted] months) in the abemaciclib arm and 53.72 months (95% CI, [redacted] to [redacted] months) in the placebo arm, that is, an absolute difference of 13.09 months in the ITT population (95% CI of absolute difference was not reported). In the Kaplan-Meier plot of OS, sustained separation favouring the abemaciclib plus NSAI arm became apparent at approximately 35 months. The OS rate at 5 years and 6 years was 54.5% (95% CI, [redacted] to [redacted]) and 45.7% (95% CI, [redacted] to [redacted]) in the abemaciclib plus NSAI arm, and 42.1% (95% CI, [redacted] to [redacted]) and 35.2% (95% CI, [redacted] to [redacted]) in the placebo plus NSAI arm, respectively.

Progression-Free Survival

In the final PFS analysis (data cut-off: November 3, 2017), after a median follow-up duration of 26.73 months, 246 investigator-assessed PFS events had occurred (138 [42.1%] events the abemaciclib plus AI arm and 108 [65.5%] events in the placebo plus AI arm). The median PFS was 28.18 months in the

abemaciclib plus AI arm compared to 14.76 months in the placebo plus AI arm (hazard ratio = 0.540; 95% CI, 0.418 to 0.698; P = 0.000002). The PFS benefit was maintained across the predefined patient subgroup analyses.

Updated PFS data were provided based on the September 29, 2023, data cut, which was the time of the final planned OS analysis. At this data cut, 350 patients experienced PFS events (i.e., progressive disease or death), including 213 (64.9%) in the abemaciclib plus NSAI group and 137 (83.0%) in the placebo plus NSAI group. Median PFS was 29.03 months (95% CI, [redacted] to [redacted] months) in the abemaciclib plus NSAI arm and 14.76 months (95% CI, [redacted] to [redacted] months) in the placebo plus NSAI arm (hazard ratio = 0.535; 95% CI, 0.429 to 0.668). These results corresponded to a 14.27-month increase in the median PFS (95% CI of difference not reported) for patients treated with abemaciclib plus NSAI. In the Kaplan-Meier plot of PFS, early and sustained separation by treatment arm was apparent beginning at approximately 2 months and continued to separate.

Harms Results

Data in this section were from the most recent data cut (i.e., September 29, 2023).

Adverse Events

Compared to placebo, a higher percentage of patients receiving abemaciclib experienced any treatment emergent adverse event (TEAE) (98.8% versus 94.4%), or grade 3 or higher TEAEs (69.4% versus 28.6%). The most frequently reported TEAE was diarrhea (83.5% versus 34.2%). Other AEs with a between-group difference of 20% included neutropenia (46.8% versus 1.9%), anemia (35.2% versus 9.9%), increased blood creatinine (25.1% versus 4.3%), and leukopenia (24.5% versus 3.1%). The most common grade 3 or higher TEAEs were neutropenia (27.5% versus 1.2%) and leukopenia (10.7% versus 0.6%).

Serious Adverse Events

The incidence of SAEs was higher in the abemaciclib plus NSAI arm compared with the placebo plus NSAI arm ([redacted]). The most common causes of SAEs in the abemaciclib plus NSAI arm by system organ class were infections and infestations ([redacted] followed by [redacted] ([redacted]%). The most common SAEs (at least 2%) regardless of causality in the abemaciclib plus NSAI arm by preferred term were [redacted] In the placebo plus NSAI arm, no SAEs occurred in more than 2% of patients. The most common SAEs were [redacted]).

Withdrawals Due to AEs

In the abemaciclib plus NSAI arm versus placebo plus NSAI arm, [redacted] patients discontinued all study treatments due to AE, respectively. The most common reason for stopping treatment due to AEs in the abemaciclib plus NSAI group was increased [redacted] All other withdrawals due to AEs were at a frequency of less than 2%.

Mortality

In total, 198 patients (60.4%) in the abemaciclib plus NSAI arm and 116 patients (70.3%) in the placebo plus NSAI arm died in the study. Deaths due to AEs in study therapy or within 30 days of treatment discontinuation were reported in 13 patients (4.0%) in the abemaciclib plus NSAI arm and 2 patients (1.2%) in the placebo plus NSAI arm. A total of [redacted] patients died after 30 days of treatment discontinuation. AEs were the cause of death in [redacted] in the abemaciclib plus NSAI arm.

Notable Harms

Prespecified AEs of special interest included neutropenia (46.8% in the abemaciclib group and 1.9% in the placebo group), [redacted] diarrhea (83.5% and 34.2%), alanine transaminase increase (22.0% and 8.1%), venous thromboembolisms (7.6% and 1.2%), and interstitial lung disease or pneumonitis (7.0% and 0.6%). The incidence of each of these events was higher in the abemaciclib plus NSAI group compared to the placebo plus NSAI group.

Critical Appraisal

The MONARCH 3 trial has previously been reviewed and appraised by CDA-AMC, and many of the critical appraisal points still apply. Briefly, critical appraisal points at the time of the initial review were as follows: the MONARCH 3 study was a phase III, double-blind, placebo-controlled randomized controlled trial that evaluated abemaciclib plus NSAI versus placebo plus NSAI as a first-line therapy in adult patients who were postmenopausal with HR-positive, HER2-negative advanced or metastatic breast cancer. Choice of NSAI therapy (letrozole or anastrozole) was determined by the treating physician in each case. Randomization, allocation, allocation concealment, and blinding methods were conducted to reduce the risk of systematic bias in the selection and assignment of patients, and in the interpretation of observed treatment effects (benefits and harms). Patients were stratified by the nature of disease (visceral metastases versus bone-only metastases versus other), and prior (neo)adjuvant endocrine therapy (AI therapy versus other versus no prior endocrine therapy). Blinded independent central review was used for assessment of radiological scans to reduce detection bias. At baseline, demographic, disease characteristics, and prior treatments in the ITT population were balanced across study arms.

In the updated efficacy analysis (data cut: September 29, 2023), the median duration of follow-up was just over 8 years in either treatment arm ([redacted]). Discontinuation of treatment was higher in the placebo group, and was most commonly due to progressive disease in both treatment groups ([redacted] but there was a higher incidence of discontinuation due to AEs in the group receiving abemaciclib ([redacted]), which is aligned with the generally higher rate of overall AEs and SAEs observed compared to the placebo group.

Though the hazard ratio at the final OS analysis (hazard ratio = 0.804; 95% CI, 0.637 to 1.015) was improved compared to the primary analysis (hazard ratio = 1.057; 95% CI, 0.683 to 1.633), and the estimated benefit in OS was an absolute difference in median OS of 13.09 months (95% CI of absolute difference not reported), the results were not statistically significant. However, in consultation with clinical experts, the reported difference in median OS was considered clinically important despite not being statistically significant.

The treatment setting, demographics, disease characteristics, and treatment history of patients who were recruited were considered to reasonably reflect the real-world clinical practice population in Canada with regards to this indication. Patients enrolled in the MONARCH 3 study were required to have an Eastern Cooperative Oncology Group (ECOG) status of 0 to 1, and therefore there is no evidence on the efficacy and safety of abemaciclib in patients with an ECOG status of 2 or greater; however, most patients in clinical practice will have a performance status of 0 to 1, and so this was not considered to represent a concern for external validity. The clinical experts consulted by CDA-AMC noted that the results of this study of abemaciclib were as expected for CDK4/6 inhibitors and were relatively similar to their experiences in clinical practice with abemaciclib as well as other CDK4/6 inhibitors, although each drug has its own unique safety profile. Overall, there were no major generalizability concerns related to the MONARCH 3 study.

Long-Term Extension Studies

No long-term extension studies were identified for this review.

Indirect Comparisons

Description of Studies

As the MONARCH-3 study was a placebo-controlled trial, there is a lack of direct evidence comparing abemaciclib to key comparators. The sponsor-submitted Bayesian NMAs to compare abemaciclib (from the MONARCH 3 study) with other CDK4/6 inhibitors and other treatments commonly used in HR-positive, HER2-negative advanced breast cancer or metastatic breast cancer in the treatment of patients who were postmenopausal without prior systemic treatment for advanced disease. The sponsor conducted a systematic literature review (SLR) to identify studies aligning with the indication.

For the purpose of this reassessment, only PFS, OS, and grades 3 or 4 AEs were assessed in depth.

Efficacy Results

Overall Survival

Results of the NMA analysis for OS did not demonstrate a difference in hazard ratios between abemaciclib plus NSAI, NSAI alone, ribociclib plus letrozole, ribociclib plus fulvestrant, palbociclib plus letrozole, fulvestrant 200 mg or 500 mg, tamoxifen, or exemestane, as all CrIs were wide and overlapped null.

Progression-Free Survival

Results of the NMA analysis for PFS favoured abemaciclib plus NSAI compared to fulvestrant 500 mg, fulvestrant 250 mg, and tamoxifen monotherapies. However, the comparisons of abemaciclib plus NSAI against ribociclib plus letrozole, ribociclib plus fulvestrant, palbociclib plus letrozole, palbociclib plus fulvestrant, and dalpiciclib plus anastrozole-letrozole, did not demonstrate a difference and the hazard ratios were comparable.

Harms Results

For the NMA of grades 3 or 4 AEs, abemaciclib plus NSAI was favoured compared to palbociclib plus letrozole, palbociclib plus fulvestrant, and dalpiciclib plus anastrozole-letrozole. Conversely, anastrozole-

letrozole, fulvestrant 500 mg, and exemestane were favoured over abemaciclib plus AI. There was no difference detected against ribociclib plus letrozole.

Critical Appraisal

The sponsor conducted an appropriate SLR to identify studies of interest for indirect treatment comparisons and assessed the study design, eligibility criteria, baseline characteristics, outcome definitions, and outcome assessment for homogeneity. Studies included in the SLR were appraised for risk of bias by the sponsor using the Cochrane tool; there was some elevated or unknown risk of bias, in particular for open-label studies which, naturally, had elevated risk of bias for domains related to allocation concealment and blinding. Bayesian NMAs were conducted for several outcomes of interest. The proportional hazards assumption was evaluated, and found to be violated in several cases, including in the MONARCH 3 study (for the outcome of OS); NMAs using the fractional polynomial method were conducted as sensitivity analyses for PFS and OS as this approach does not rely on the proportional hazards assumption. There were important differences in the trial design, eligibility criteria, and patient baseline characteristics across several domains that could impact comparability with the MONARCH 3 study, for example, HR status, country that the study was conducted in, open-label trials, disease severity, and location of disease. The results of the NMA analyses generally suggested that there was no difference between abemaciclib plus NSAI to other available combination CDK4/6 inhibitors for OS, PFS, and grades 3 or 4 AEs. The clinical experts noted that it is important to consider specific, individual AEs (e.g., diarrhea or neutropenia), rather than aggregate AEs as this is an important consideration in treatment selection. Regardless, the limitations previously outlined, in combination with the wide 95% CrIs, reduce the precision of the results, and preclude definitive conclusions on the comparative effectiveness of abemaciclib and other CDK4/6 inhibitors.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description and Appraisal of Studies

The sponsor submitted 4 observational studies to address the safety issues identified in the pivotal evidence; however, only 2 were summarized and appraised as they were deemed to contain potentially relevant information of interest to this review. The other 2 studies were not considered relevant as they mostly evaluated a population that received abemaciclib plus fulvestrant as the endocrine partner, which was not the indication under review.

US Database Study

The US database study by Price et al. (2022) was provided by the sponsor to address the gap in the pivotal study concerning safety issues of abemaciclib relative to other CDK4/6 inhibitors. This was a retrospective study examining the management of AEs among female patients with HR-positive, HER2-negative metastatic breast cancer receiving CDK4/6 inhibitors. Data for 396 patients from the US Oncology Network iKnowMed electronic health record database were analyzed, of which 163 patients received palbociclib, 142 patients received abemaciclib, and 91 patients received ribociclib. The mean age was 64.3 years (standard deviation = 11.9 years) and included patients with varying stages of disease (stage I = 10.1%; stage II = 35.6%; stage IIIA = 18.2%; and stage IV = 31.1%). More than one-half of patients received CDK4/6 inhibitors as first-line therapy (84.6% for ribociclib, 65.5% for abemaciclib, and 63.8% for palbociclib). For patients

receiving palbociclib and ribociclib, letrozole was the most prescribed combination therapy in first line, while for the abemaciclib cohort, fulvestrant was the most prescribed combination therapy in first line (N = 45 of 93; 31.7%). Across all lines of therapy, one-half of patients in the abemaciclib cohort received fulvestrant as combination therapy, and one-half received either anastrazole or letrozole.

The most common AEs reported included neutropenia (palbociclib: 44.8%, abemaciclib: 10.6%, and ribociclib: 36.3%), diarrhea (palbociclib: 8.0%, abemaciclib: 43.0%, and ribociclib: 8.8%), and fatigue (palbocilib: 12.9%, abemacicib: 17.6%, and ribociclib: 16.5%). Treatment holds due to neutropenia were reported in 47 patients and were more frequently reported in the palbociclib (N = 33 [45.2%]) and ribociclib cohorts (N = 13 [39.4%]) than the abemaciclib cohort (N = 1 [6.7%]). Dose reductions due to neutropenia were reported in 25 patients (34.2%) who received palbociclib, 8 patients (53.3%) who received abemaciclib, and 11 patients (33.3%) who received ribociclib. Treatment discontinuations due to neutropenia were reported in 10 patients in the palbociclib cohort and 2 patients in the ribociclib cohort. Treatment holds due to diarrhea were reported in 24 patients, 5 in the palbociclib cohort, 18 in the abemaciclib cohort, and 1 in the ribociclib cohorts. Dose reductions due to diarrhea were reported in 22 patients, most frequently in the abemaciclib cohort (N = 18), followed by 3 patients who received palbociclib and 1 patient who received ribociclib. In total, 17 patients discontinued treatment due to diarrhea, most frequently in the abemaciclib cohort (N = 11), followed by palbociclib (N = 4) and ribociclib cohorts (N = 2). Eleven patients discontinued treatment due to fatigue, of which 9 patients received abemaciclib and 1 patient received palbociclib and ribociclib. Hospitalizations due to AEs occurred for 13 patients (3.3%) overall (4.3%, 3.5%, and 1.1% for patients in the palbociclib, abemaciclib, and ribociclib cohorts, respectively). The study noted lower frequencies of AEs but higher dose reductions when compared to data from clinical trials.

The study had some notable limitations. Data were collected from an electronic health record system, and any AE-related data managed outside of the network and not documented may lead to underreporting. An unadjusted observational analysis limits the reported estimates to be interpreted causally. Furthermore, documentation of the validity and accuracy of data were not provided. The analysis did not adjust for baseline demographic, disease characteristics, or comorbidities, and included patients with varying disease stages which could impact response to treatment and tolerability of treatment. It is unclear how many patients included in the analysis aligned with the indication under review given the different lines of therapy, and differing endocrine partners received with abemaciclib (i.e., one-half of all patients received combination fulvestrant, which is not part of the reimbursement request for this review). The National Cancer Institute Common Terminology Criteria for Adverse Events grading was not collected during clinical practice and not available for this study. The study was only conducted in the US. As such, the generalizability of the results of this retrospective chart study to the population under review is unclear.

Slovenian Real-World Evidence Study

The sponsor-provided Slovenian real-world evidence study by Matos et al. (2024), provides additional safety and efficacy data for abemaciclib in the real-world setting, as well as insight into relevant subgroups such as older patients (age groups analyzed < 70 years and ≥ 70 years). This study was an institutional retrospective study evaluating the real-world efficacy and safety of abemaciclib in patients with HR-positive,

HER2-negative metastatic breast cancer. Data for 134 patients (133 females, 1 male) who were prescribed abemaciclib with AI or fulvestrant in the first, second, or subsequent line of treatment were retrospectively collected from institutional medical records. Real-world progressive disease was determined by the treating physician based on radiological, laboratory, or clinical assessment. Median follow-up was 42 months (95% CI, 28.28 to 45.71 months). The median age at treatment initiation was 62 years, and most patients had recurrent metastatic disease at presentation (100 [74.6%]). A total of 69 patients (51.5%) received abemaciclib in combination with endocrine therapy in first line, of which 47 patients (68.1%) received AI and 22 patients (31.9%) received fulvestrant as the endocrine partner. Thirty-two patients received abemaciclib in the second line and 33 patients received abemacilib in the third or later lines, respectively.

The median real-world PFS for the entire cohort was 15 months (95% CI, 9.52 to 20.48 months) and was 21 months in the first line (95% CI, 15.12 to 26.88 months), 20 months in the second line (95% CI, 6.38 to 33.60 months), and 7 months in the third line (95% CI, 4.19 to 9.81 months), respectively. For the entire cohort, the median OS was 29 months (95% CI, 24.15 to 33.84 months). Median OS was not reached in the first-line setting but was 29 months for second line (95% CI, 26.09 to 39.90 months) and 19 months for third or later lines (95% CI, 7.59 to 30.49 months), respectively.

The most common AEs (any grade) were diarrhea (68.7%), anemia (64.9%), and increased serum creatinine (63.4%). Grades 3 or 4 diarrhea were reported in 7 patients, and grade 2 diarrhea in 27 patients. Grade 2 neutropenia was reported in 39 patients and grades 3 or 4 neutropenia were reported in 17 patients, respectively. Grade 2 anemia was reported in 21 patients. Dose reductions occurred in 41 patients (30.6%), primarily due to diarrhea (19 [32.2%]). Dose reductions were more frequent in patients aged 70 years or older (40%) compared to patients aged younger than 70 years (28%). Eighty-seven patients discontinued abemaciclib either due to disease progression (n = 64) or AEs (n = 23). Grades 3 or 4 neutropenia were more common in patients aged younger than 70 years (16%) versus 70 years or older (5%). Grades 3 or 4 diarrhea were more frequently reported in patients aged 70 years or older (7.5%) versus patients aged younger than 70 years (4.3%).

Several limitations were noted for this study. Data were collected from an electronic health record system, and any inconsistent AE incident collection may lead to underreporting. An unadjusted observational analysis limits the reported estimates to be interpreted causally. There was heterogeneity in the patient population analyzed with respect to age, line of treatment, and endocrine therapy used, though it was primarily AI. This study also had a small sample size, and many patients (n = 87) discontinued abemaciclib at study cut-off due to disease progression or AEs. It is worth noting that the results for median PFS and OS were numerically lower in this study compared to the pivotal trial, though the reason for this naive difference is unknown, which further undermines the generalizability of the results.

Economic Evidence

Economic Evaluation and Budget Impact

- Abemaciclib is available as 50, 100, and 150 mg tablets. At the submitted price of $116.22 per 150 mg, the 28-day cycle of abemaciclib is predicted to be $6,508 per patient, based on the Health Canada–recommended dosage. The 28-day per patient cost of abemaciclib plus NSAI for advanced or metastatic breast cancer as initial endocrine-based therapy is predicted to be $6,535 if using anastrozole and $6,547 if using letrozole. Treatment should be continued until disease progression or unacceptable toxicity.
- Clinical efficacy in the economic analysis for abemaciclib plus NSAI versus NSAI alone was derived from the MONARCH 3 trial. Evidence submitted by the sponsor indicates that abemaciclib plus NSAI resulted in clinically significant improvement in PFS. There is uncertainty regarding the benefit and magnitude of abemaciclib plus NSAI in OS, compared with NSAI alone, in the first line among patients with advanced or metastatic breast cancer as the results for OS were not statistically significant, although the clinical experts consulted for this review noted that they are clinically important. For abemaciclib plus NSAI compared to ribociclib plus NSAI and palbociclib plus NSAI, clinical efficacy was informed by sponsor-submitted NMA, which was subject to considerable uncertainty due to imprecise estimates and methodological limitations. It is possible for abemaciclib to have better or worse effectiveness with regards to the outcomes of PFS and OS when compared to the other CDK4/6 inhibitors, ribociclib or palbociclib, in the setting in Canada. Grades 3 or 4 AEs were assessed in the NMA, although there is no strong evidence of substantial differences in the overall safety profile of abemaciclib compared to the other CDK4/6 inhibitors, based on clinical experience each drug is associated with an elevated risk of different types of AEs. Diarrhea, neutropenia, and infections were the most commonly reported AEs associated with abemaciclib in the MONARCH 3 trial, and most were manageable with dose adjustments and supportive care.
- The results of the CDA-AMC base case suggest:
  - Abemaciclib plus NSAI is predicted to be associated with the highest costs to the health care system and higher quality-adjusted life-years (QALYs) than all comparators.
  - When considering the next most cost-effective treatment (ribociclib plus NSAI), abemaciclib plus NSAI is associated with greater costs (incremental costs = $64,375 primarily driven by increased drug acquisition costs associated with abemaciclib).
  - When considering the next most cost-effective treatment (ribociclib plus NSAI), abemaciclib plus NSAI is predicted to be associated with a gain of 0.02 life-years and may result in a gain of 0.06 QALYs.
  - The incremental cost-effectiveness ratio of abemaciclib plus NSAI compared to ribociclib plus NSAI is $1,047,838 per QALY gained in the CDA-AMC base case. The estimated incremental cost-effectiveness ratio was highly sensitive to assumptions about treatment duration and long-term efficacy. Approximately 14% of the incremental benefit was gained in the extrapolated period (i.e., after 103 months).

    - These findings are highly uncertain due to the limitations with the indirect comparative evidence and the lack of comparative evidence on time to treatment discontinuation across combination therapies; both of which were key drivers of the submitted economic model. Therefore, there is no robust evidence to support a price premium for abemaciclib plus NSAI versus other relevant combination therapies to treat the same patient population. The incremental cost of abemaciclib plus NSAI is driven primarily by the drug acquisition cost. Of note, there has been recent availability of generic drugs for palbociclib which has a similar mechanism of action (i.e., CDK 4/6 inhibitor).
- CDA-AMC estimates that the budget impact of reimbursing abemaciclib plus NSAI for the treatment of HR-positive, HER2- advanced or metastatic breast cancer in patients who were postmenopausal as initial endocrine-based therapy will be approximately $83 million over the first 3 years of reimbursement compared to the amount currently spent on comparators. The expenditure on abemaciclib plus NSAI is predicted to be $261 million over this period. The actual budget impact of reimbursing abemaciclib plus NSAI will depend on the remaining number of people eligible for treatment with abemaciclib due to previous exposure, and the uptake of generic drugs for palbociclib. At the submitted price, the incremental budget impact of reimbursing abemaciclib plus NSAI is predicted to be greater than $40 million in year 3, and the economic feasibility of adoption must be addressed. Additionally, 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.

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

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

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