Canadian Journal of Health Technologies

Canada's Drug Agency
L'Agence des médicaments du Canada

January 2026 Volume 6 Issue 1

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Aripiprazole

Reimbursement request: Adjunct to antidepressants for the treatment of major depressive disorder in adult patients who had an inadequate response to at least 1 prior antidepressant treatment

Requester: Public drug programs

Final recommendation: Reimburse

Summary

What Is the Reimbursement Recommendation for Aripiprazole?

The Formulary Management Expert Committee (FMEC) recommends that oral aripiprazole be reimbursed as an adjunct to antidepressants for the treatment of major depressive disorder (MDD) in adult patients who have an inadequate response to at least 1 prior antidepressant treatment.

What Are the Conditions for Reimbursement?

The committee determined that there are no conditions necessary for the reimbursement recommendation.

Why Did CDA-AMC Make This Recommendation?

FMEC reviewed the report by Canada's Drug Agency (CDA-AMC), which included a review of the clinical evidence, specifically 1 trial, 3 indirect treatment comparisons, and a cost comparison of aripiprazole versus other treatments used in Canada. Aripiprazole is available as a generic drug in Canada. FMEC also considered input received from the Mood Disorders Society of Canada (MDSC). Overall, the evidence reviewed demonstrates that aripiprazole, risperidone, quetiapine, olanzapine, and brexpiprazole have at least similar efficacy and safety in patients with MDD. There is no clear signal that aripiprazole worsens response, remission, disease severity, function, and health-related quality of life (HRQoL), or increases tolerability compared to other antipsychotic drugs currently being reimbursed by the public drug plans as adjunctive treatment for MDD.

FMEC concluded that oral aripiprazole demonstrates acceptable clinical value; the reimbursement recommendation also considered unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems.

Review Background

What Is MDD?

In accordance with the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, MDD is characterized by the occurrence of 1 or more major depressive episodes, by depressed mood or anhedonia (markedly diminished interest or pleasure in previously enjoyed activities), and 4 or more of the following symptoms for at least 2 weeks: psychomotor slowing or agitation, fatigue or low energy, poor concentration or memory, changes in appetite or weight, changes in sleep, suicidal thoughts or ideation, and feelings of worthlessness or guilt. MDD is a common chronic mental health condition, with an annual prevalence in Canada ranging from 5.4% among adults who were employed and 11.7% among adults who were not employed.

What Are the Current Treatment Options?

The usual first-line and second-line treatments for MDD include evidence-based psychotherapies (e.g., cognitive behavioural therapy, interpersonal therapy, and behaviour therapy), antidepressants with various pharmacologic mechanisms of action, or a combination of these 2 modalities. Beyond these typical first-line and second-line therapies, there are other evidence-based treatments for MDD including transcranial magnetic stimulation, electroconvulsive therapy, IV ketamine, and intranasal esketamine (which are out of scope for this review).

What Is the Treatment Under Review?

Aripiprazole is a second-generation antipsychotic drug. The proposed mechanism of action is through a combination of partial agonist activity at dopamine D2 and serotonin 5-HT1A receptors and antagonist activity at 5HT2A receptors. The recommended dosage range is 2 mg to 15 mg per day administered orally. Aripiprazole has been approved by Health Canada as an adjunct to antidepressants for the treatment of MDD in adult patients who had an inadequate response to prior antidepressant treatments during the current episode. The reimbursement request is as adjunct to antidepressants for the treatment of MDD in adult patients who had an inadequate response to at least 1 prior antidepressant treatment. This review is for on-label use.

Why Did We Conduct This Review?

The participating public drug programs have requested that a nonsponsored Reimbursement Review be conducted to inform whether oral aripiprazole should be reimbursed for the adjunctive treatment of MDD, prompted by emerging availability of evidence over the last decade for a treatment regimen with potential to fulfill an unmet need in patients with MDD. Aripiprazole for MDD was initially reviewed by CDA-AMC on October 22, 2014, and received a “do not list” recommendation. There are 13 generic drugs currently approved for aripiprazole, as well as 4 generic drugs under review at Health Canada, and the data protection for aripiprazole expired in 2018 (January 9, 2018), making this drug eligible for a nonsponsored Reimbursement Review as per the *Procedures for Reimbursement Reviews*.

Highlights of Input From Interested Parties

MDSC, as a patient group, conducted extensive direct discussions with patients (including focus groups, meetings, and online discussions); obtained input from family members and caregivers; distributed a national online survey between March 3 and 22, 2018, with 119 respondents; and engaged with its community over a variety of multimedia channels. Patients reported that MDD has a profound and often devastating impact on day to day functioning and overall quality of life, for both individuals and their families or caregivers (e.g., emotional distress, stigma, and financial strain). The impacts extend to the community and society at large (e.g., economic burden). Patients report that the mental, emotional, and physical toll of depression can be relentless, especially in cases of treatment-resistant depression, or difficult to treat depression, which is now recognized by clinicians as a chronic illness. MDSC also gathered insight from a patient currently undergoing treatment for MDD with aripiprazole. This patient had access to aripiprazole through private work insurance. They expressed that success with aripiprazole would mean having more day to day stability in their mental health. The patient did not expect aripiprazole to eliminate depression but hoped it could reduce the intensity and frequency of severe low periods, allowing for more moments of clarity, hope, and motivation. Small improvements, such as having more days where getting dressed does not feel overwhelming, were seen as meaningful signs of progress. The patient described the overall effects of aripiprazole as “about the same” compared to previous antidepressants. They did experience side effects while receiving aripiprazole, such as dizziness and lightheadedness, which were overwhelming at first but subsided after a few days. These side effects were somewhat better than those they had experienced with previous treatments and were manageable without adjustments.

► **Refer to the main report and the supplemental material document for this review.**

Person With Lived Experience

A person with lived experience from Nova Scotia shared her journey living with MDD since adolescence. She was finally diagnosed at age 20. She spoke about the exhausting toll of the illness, feeling like “10-pound weights” on her arms and legs that made it physically hard to do things. She underwent 10 years of trial and error with antidepressants and add-on therapies that often stopped working or caused unbearable side effects. Access to psychiatric care required long waits and travel. Relief came when aripiprazole was added to her antidepressant, lifting what she called the “black veil” where her mood improved greatly, irritability over minor things disappeared, and she had energy to get through her days without forcing herself. She experiences akathisia while taking aripiprazole but is happy to manage this symptom through movement and exercise, as the improvement in her mood and daily functioning far outweighs the discomfort. Her insurance did not cover aripiprazole, but her psychiatrist provided samples for her to ensure she could access treatment. She stressed the importance of having more options covered to help patients find the treatment that works best for them.

Disclaimer: The perspectives shared by people with lived experience who present to the committee reflect their individual experiences and are not necessarily representative of all people with the same condition or course of treatment. Their insights provide valuable context about what a patient, support person, or caregiver might go through when facing this condition or treatment, helping to inform the committee's deliberations. These narratives complement other forms of evidence and input and should be considered as part of a broader understanding of the condition and treatment under review. Where gender or gendered pronouns are used in these narratives, they are included with the permission of the individual.

Recommendation

With a vote of 9 to 0, FMEC recommends that oral aripiprazole as adjunct to antidepressants for the treatment of MDD in adult patients who had an inadequate response to at least 1 prior antidepressant treatment be reimbursed.

The committee determined that there are no conditions necessary for the reimbursement recommendation.

Summary of Deliberation

FMEC deliberated on all domains of value of the deliberative framework before developing their recommendation: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems. For further information on the domains of value, refer to the Expert Committee Deliberation at Canada's Drug Agency document.

FMEC considered the following key discussion points, organized by the 5 domains of value.

Clinical Value

- **FMEC concluded aripiprazole demonstrates acceptable clinical value versus appropriate comparators in the Canadian setting.**
- Through reflection on the input from patient groups or insights shared by the person with lived experience, FMEC members noted the following important patient values or perspectives. Because MDD is heterogenous, patients want a broad spectrum of options to manage it. They value improved day to day functioning and while they want meaningful symptom relief, the patient interviewed would tolerate mild symptoms as a trade-off for day to day stability. Patients hope for treatments without significant side effects and raised concerns about long-term side effects, such as thyroid issues.
- **FMEC** members highlighted the following discussion points:
  - **Appropriate comparators.** FMEC noted that there is alignment of study comparators with clinical practice in Canada. Numerous first-line therapies are available in Canada. Adjunctive therapies used in Canada include aripiprazole, brexpiprazole, olanzapine, and quetiapine. Clinical experts indicated that brexpiprazole and quetiapine are the most relevant comparators in clinical practice in Canada.

- **Efficacy and clinical importance of treatment effects.** FMEC concluded that there is no clear indication that short to medium adjunct treatment with aripiprazole has worse efficacy than the comparators. Findings from indirect comparisons (3 network meta-analyses) suggest:
  - Aripiprazole may have similar effects on response rate, remission rate, symptom severity, and social function or HRQoL compared to risperidone and quetiapine.
  - Aripiprazole may result in a higher response rate compared to olanzapine, but clinical significance is uncertain. Aripiprazole may have similar effects on remission rate, symptom severity, and social function or HRQoL compared to olanzapine.
  - Aripiprazole may result in a higher remission rate compared to brexpiprazole, but clinical significance is uncertain. Aripiprazole may have similar effects on response rate, symptom severity, and social function or HRQoL compared to brexpiprazole.
- **Safety.** FMEC acknowledged that there is no clear indication that aripiprazole has more potential harms than the comparators. Findings from indirect treatment comparisons (3 network meta-analyses) suggest:
  - No difference in rates of adverse events, severe adverse events, and weight gain between aripiprazole and brexpiprazole.
  - No difference in rates of discontinuation due to adverse events with aripiprazole compared to risperidone, quetiapine, olanzapine, and brexpiprazole.
  - FMEC concluded that aripiprazole does meet clinical needs by providing a drug with similar efficacy to comparators with a varied adverse effect profile. As indicated by clinical experts, aripiprazole may have a better metabolic profile compared to drugs such as olanzapine and quetiapine and is well tolerated at the lower end of the dose range. Clinical experts indicate that it may provide meaningful efficacy in targeting residual symptoms, including low interest and low motivation, while avoiding metabolic issues, which FMEC noted was a concern expressed by the patient group.
- **Place in therapy.** The Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 guideline recommended aripiprazole as 1 of the first-line options for adjunct treatments for treatment-resistant depression.
  - FMEC heard from the clinical expert that it may be beneficial to add aripiprazole to existing treatment with an antidepressant for which a patient has experienced a meaningful improvement in anticipation of maintaining that existing benefit and adding incremental benefit.

Unmet Clinical Need

- **FMEC concluded that there is a significant clinical need arising from MDD despite available treatments.**
- Through reflection on the input from patient groups or insights shared by the person with lived experience, FMEC members noted the following important patient values or perspectives. MDD

has a profound, often devastating impact on day to day functioning. The disease affects families, caregivers, the community, and society at large. Current treatments offer symptom relief and improve daily functioning, but for many, efficacy often diminishes over time. Challenging side effects may lead patients to discontinue treatments or undergo a challenging trial and error process to find a tolerable treatment.

- **FMEC** members highlighted the following discussion points:
  - **Availability of treatment options**. FMEC discussed that there are multiple alternative therapies available for MDD and include psychotherapies and multiple pharmacologic therapies. Despite multiple therapies, about one-half of patients respond to first-line therapies. A significant proportion suffer symptoms for 2 years or more. Although drugs have similar efficacy rates, adverse effects vary in type, frequency, and severity.
  - The clinical expert felt there was room for relatively early augmentation, given patient willingness, and reasonable initial response to the first drug. Timeliness of treatment is important when people are experiencing an acute major depressive episode, especially if the patient is not working. MDD is a major cause of occupational disability in Canada.
  - **Significant unmet clinical need.** FMEC discussed the unmet clinical needs identified by patients, including the need for a broad spectrum of options given variable individual response. Therapies that provide meaningful symptom relief and a return to full function and drugs that provide benefits without significant side effects or long-term health risks are sought.
  - FMEC noted that patients reported to be willing to tolerate mild continuing symptoms (e.g., mild sadness, low energy) in return for better function during the day.
  - The clinical expert stated that patients vary in their desire and access to psychotherapy. Depending on the form of MDD, an average patient may benefit from time-limited psychotherapy. However, patients with severe MDD may not benefit from psychotherapy for various reasons.
  - **Evidence generation.** FMEC noted that this is a prevalent condition that has a large volume of clinical studies (e.g., 69 RCTs included in the network meta-analysis by Saelens et al. [2025]; 15 of these RCTs were relevant to this review). Despite some challenges of research in patients living with a mental health disorder including heterogeneity of disease, subjective symptomatology, and vulnerable populations, significant evidence does exist. FMEC noted that specifically targeting subpopulations including those with residual symptoms including low interest and low motivation, as well as those in whom avoiding metabolic issues would be helpful.

Distinct Social and Ethical Considerations

- **FMEC did not identify any important measures that should be implemented to ensure that the use of aripiprazole addresses relevant social and ethical implications.**
- **FMEC concluded that aripiprazole would not address a significant nonclinical need arising from MDD despite available treatments.**

- Through reflection on the input from patient groups or insights shared by the person with lived experience, FMEC members noted the following important patient values or perspectives. Stigma about mental illness and depression prevents many patients from seeking treatment. Funding for medications varies in both public and private forms of coverage. Some patients may have access to private drug coverage; however, even with this, there can be significant delays in reimbursing claims. Patients may access treatment via primary care providers as access to psychiatric care is challenging. The full spectrum of care for depression includes medication along with therapy and psychosocial supports but these are rarely publicly funded, causing another inequity. Those in lower socioeconomic groups or underserved regions face additional barriers.
- Aripiprazole does not address nonclinical needs.
- **FMEC** members highlighted the following discussion points:
  - **Significant unmet nonclinical need or health inequity.** FMEC discussed that individuals living with MDD report challenges with their conditions including limited ability to participate in activities of daily living, a significant negative effect on overall quality of life, the need for meaningful symptom relief, stigma, financial burden, and the need to adapt to available treatments. Funding for medications varies in both public and private insurance. Equity and access to timely care is an important consideration for patients with MDD.

Economic Considerations

- **FMEC concluded that there are no economic considerations that are feasible to address when implementing aripiprazole, given that aripiprazole is a generic drug and its pricing is subject to a defined pan-Canadian Pharmaceutical Alliance tiered pricing framework.**
- **FMEC** members highlighted the following discussion points:
  - MDD imposes a significant economic burden on Canada, with an estimated annual cost exceeding $32 billion. This includes both direct costs, such as health care services, medications, hospitalizations, and physician consultations, as well as indirect costs like lost productivity due to absenteeism, presenteeism, disability claims, and early retirement.
  - At publicly available prices, the reimbursement of aripiprazole is expected to increase overall drug acquisition costs compared with all the relevant comparators, except for brexpiprazole.
  - Based on the available evidence, aripiprazole has similar clinical effectiveness against its comparators.
  - The cost-effectiveness of aripiprazole compared with relevant comparators is unknown.
  - Aripiprazole is available as a generic drug in Canada and therefore its cost is subject to the pan-Canadian Pharmaceutical Alliance tiered pricing framework for generic drugs.

Impacts on Health Systems

- **FMEC did not identify any impacts on health systems that are important to address when implementing aripiprazole.**
- **FMEC** members highlighted the following discussion points:
  - **Organizational implications.** FMEC noted that the impacts on health systems in implementing this drug would be minimal as aripiprazole is already in use for this indication in clinical practice. Aripiprazole is currently established in practice guidelines in Canada. Although already used in clinical practice, enhanced access should come with appropriate education to ensure the most appropriate use.
  - **Budget impact analysis.** The CDA-AMC team did not identify any published budget impact analyses.
  - **Considerations for health system sustainability.** FMEC concluded that there may be a minimal impact on alleviating current challenges within health system sustainability if this is implemented through improved control for those benefiting from this drug.
  - **Equity considerations.** FMEC did not identify factors that need to be addressed to support the equitable implementation of aripiprazole.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information (links to the full documents for the review can be found on the project webpage):

- the CDA-AMC review of the clinical and pharmacoeconomic evidence related to aripiprazole (refer to the Main Report and Supplemental Material document)
- patients' perspectives gathered by 1 patient group, the MDSC
- input from a person with lived experience who delivered a brief presentation and answered questions from the committee (refer to the Person with Lived Experience section earlier in this document)
- input from public drug programs that participate in the reimbursement review process (refer to the Questions From the Drug Program Input Document)
- input from 2 clinical experts with expertise in the management of MDD consulted by CDA-AMC.

Feedback on Draft Recommendation

CDA-AMC received feedback from the public drug programs. The public drug programs agreed with the recommendation, with no requested revisions.

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

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Zaina Albalawi, Dr. Hardit Khuman, Ms. Valerie McDonald, Ms. Marilyn Barrett, Dr. Bill Semchuk, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik. Two guest specialists (clinical experts) from Ontario and the Prairies participated in this review.

Regrets: One guest specialist did not attend the meeting. Two clinical experts were consulted for the clinical and pharmacoeconomic report. One clinical expert was unable to attend the meeting.

Meeting date: November 20, 2025

Conflicts of interest: None

Special thanks: CDA-AMC extends our special thanks to the individual who presented directly to FMEC, and to the patient organizations representing the community of those living with MDD, including the MDSC.

Note: CDA-AMC makes every attempt to engage with people with lived experience as closely to the indication and treatments under review as possible; however, at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys or experience with comparators under review to ensure lived experience perspectives are included and considered in Reimbursement Reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journey with FMEC.

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

ISSN: 2563-6596

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

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