



CDEC FINAL RECOMMENDATION

ARIPIPRAZOLE

(Abilify — Bristol-Myers Squibb Canada)

New Indication: Major Depressive Disorder

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that aripiprazole not be listed as an adjunct to antidepressants for the treatment of major depressive disorder (MDD).

Reasons for the Recommendation:

1. Three double-blind randomized controlled trials (RCTs) demonstrated that aripiprazole was statistically superior to placebo for improvement in the physician-rated Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Depression (HAM-D17); however, the magnitude of improvement was limited and failed to clearly and consistently exceed the minimal clinically-important differences for these endpoints. In addition, clinical benefit was not consistently observed in patient-reported outcomes, such as the Inventory of Depressive Symptomatology Self-Report (IDS-SR) or the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR). CDEC considered the clinical benefit of treatment with aripiprazole to be uncertain, given the lack of evidence that consistently demonstrates clinically relevant improvement in the quality of life of patients living with MDD.
2. The safety and efficacy of aripiprazole as an adjunctive treatment in MDD have not been evaluated in RCTs longer than six weeks, a relatively short duration for evaluating clinical benefit. Given the absence of data beyond six weeks of treatment, CDEC considered the clinical benefit of treatment with aripiprazole to be uncertain.
3. There are no RCTs evaluating the comparative clinical benefit of adjunctive treatment with aripiprazole against other available treatment strategies for the management of MDD.

Background:

Aripiprazole has multiple approved indications, including the treatment of schizophrenia and related psychotic disorders, the treatment of manic or mixed episodes in bipolar I disorder, and as an adjunct to antidepressants for the treatment of MDD. The current Common Drug Review (CDR) submission for aripiprazole is for use as an adjunct to antidepressants for the management of MDD in adult patients who have had an inadequate response to prior antidepressant treatments (ADTs) during the current episode.

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Aripiprazole is available as tablets of 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg. The efficacy of aripiprazole as an adjunctive therapy for the treatment of MDD was established within a dose range of 2 mg per day to 20 mg per day. The recommended dose ranges from 2 mg to 15 mg administered once a day, with a starting dose of 2 mg per day to 5 mg per day. Dose adjustments of up to 5 mg per day should occur gradually, at intervals of no less than one week.

Summary of CDEC Considerations

CDEC considered the following information prepared by CDR: a systematic review of RCTs of aripiprazole in MDD, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to individuals living with MDD.

Patient Input Information:

The following is a summary of information provided by one patient group that responded to the CDR call for patient input:

- Depression is common, can last for a period of weeks, months or years, and has many symptoms that can affect all aspects of people's lives.
- Caregivers often have to educate family members and friends about the condition while combating prejudice and the stigma that isolates patients and their families, monitor their loved one's mental state and use of medication without becoming intrusive, and take care of their own health.
- Currently available pharmaceutical therapies for the treatment of MDD are limited by moderate to severe adverse effects.
- Individuals living with MDD believe that new therapies with fewer side effects or side effects that are no worse than those they have experienced should be made available promptly, in part because some drug therapies lose their effectiveness over time and because patients often need to try several drug therapies before finding one that works.
- Individuals living with MDD particularly desire drug therapies that are not associated with weight gain. They believe such therapies will have higher rates of adherence.

Clinical Trials

The CDR systematic review included three double-blind, placebo-controlled RCTs of adults who had an inadequate response to prior ADTs. Study 139 (N = 362), study 163 (N = 381) and study 165 (N = 349) were identically designed and consisted of three phases:

- Screening phase (phase A) — the objective of phase A was to select patients with a diagnosis of major depressive episodes, as defined by DSM-IV-TR criteria, and to ensure discontinuation of previous psychotropic drugs.
- Run-in phase (phase B) — the objective of phase B was to identify patients with MDD who were inadequately responding to ADT. Patients in phase B were assigned to open-label ADT including escitalopram, fluoxetine, paroxetine controlled release (CR), sertraline or venlafaxine extended release (XR) plus placebo and their response was measured at eight weeks.
- Double-blind phase (phase C) — the objective of phase C was to establish the comparative efficacy and safety of aripiprazole over placebo as an adjunct to ADT in patients with MDD who had inadequately responded to ADT. Patients were randomized (1:1) to receive aripiprazole or placebo.

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Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- MADRS — a 10-item clinician-rated questionnaire used to measure the severity of depressive symptoms. The score ranges from 0 to 60, where higher scores indicate more severe symptoms.
 - Response — defined by $\geq 50\%$ reduction in the MADRS total score during phase C.
 - Remission — defined by $\geq 50\%$ reduction in the MADRS total score during phase C and a MADRS total score of ≤ 10 .
- IDS-SR — a self-reported 30-item tool that measures depressive symptom severity.
- QIDS-SR — a self-reported 16-item tool that measures depressive symptom severity derived from the IDS.
- HAM-D17— a clinician-rated questionnaire used to assess the severity of depression. The score ranges from 0 to 53, where higher scores represent more severe symptoms.
- Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) short form — a 16-item self-reported questionnaire used to assess quality of life.
- Sheehan Disability Scale (SDS) — a 3-item self-reported questionnaire used to assess the degree to which the symptoms of depression, anxiety, panic, and phobia interfere with the patient's work, family, and social life.
- Serious adverse events, total adverse events, extrapyramidal symptom (EPS)-related adverse events, and withdrawals due to adverse events.

Efficacy

- Aripiprazole was superior to placebo for changes in MADRS total score in all three studies. The mean difference (MD) for aripiprazole versus placebo was -3.01 (95% CI: -4.66 to -1.37) in study 139, -2.84 (95% CI: -4.53 to -1.15) in study 163, and -3.73 (95% CI: -5.44 to -2.02) in study 165.
- There were no statistically significant differences between aripiprazole and placebo for changes in the IDS-SR or QIDS-SR in any of the included studies.
- A statistically significantly greater proportion of aripiprazole-treated patients demonstrated a response and/or remission compared with placebo (CDR-calculated absolute risk increase):
 - Response: 10% (95% CI: 0% to 19%) in study 139; 15% (95% CI: 6% to 24%) in study 163; and 20% (95% CI: 10% to 30%) in study 165.
 - Remission: 10% (95% CI: 2% to 19%) in study 139; 10% (95% CI: 2% to 19%) in study 163; and 18% (95% CI: 9% to 26%) in study 165.
- Aripiprazole was superior to placebo for changes in HAM-D17 total score, with MDs of -0.28 (95% CI: -3.54 to -1.02) in study 139, -2.35 (95% CI: -3.60 to -1.11) in study 163, and -2.52 (95% CI: -3.84 to -1.20) in study 165.
- There was a statistically significant difference between aripiprazole and placebo for change in SDS mean score in study 163 (MD: -0.57 ; 95% CI: -1.02 to -0.13); however, there was no statistically significant difference in study 139 (MD: -0.46 ; 95% CI: -0.93 to 0.01) or study 165 (MD: -0.42 ; 95% CI: -0.88 to 0.04).
- Results for the Q-LES-Q were reported as follows:
 - Overall life satisfaction: Statistically significant difference favouring aripiprazole in all three studies, with MDs of 0.25 (95% CI: 0.07 to 0.44) in study 139, 0.19 (95% CI: 0.01 to 0.36) in study 163, and 0.33 (95% CI: 0.13 to 0.52) in study 165.

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- Overall general subscore: Statistically significant difference favouring aripiprazole in study 163 (MD: 4.15; 95% CI: 1.26 to 7.05) and study 165 (MD: 4.65; 95% CI: 1.50 to 7.81); however, there was no statistically significant difference in study 139 (MD: 2.33; 95% CI: -0.49 to 5.15).
- Satisfaction with medication: no statistically significant differences between aripiprazole and placebo in any of the included studies.

Harms (Safety and Tolerability)

- The proportion of patients with at least one serious adverse event was reported as follows:
 - Study 139: 1.1% with aripiprazole and 1.7% with placebo
 - Study 163: 0.5% with aripiprazole and 0% with placebo
 - Study 165: 0.6% with aripiprazole and 0.6% with placebo.
- The proportion of patients with at least one adverse event was reported as follows:
 - Study 139: 81.9% with aripiprazole and 62.5% with placebo
 - Study 163: 81.5% with aripiprazole and 63.2% with placebo
 - Study 165: 80.7% with aripiprazole and 68.6% with placebo.
- The most commonly reported adverse events were akathisia, restlessness, fatigue, insomnia, vision blurred, somnolence, and constipation. A greater proportion of aripiprazole-treated patients (range: 25.6% to 33.9%) reported EPS-related adverse events than those in the placebo group (range: 7.6% to 9.7%). Weight gain was infrequent and comparable in both the aripiprazole and placebo treatment groups.
- The proportion of patients who withdrew from the trial due to adverse events was reported as follows:
 - Study 139: 3.3% with aripiprazole and 2.2% with placebo
 - Study 163: 3.7% with aripiprazole and 1.1% with placebo
 - Study 165: 6.2% with aripiprazole and 1.7% with placebo.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis (CUA) comparing aripiprazole with quetiapine (extended release formulation) in the primary analysis, and aripiprazole with quetiapine, risperidone, and olanzapine in the secondary analysis. The CUA was based on an indirect treatment comparison, funded by the manufacturer, which compared aripiprazole with other selected atypical antipsychotics for the treatment of MDD (i.e., quetiapine, risperidone, and olanzapine). The manufacturer reported that, over a lifetime horizon, aripiprazole was associated with an incremental cost per quality-adjusted life-year (QALY) gained of \$4,829. The secondary analysis showed that risperidone dominated aripiprazole, quetiapine, and olanzapine (i.e., risperidone was both less costly and more effective than the comparators).

CDR identified a number of limitations with the manufacturer's CUA: uncertainty with respect to the comparative clinical efficacy among the treatments, the assumption that quetiapine would be used at 300 mg daily instead of a range from 150 mg to 300 mg daily, and the use of an extremely long time horizon (appeared to be set at 999 years). Given the issues identified with the manufacturer's model, CDR conducted a reanalysis based on:

- A lifetime horizon of 30 to 55 years, based on life expectancy of 75 to 100 years.
- Assuming an equal distribution of the three quetiapine doses 150 mg per day, 200 mg per day, and 300 mg per day among the simulated patients, instead of 300 mg per day for all patients.

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- Half of the patients treated with quetiapine as monotherapy, instead of adjunct to other antidepressants.

Based on the CDR re-analysis, the incremental cost per QALY of aripiprazole was \$8,231 when compared with quetiapine. Issues regarding uncertainty with the comparative clinical efficacy could not be accounted for in the CDR reanalyses.

Aripiprazole is priced at \$3.00 per 2 mg tablet, \$3.38 per 5 mg tablet, and \$3.89 per 10 mg, 15 mg, 20 mg, or 30 mg tablet. At the recommended daily doses, aripiprazole costs \$3.00 to \$3.89 daily (2 mg to 15 mg daily), which is more costly than the extended release formulation of quetiapine (\$0.40 to \$1.54, 50 mg to 300 mg daily).

Other Discussion Points:

CDEC noted the following:

- There is uncertainty regarding the effectiveness of adjunctive treatment compared with switching to another drug as monotherapy for patients with MDD refractory to initial monotherapy.
- Aripiprazole is the only drug indicated for use as adjunctive treatment for MDD in Canada; however, other less costly atypical antipsychotics are also used adjunctively for MDD in Canadian clinical practice.
- A network meta-analysis submitted by the manufacturer suggested that there were no statistically significant differences in remission rates between aripiprazole and other atypical antipsychotics (e.g., quetiapine, olanzapine, and risperidone); however, the considerable heterogeneity between the included studies limits the ability to draw conclusions regarding the comparative efficacy of these drugs for the management of MDD.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no head-to-head trials comparing aripiprazole against other treatment strategies used for the treatment of patients with MDD.
- The following relevant patient groups were excluded from the RCTs: patients younger than 18 or older than 65 years; those with significant comorbidities; or those who had failed > 3 antidepressants.
- All of the included RCTs were limited to six weeks in duration; therefore, long-term controlled trials regarding the efficacy and safety of aripiprazole in the management of MDD is needed.

June 18, 2014 Meeting

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

Regrets:

None

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Conflicts of Interest:

None

October 15, 2014 Meeting**CDEC Members:**

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets:

None

Conflicts of Interest:

None

About This Document:

CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

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