



Canadian Agency for  
Drugs and Technologies  
in Health

# COMMON DRUG REVIEW

## CEDAC FINAL RECOMMENDATION

### ARIPIPRAZOLE

(Abilify – Bristol-Myers Squibb Canada)

**Indication: Schizophrenia and Related Psychotic Disorders**

#### **Recommendation:**

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that aripiprazole not be listed.

#### **Reasons for the Recommendation:**

Based on a CDR systematic review of 12 randomized controlled trials, efficacy outcomes, such as the Positive and Negative Syndrome Scale scores, were similar between aripiprazole and less expensive antipsychotic agents. The average daily cost of treatment with aripiprazole is more than the cost of risperidone and most other antipsychotic agents.

#### **Of Note:**

1. Based on a review of the clinical evidence, the Committee felt that a reduced price would increase the likelihood of a recommendation to “list” or “list with criteria.”
2. The Committee considered that antipsychotic agents are often used off-label to treat agitation and behavioural problems in elderly patients with dementia and concerns have been raised regarding the safety and efficacy of treating these patients with antipsychotic agents.

#### **Background:**

Aripiprazole has a Health Canada indication for the treatment of schizophrenia and related psychotic disorders, which is the focus of this recommendation. Aripiprazole also has a Health Canada indication for the acute treatment of manic or mixed episodes in Bipolar I Disorder. It has partial agonist activity at the dopamine D2 and serotonin 5-HT1A receptors and antagonist activity at the serotonin 5-HT2A receptors.

The Health Canada-recommended starting dose for aripiprazole is 10 mg to 15 mg once a day, with a maximum daily dose of 30 mg. It is available as 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg tablets.

## Common Drug Review

## Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind randomized controlled trials (RCTs) of aripiprazole and a critique of the manufacturer's pharmacoeconomic evaluation.

## Clinical Trials

The CDR systematic review included 12 double-blind, RCTs evaluating aripiprazole and other antipsychotic agents in the treatment of patients with schizophrenia and related disorders (N = 4,837):

**Table 1. Aripiprazole Trials Included in the CDR Systematic Review**

Comparator(s)	Study Design	N	Duration
Placebo, Haloperidol	Superiority versus placebo	103	4 weeks
Placebo, Haloperidol	Superiority versus placebo	307	4 weeks
Placebo, Haloperidol	Superiority versus placebo	414	4 weeks
Haloperidol	Superiority versus active therapy (2 pooled studies)	1294	52 weeks
Olanzapine	Superiority versus active therapy	703	52 weeks
Olanzapine	Superiority versus active therapy	566	28 weeks
Olanzapine	Superiority versus active therapy	173	16 weeks
Olanzapine	Superiority versus active therapy	317	26 weeks
Placebo, Risperidone	Superiority versus placebo	404	4 weeks
Ziprasidone	Non-inferiority	256	4 weeks
Perphenazine	Superiority versus active therapy	300	6 weeks

While the doses of aripiprazole and comparators varied across trials, the doses evaluated were reflective of those used in clinical practice.

The majority of enrolled patients had chronic schizophrenia and were experiencing an acute relapse. Nine trials required that patients were in acute relapse and/or hospitalized at the time of enrolment. Seven trials specified that patients needed to have been outpatients for at least three months during the past year. One trial enrolled only patients who were not experiencing satisfactory symptom relief despite at least two six-week periods of treatment with adequate doses of antipsychotic agents during the two years before the study.

The inclusion criteria of the trials and the baseline characteristics suggested that patients had moderately severe disease. The mean age ranged from 32 years to 43 years and the mean number of prior hospitalizations ranged from six to 12, as reported in three trials. In the four trials that enrolled a mixed schizophrenia and schizoaffective population, the majority of patients had schizophrenia. The mean Positive and Negative Syndrome Scale (PANSS) scores at baseline ranged from 80 to 100. Baseline scores on the Clinical Global Impressions–Severity (CGI-S) scale ranged from 2.9 to 4.9. There were a high proportion of withdrawals ranging from 21% to 72% across studies. The loss of a high proportion of patients and the use of the last observation carried forward approach to handling missing data are common in studies of schizophrenia, but limit the strength of conclusions that can be drawn from these RCTs.

## Outcomes

The primary outcome(s) of nine trials included the change from baseline in PANSS, Brief Psychiatric Rating Scale (BPRS), CGI-Improvement (CGI-I), or CGI-S scores. In three trials, body weight change was a primary outcome and in one trial, all-cause discontinuation was the primary outcome. Some trials had more than one primary outcome.

The PANSS and BPRS are rating scales that evaluate the severity of schizophrenia. The CGI assesses overall severity and response to treatment of mental disorders and is correlated with the PANSS. A 15-point absolute reduction in the total PANSS score corresponds to “minimally improved” on the CGI-I scale and a reduction of one severity level on the CGI-S scale.

The Committee discussed other outcomes that were defined a priori in the CDR systematic review protocol including relapse, quality of life, mortality, and serious adverse events. Quality of life was evaluated in two of the 12 studies and reported in only one of these.

## **Results**

### ***Efficacy or Effectiveness***

- In the four trials that compared aripiprazole with placebo, statistically significant improvements in total PANSS and CGI-I were observed, favouring aripiprazole. Similar improvements for haloperidol and risperidone compared with placebo were also observed in these trials.
- In two active comparator trials, there were no statistically significant differences in total PANSS between aripiprazole and haloperidol or perphenazine. In two active comparator trials evaluating olanzapine, statistically significantly greater improvements in the total PANSS were observed for olanzapine compared with aripiprazole; however, the improvement was less than 15 points in both trials and the clinical significance of these results are uncertain. BPRS results generally correlated with PANSS results.
- In one trial, aripiprazole was non-inferior to ziprasidone based on changes in CGI-S but not based on changes in BPRS.
- In a pooled analysis of two large trials there were fewer withdrawals in the aripiprazole groups compared with haloperidol. No other trials demonstrated statistically significantly lower withdrawals for aripiprazole compared with active therapies.
- The only study reporting quality of life found no statistically significant difference between aripiprazole and perphenazine.

### ***Harms (Safety and Tolerability)***

- In all studies, serious adverse events, adverse events, and withdrawals due to adverse events were similar between treatment groups.
- In three of four studies, aripiprazole had statistically significantly fewer patients with a > 7% increase in weight gain compared with placebo and compared with olanzapine. Aripiprazole patients experienced approximately 4 kg less weight gain relative to olanzapine in all four studies. Aripiprazole had a similar effect on weight as risperidone, ziprasidone, haloperidol, or perphenazine.

### ***Cost and Cost-Effectiveness***

The manufacturer submitted a cost-utility analysis in adults with schizophrenia who had failed therapy after initiating an atypical antipsychotic agent (risperidone, ziprasidone, or quetiapine) and were required to switch to another atypical antipsychotic therapy because of lack of efficacy, inadequate response, or intolerance (aripiprazole, olanzapine, risperidone, quetiapine, and ziprasidone). Given that similar efficacy was observed between aripiprazole and comparators in head-to-head clinical trials included in the CDR systematic review, the

Committee placed more emphasis on the costs of aripiprazole and comparators. The average daily cost of treatment with aripiprazole 15 mg (\$4.50) is less than olanzapine 15 mg (\$7.59) but more than risperidone 3 mg (\$1.44), ziprasidone 80 mg (\$4.06), and quetiapine 600 mg (\$4.25).

## Other Discussion Points:

- The Committee discussed reimbursement of aripiprazole in patients who have failed a trial of less expensive antipsychotic agents due to a contraindication, intolerance or lack of response, if there were a reduction in the price of aripiprazole.
- The Committee considered that the mechanism of action of aripiprazole differs from other antipsychotic drugs as it includes partial agonist effects at the dopamine D2 receptor, but noted that there is no evidence that this is associated with a clinically meaningful benefit.
- The Committee discussed that adverse event profiles may differ across antipsychotic agents, but that efficacy appears to be similar among agents.
- It was noted that in RCTs there was no discernable pattern of dose response for the different recommended doses of aripiprazole (10 mg, 15 mg, 30 mg) relative to placebo, and the Health Canada-approved product monograph notes that in clinical trials greater efficacy has not been demonstrated at doses higher than 10 mg/day.
- The Committee considered that more data on quality of life in patients receiving aripiprazole would have provided important information about the effects of aripiprazole.
- There was limited information available on hyperlipidemia requiring treatment, diabetes requiring treatment, or discontinuation due to hyperprolactinemia.

## CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

## Regrets:

None

## Conflicts of Interest:

CEDAC members reported no conflicts of interest related to this submission.

## About this Document:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

---

## Common Drug Review

# *COMMON DRUG REVIEW*

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.

---

## **Common Drug Review**