



## CDEC FINAL RECOMMENDATION

### ARIPIPRAZOLE LONG-ACTING INJECTION

(Abilify Maintena — Otsuka Pharmaceuticals Co. & Lundbeck Canada Inc.)

Indication: Schizophrenia

#### Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that aripiprazole long-acting injection (LAI) be listed for the maintenance treatment of schizophrenia in adult patients who are stabilized on oral aripiprazole, if the following condition is met:

#### Condition

- List in a manner similar to other long-acting atypical antipsychotic drugs.

#### Reasons for the Recommendation:

1. Two randomized controlled trials (RCTs), conducted in patients with schizophrenia who were stabilized on oral aripiprazole, demonstrated that aripiprazole LAI was non-inferior to oral aripiprazole for the estimate rate of impending relapse (study 247; N = 662) and superior to placebo for delaying the time to impending relapse (study 246; N = 403).
2. At the submitted price of \$456.18 per 300 mg or 400 mg single-use vial, aripiprazole LAI (\$16.29 per day) is less costly than 75 mg paliperidone LAI (\$17.03 per day) and 37.5 mg risperidone LAI (\$17.48 per day).

#### Background:

Aripiprazole LAI is an atypical antipsychotic drug indicated for the maintenance treatment of schizophrenia in stabilized adult patients. Aripiprazole LAI is available in 300 mg and 400 mg vials. The product monograph recommends a starting and maintenance dose of 400 mg administered once monthly as a single injection. If there are adverse effects with the 400 mg dose, reducing it to 300 mg once monthly should be considered.

#### Summary of CDEC Considerations:

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of aripiprazole LAI, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to individuals living with schizophrenia.

### **Patient Input Information**

The following is a summary of key information provided by two patient groups that responded to the CDR call for patient input:

- The symptoms of schizophrenia significantly interfere with the daily activities of employment, education, socialization, and maintenance of relationships with family and friends. In addition, there is a considerable emotional burden in caring for someone with schizophrenia.
- Patient groups reported that many of the available treatments are limited by significant side effects, such as inability to concentrate, fatigue, sleep problems, weight gain, negative impact on sex life, restlessness, and muscle spasms.
- There is a need for additional antipsychotic treatment options for individuals with schizophrenia. Patient groups indicated that many antipsychotic medications have similar efficacy across a patient population; however, there is variability in individual patient response, such that a particular drug may not be effective in some patients but could be in others.
- Adherence to daily schedules for drug administration is a challenge for some patients, and a long-acting injectable provides an alternative that may result in increased compliance.

### **Clinical Trials**

Two double-blind, RCTs (study 246 and study 247) were included in the CDR systematic review. Study 246 was a 52-week placebo-controlled RCT consisting of a screening phase and four treatment phases: conversion; oral aripiprazole stabilization; aripiprazole LAI stabilization; and a double-blind, placebo-controlled phase. The objective of the screening phase was to select patients with schizophrenia; the objective of the conversion phase was to convert patients using any non-aripiprazole oral antipsychotic drugs to oral aripiprazole monotherapy. The objective of oral and LAI aripiprazole stabilization phases was to ensure patients responded and were stabilized with oral and LAI treatment respectively. The objective of the RCT phase of study 246 (N = 403) was to evaluate the efficacy of aripiprazole LAI compared with placebo in reducing time to relapse, in this stabilized population. Study 246 was a withdrawal RCT: that is, patients stabilized with aripiprazole LAI were randomized to continue treatment with aripiprazole LAI or placebo (i.e., withdrawal from aripiprazole LAI). Study 247 was a 38-week, active-controlled, randomized non-inferiority study. The study consisted of a screening phase and three treatment phases: conversion, oral stabilization, and an oral aripiprazole-controlled RCT phase. The objective of the RCT phase of study 247 (N = 662) was to evaluate the comparative efficacy, safety, and tolerability of aripiprazole LAI compared with oral aripiprazole as maintenance treatment in stabilized patients with schizophrenia.

### **Outcomes**

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

- Impending relapse — defined as meeting any or all of the following 4 criteria:
  - Clinical Global Impression of Improvement (CGI-I) of  $\geq 5$  (minimally worse) and one of the following: an increase on any of the following individual Positive and Negative Syndrome Scale (PANSS) items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content) to a score  $> 4$  with an absolute increase of  $\geq 2$  on that specific item since randomization; or an increase on any of the following individual PANSS items to a score  $> 4$  and an absolute increase of  $\geq 4$  on the combined 4 PANSS items since randomization.

- Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), but excluding hospitalization for psychosocial reasons.
- Clinical Global Impression of Severity of Suicidality (CGI-SS) of 4 (severely suicidal) or 5 (attempted suicide) on part 1, and/or 6 (much worse) or 7 (very much worse) on part 2.
- Violent behaviour resulting in clinically relevant self-injury, injury to another person, or property damage.
- Suicidality — defined as reporting any suicidal ideation or behaviour. It was assessed using the CGI-SS, Columbia-Classification Algorithm of Suicide Assessment (C-CASA), and the Columbia Suicide Severity Rating Scale (C-SSRS).
- Remission — defined as patients who achieved and maintained for six months a score of  $\leq 3$  on each of the following specific PANSS items: delusions, unusual thought content, hallucinatory behaviour, conceptual disorganization, mannerisms/posturing, blunted affect, social withdrawal, and lack of spontaneity.
- PANSS — a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia that consists of three subscales (positive, negative, and general psychopathology).
- Clinical Global Impression of Severity (CGI-S) — measures the global severity of illness by rating the patient's illness on a seven-point scale ranging from one (no symptoms) to seven (very severe).
- CGI-I — measures global improvement relative to baseline on a on a seven-point scale ranging from one (very much improved) to seven (very much worse).
- Personal and Social Performance (PSP) — a clinician-rated scale that measures personal and social functioning in four domains: socially useful activities (e.g., work and study), personal and social relationships, self-care, and disturbing and aggressive behaviours. Scores range from 0 to 100, with higher scores indicating greater functioning.
- Serious adverse events, total adverse events, and withdrawal due to adverse events.

The primary outcome in study 246 was the time to impending relapse and the key secondary outcome was the impending relapse rate. In study 247, the primary outcome was impending relapse rate and the key secondary outcome was the time to impending relapse.

### **Efficacy**

- The impending relapse rate in study 246 was statistically significantly lower ( $P < 0.0001$ ) in the aripiprazole LAI group compared with the placebo group in both the interim (9.6% versus 36.8%) and final analyses (10.0% versus 39.6%).
- In study 247, the impending relapse rate by the end of week 26 was 7.12% in the aripiprazole LAI group and 7.76% in the oral aripiprazole group. The between-group difference was  $-0.64\%$  (95% CI,  $-5.26$  to  $3.99$ ) demonstrating non-inferiority between LAI and oral aripiprazole.
- In study 246, both interim and final analyses demonstrated that the time to impending relapse was statistically significantly reduced for placebo-treated patients compared with those treated with aripiprazole LAI ( $P < 0.0001$ ). In study 247, there was no statistically significant difference between LAI and oral aripiprazole for time to relapse ( $P = 0.99$ ). The hazard ratios for the comparisons in study 246 and 247 were reported as follows:
  - Aripiprazole LAI versus placebo: 4.72 (95% CI, 2.81 to 7.94) in the interim analysis and 5.03 (95% CI, 3.15 to 8.02) in the final analysis.
  - Aripiprazole LAI versus oral aripiprazole: 0.99 (95% CI, 0.55 to 1.80).
- There were no statistically significant differences in remission rates between aripiprazole LAI and placebo in study 246 or aripiprazole LAI and oral aripiprazole in study 247:

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- Aripiprazole LAI versus placebo: 52.9% versus 38.7%;  $P = 0.1756$ .
- Aripiprazole LAI versus oral aripiprazole: 48.8% versus 53.2%;  $P = 0.37$ .
- The response rate was statistically significantly greater with aripiprazole LAI compared with placebo in study 246. There was no statistically significant difference between aripiprazole LAI and oral aripiprazole in study 247:
  - Aripiprazole LAI versus placebo: 87.6% versus 56.0%;  $P < 0.0001$ .
  - Aripiprazole LAI versus oral aripiprazole: 89.8% versus 89.4%;  $P = 0.88$ .
- Aripiprazole LAI demonstrated statistically significant improvements in PANSS total score compared with placebo in study 246 and oral aripiprazole in study 247. The mean differences in change from baseline were:
  - Aripiprazole LAI versus placebo:  $-10.11$  (95% CI,  $-12.68$  to  $-7.54$ );  $P < 0.0001$ .
  - Aripiprazole LAI versus oral aripiprazole:  $-2.24$  (95% CI,  $-4.23$  to  $-0.25$ );  $P = 0.0272$ .
- Aripiprazole LAI demonstrated statistically significant improvements in CGI-S compared with placebo in study 246 and oral aripiprazole in study 247. The mean differences in change from baseline in CGI-S were:
  - Aripiprazole LAI versus placebo:  $-0.52$  (95% CI,  $-0.70$  to  $-0.35$ );  $P < 0.0001$ .
  - Aripiprazole LAI versus oral aripiprazole:  $-0.17$  ( $-0.31$  to  $-0.04$ );  $P = 0.0123$ .
- The proportion of study participants who experienced an event related to suicidal ideation/suicide was reported as follows: 2.6% with aripiprazole LAI and 0% with placebo in study 246; and, 3.5% with aripiprazole LAI and 3.2% with oral aripiprazole in study 247.
- There was a statistically significantly greater deterioration in PSP total scores in the placebo group ( $-6.20$ ) compared with the aripiprazole LAI group ( $-1.74$ ) in study 246 ( $P = 0.0002$ ). There was no statistically significant difference between aripiprazole LAI and oral aripiprazole in study 247.

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

- The proportion of patients with at least one serious adverse event was reported as follows:
  - Study 246: 4.1% with aripiprazole LAI and 6.7% with placebo.
  - Study 247: 5.7% with aripiprazole LAI and 5.6% with oral aripiprazole.
- The proportion of patients with at least one adverse event was reported as follows:
  - Study 246: 63.2% with aripiprazole LAI and 61.9% with placebo.
  - Study 247: 82.6% with aripiprazole LAI and 82.1% with oral aripiprazole.
- Akathisia, injection-site pain, and infections were more common with aripiprazole LAI compared with oral aripiprazole in study 247.
- The proportion of patients who withdrew from the studies as a result of adverse events was:
  - Study 246: 4.1% with aripiprazole LAI and 9.7% with placebo.
  - Study 247: 4.9% with aripiprazole LAI and 4.5% with oral aripiprazole.

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

The manufacturer submitted a cost-minimization analysis comparing aripiprazole LAI (300 mg or 400 mg every four weeks) with paliperidone LAI (50 mg, 75 mg, 100 mg, or 150 mg every four weeks) and risperidone LAI (12.5 mg, 25 mg, 37.5 mg, or 50 mg every two weeks) in adult patients with schizophrenia during a two-year time frame. The assumption of similar clinical efficacy, safety, and tolerability was based on a manufacturer-funded unpublished network meta-analysis (NMA), which compared aripiprazole LAI with risperidone LAI, paliperidone LAI, olanzapine LAI, haloperidol LAI, oral risperidone, and oral aripiprazole. Costs included in the analysis were drug costs, loading regimen costs, and administration costs.

CDR identified a number of key limitations in the manufacturer's analysis, which included:

- Uncertainty in the clinical similarity and dose equivalency of aripiprazole LAI as compared with paliperidone LAI or risperidone LAI. The utilization analysis performed by both the manufacturer and CDR yielded a weighted-average dose for paliperidone LAI of approximately 115 mg, which differs from the weighted-average dose of approximately 83 mg in the paliperidone LAI study included in the NMA.
- Absence of oral atypical antipsychotic drugs as comparators given the indicated population of stable patients.
- Uncertainty in the assumptions and data sources used in the real-world multivariate sensitivity analysis.

At the submitted price of \$456.18 per 300 mg or 400 mg single-use vial, aripiprazole LAI (\$16.29 daily) costs substantially more than oral antipsychotic drugs, including oral aripiprazole (\$4.13 to \$4.88 daily), as well as long-acting typical antipsychotic drugs (\$0.30 to \$2.89 daily), but is less costly than recommended doses of paliperidone LAI (75 mg every four weeks, \$17.03 daily) and risperidone LAI (37.5 mg every two weeks, \$17.48 daily). Aripiprazole LAI remained less costly than paliperidone LAI and risperidone LAI when a variety of real-world utilization estimates were explored.

### Other Discussion Points:

- Patients in studies 246 and 247 were stabilized on oral aripiprazole before randomization; therefore, it unclear if the results of the studies are generalizable to a broader population of patients with schizophrenia (e.g., those stabilized on other atypical antipsychotic drugs).
- The manufacturer's NMA reported that aripiprazole LAI was associated with similar efficacy relative to other LAI antipsychotic drugs; however, important limitations with this analysis restrict the ability to draw any conclusions.
- The listing status of LAI antipsychotic drugs varies across the CDR-participating drug plans.

### Research Gaps:

- There is no direct evidence comparing the efficacy and safety of aripiprazole LAI with other available LAI antipsychotic drugs.
- There are insufficient data on quality of life outcomes.

### 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.

### November 19, 2014 Meeting

### 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.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

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