# CDEC FINAL RECOMMENDATION

## ASENAPINE
## (Saphris – Lundbeck Canada Inc.)
## Indications: Schizophrenia and Bipolar I Disorder

**Note**: The Canadian Drug Expert Committee (CDEC) considered each of the two approved indications for asenapine separately.

## Schizophrenia

**Recommendation:**
The CDEC recommends that asenapine not be listed for the treatment of schizophrenia.

**Reason for the Recommendation:**
In the eight double-blind randomized controlled trials (RCTs) reviewed by CDEC, asenapine failed to consistently demonstrate superiority in the five placebo-controlled trials; and in one of three trials comparing olanzapine with asenapine, olanzapine was superior to asenapine based on the primary outcome and a number of secondary outcomes. Thus, the key assumption of equivalent efficacy between asenapine and all comparators in the manufacturer's economic analysis was not consistently supported, resulting in uncertain cost-effectiveness.

## Bipolar I Disorder

**Recommendation:**
The CDEC recommends that asenapine be listed for the acute treatment of manic or mixed episodes associated with bipolar I disorder as either:

- Monotherapy, after a trial of lithium or divalproex sodium has failed, and trials of less expensive atypical antipsychotic agents have failed due to intolerance or lack of response
- Co-therapy with lithium or divalproex sodium, after trials of less expensive atypical antipsychotic agents have failed due to intolerance or lack of response.

**Reasons for the Recommendation:**

1. In the three double-blind RCTs reviewed by CDEC, asenapine was superior to placebo as both monotherapy (ARES-3A and ARES-3B) and co-therapy (APOLLO-12) in patients with bipolar I disorder, based on reductions in the Young Mania Rating Scale (YMRS) score at 21 days; in APOLLO-12 asenapine maintained superiority over placebo at 84 days.

2. The daily cost of asenapine (10 mg twice daily, $2.86) is higher than quetiapine (400 mg to 800 mg, $1.32 to $2.64), risperidone (2 mg to 6 mg, $0.61 to $1.82), lithium (900 mg to 2,100 mg, $0.13 to $0.31), and divalproex sodium (750 mg to 2,000 mg, $0.39 to $1.04); within the range of olanzapine (5 mg to 20 mg, $0.90 to $3.59); and lower than aripriprazole (15 mg, $4.50) and ziprasidone (40 mg to 80 mg twice daily, $3.78).

**Background:**
Health Canada simultaneously approved asenapine for the following two indications: (i) the treatment of schizophrenia, and (ii) the acute treatment of manic or mixed episodes associated with bipolar I disorder, for which asenapine may be used as acute monotherapy or co-therapy with lithium or divalproex sodium. Asenapine is an antipsychotic agent available as 5 mg and 10 mg sublingual tablets. The Health Canada approved doses are:

Schizophrenia: the recommended starting and target dose is 5 mg twice daily.

Bipolar I disorder: the recommended starting and target dose is 5 mg to 10 mg twice daily.

The manufacturer made one submission to the Common Drug Review (CDR) for the above two indications.

**Summary of CDEC Considerations:**
The Committee considered the following information prepared by the CDR: systematic reviews of double-blind RCTs for both indications, critiques of the manufacturer's pharmacoeconomic evaluations, and patient-group submitted information about outcomes and issues important to patients.

Committee considerations for each of the indications for asenapine are provided separately below.

## Schizophrenia

### *Clinical Trials*
The systematic review included eight double-blind RCTs of schizophrenia: four trials of six weeks duration [HERA-4 (n = 182), HERA-21 (n = 458), HERA-22 (n = 417), and HERA-23 (n = 277)], three trials of six months duration [A7501012 (n = 386), APHRODITE-I (n = 481), and APHRODITE-II (n = 468)], and one trial of 12 months duration designed to assess safety [ACTAMESA (n = 1,225)].

Three of the six-week trials used fixed-doses for asenapine (5 mg or 10 mg twice daily) and one used a flexible-dose regimen (5 mg to 10 mg twice a day). All of the six-week trials included a placebo-control group and an active comparator (i.e., risperidone, olanzapine, or haloperidol); none of the trials were powered for comparisons between asenapine and active comparators.

All of the longer-term trials used a flexible dose regimen for asenapine (5 mg to 10 mg twice daily). A7501012 compared asenapine with placebo in patients who had received open-label asenapine for 26 weeks before randomization. APHRODITE-I, and APHRODITE-II compared asenapine with olanzapine (5 mg to 20 mg once daily) in patients with predominantly persistent negative symptoms, and ACTAMESA compared asenapine with olanzapine (10 mg to 20 mg once daily).

Limitations of the trials include the high frequency of early withdrawals, which is generally consistent with the inherently poor adherence to treatment associated with schizophrenia. Differential withdrawals between treatment groups were most prominent in the longer-term trials (APHRODITE-I, APHRODITE-II, and ACTAMESA), where asenapine was consistently shown to have a higher proportion of early discontinuations than olanzapine. For example, in ACTAMESA, the percentage of patients withdrawing from the trial and withdrawing due to insufficient therapeutic effect was 61% and 25% in the asenapine group, compared with 43% and 15% for the olanzapine group. However, the exclusion of patients having a history of inadequate response and/or intolerable adverse effects with olanzapine from these trials introduces a potential selection bias favouring olanzapine in a comparison of discontinuation rates. Finally, no trials that included an active comparator were designed to test the non-inferiority of asenapine.

***Outcomes***

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: changes in the Positive and Negative Syndrome Scale (PANSS), Negative Symptom Scale (NSA), and Clinical Global Impression Severity of Illness (CGI-S) scores, relapse, quality of life, serious adverse events, and adverse events including extrapyramidal symptoms and weight changes.

The primary efficacy end point in five trials was the change in PANSS scores from baseline to end point. The change in the NSA scale was the primary outcome in two of the included RCTs, and time to relapse or impending relapse was the primary efficacy end point in one trial.

- The PANSS is a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia, with higher scores indicating greater severity of symptoms. PANSS Marder factors refer to five specific categories of PANSS items: positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility and/or excitement, and anxiety and/or depression. The definition of relapse, in A7501012, was based on pre-specified changes in PANSS scores.
- The NSA scale is a 16-item clinician-rated instrument for assessing the negative symptomatology of schizophrenia, with higher scores indicating greater severity.
- The CGI-S is a seven-point scale that measures the clinician's impression about the severity of illness (1 = normal; 7 = extremely ill).
- Quality of life measures included the Quality of Life Scale, Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), and the 12-item Short Form Health Survey.

***Results***

***Efficacy or Effectiveness***

- Results from the six-week trials were variable, with only HERA-4 and HERA-23 reporting statistical superiority of asenapine (5 mg twice daily) compared with placebo for changes in total PANSS score; mean difference (MD) (95% confidence interval [CI]), –10.6 (–17.4 to –3.8) and –5.5 (–10.0 to –1.0) respectively.
- In A7501012, the proportion of patients experiencing relapse was 12% in the asenapine group compared with 47% in the placebo group. There was a statistically significant difference favouring the asenapine group for time to relapse or impending relapse, time to early termination for any reason, and change in total PANSS score.

- In APHRODITE I and APHRODITE II, there were no statistically significant differences between the asenapine and olanzapine groups for any of the following: changes in total PANSS, Marder factor for negative symptoms, and NSA scores. Reductions in the Marder factor for positive symptoms scores were statistically significantly greater for olanzapine compared with asenapine.
- In ACTAMESA, there was a statistically significant difference favouring olanzapine compared with asenapine in the change from baseline in total PANSS score; MD (95% CI), 6.5 (3.5 to 9.5). Between-treatment differences were also statistically significant and favoured olanzapine for changes in CGI-S and PANSS Marder factors for positive symptoms, negative symptoms, disorganized thought, hostility/excitement, and anxiety/depression.
- There were no notable between-treatment differences in quality of life.

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

- The incidence of adverse events and serious adverse events was comparable across the treatment groups in the six-week trials. In APHRODITE I, APHRODITE II, and ACTAMESA the proportion of patients experiencing serious adverse events and withdrawals due to adverse events was numerically greater for asenapine compared with placebo. A majority of the serious adverse events were attributable to the worsening of patients' underlying disease.
- The manufacturer noted that there appears to be a dose-response relationship with asenapine and extrapyramidal symptoms. In ACTAMESA, the incidence of extrapyramidal symptoms was 18% in the asenapine group, compared with 8% for olanzapine.
- Compared with placebo, all studies reported numerically greater increases in body weight with asenapine, regardless of the dose; the MD ranged from 0.3 kg to 1.8 kg in the six-week trials and was 1.2 kg in A7501012. Asenapine had a more favourable effect on body weight compared with olanzapine; the difference in change in body weight between olanzapine and asenapine increased with time with the largest difference observed at the end of ACTAMESA (MD –3.3 kg). The proportion of patients experiencing a ≥ 7% increase in body weight was consistently higher in olanzapine groups (range 12% to 36%) than asenapine groups (range 4% to 15%); between-treatment differences were statistically significant in the majority of trials.

***Cost and Cost-Effectiveness***

The manufacturer conducted a cost-utility analysis comparing asenapine with olanzapine for patients with schizophrenia. Additional analyses were submitted comparing asenapine with quetiapine, ziprasidone, aripriprazole, and risperidone. The key assumption to support the analysis was equivalent efficacy between asenapine and all comparators based on an unpublished network meta-analysis. As a result, the economic model was focused on the clinical implications of adverse events: extrapyramidal symptoms-related events (e.g., akathisia, parkinsonism, hypertonia), weight gain (7% or greater increase in body weight), and the incidence of the long-term complications resulting from weight gain (e.g., diabetes, hypertension, coronary heart disease, and stroke). The manufacturer reported that asenapine is dominant compared with olanzapine and quetiapine (less expensive and better safety profile); is less expensive and worse in safety profile than aripriprazole and ziprasidone; and is associated with an incremental cost per quality-adjusted life-year (QALY) of $72,623 compared with risperidone.

The CDR identified the following limitations with the manufacturer's economic submission: the model does not consider efficacy outcomes despite evidence suggesting that asenapine and olanzapine may not be equivalent; it uses a weighted average of the generic and brand prices for comparators, which overestimates the cost of comparators for payers who reimburse only the generic price; and, the model is highly sensitive to the disutility associated with clinically significant weight gain.

The daily cost of asenapine (5 mg twice daily, $2.86) is higher than quetiapine (300 mg to 600 mg, $0.97 to $1.93) and risperidone (2 mg to 10 mg, $0.61 to $3.04); within the range of olanzapine (5 mg to 20 mg, $0.90 to $3.59); and lower than aripriprazole (10 mg to 15 mg, $3.89 to $4.50) and ziprasidone (40 mg to 80 mg twice daily, $3.78).

**Other Discussion Points:**

- The Committee noted with concern a non-statistically significant trend toward a higher incidence of suicidal ideation and completed suicides among asenapine-treated patients compared with olanzapine in ACTAMESA.
- The Committee noted that asenapine is dosed twice daily; whereas, there are several atypical antipsychotic agents that may be dosed once daily (e.g., risperidone, olanzapine, and aripriprazole).
- The Committee did not consider the sublingual dosage form to be an advantage given that other atypical antipsychotic agents are available in oral disintegrating formulations, and that swallowing sublingual asenapine results in reduced bioavailability.

## Bipolar I Disorder

### *Clinical Trials*

The systematic review included three double-blind RCTs of patients with a current manic or mixed episode of bipolar I disorder.

- ARES-3A (n = 488) and ARES-3B (n = 489) randomized patients to one of three treatment groups for three weeks: placebo, olanzapine (5 mg to 20 mg daily), or asenapine (5 mg to 10 mg twice a day). Neither trial was designed or adequately powered for comparisons between asenapine and olanzapine.
- APOLLO-12 (n = 326) randomized patients to placebo or asenapine (5 mg to 10 mg twice a day), for 12 weeks. In addition, patients were to continue pre-trial treatment with either lithium or divalproex sodium.

Limitations of the trials include the high frequency of early withdrawal. In both ARES-3A and 3B, a larger proportion of patients discontinued prematurely in the asenapine groups (ARES-3A = 33% and ARES-3B = 37%) compared with olanzapine (ARES-3A = 21% and ARES-3B = 20%), and discontinuations were most common in the placebo groups (ARES-3A = 42% and ARES-3B = 39%). In APOLLO-12, 62% of patients in the asenapine group discontinued prematurely compared with 67% for placebo. Further, Health Canada concerns regarding several study sites in ARES-3A reduced the Committee's dependency on that trial's findings. Finally, given the short duration of the RCTs and the low completion rates in the 40-week extensions to the above trials, there is a lack of long-term efficacy and safety data; an important limitation given that bipolar disorder is a chronic condition.

***Outcomes***

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: change in the YMRS, percent responders, percent remitters, Clinical Global Impression Scale for Use in Bipolar Disorder (CGI-BP), quality of life, serious adverse events, and adverse events.

In all three included trials, the primary efficacy end point was defined as change from baseline to day 21 in the YMRS total score.

- The YMRS is an 11-item scale with scores ranging from 0 to 60 with questions designed to examine the impact of treatment on elevated mood, increased motor activity, sexual interest, sleep, irritability, speech (rate and amount), language-thought disorder, content, disruptive-aggressive behaviour, appearance, and insight.
- Responders were defined as patients who experienced a 50% decrease from baseline in YMRS score at a given visit.
- Remitters were defined as patients with a YMRS total score of $\leq$ 12.
- The CGI-BP is a seven-point clinician rated scale for assessing the severity of manic, depressive, and overall symptoms of bipolar disorder (1 = normal and 7 = very severely ill).
- Quality of life measures included the 36-item Short Form Health Survey (version 2), and the Q-LES-Q.

***Results***

***Efficacy or Effectiveness***

- Compared with placebo, reductions (improvements) in the YMRS at 21 days were statistically significantly greater for asenapine in all trials; MD (95% CI), –3.7 (–6.4 to –1.0), –5.3 (–7.8 to –2.8), and –2.4 (–4.5 to –0.3) in ARES-3A, ARES-3B, and APOLLO-12 respectively. The statistical superiority of asenapine compared with placebo was maintained at 12 weeks in APOLLO-12.
- The ARES trials were not designed or powered to compare asenapine with olanzapine; however, in a CDR analysis of the primary outcome (YMRS at day 21) the mean reduction in YMRS was statistically significantly greater for olanzapine compared with asenapine in ARES-3A and numerically greater for olanzapine compared with asenapine in ARES-3B.
- The proportion of remitters was statistically significantly greater for asenapine groups compared with placebo in ARES-3B (40% versus 22% at 21 days) and in APOLLO-12 (43% and 30% at 12 weeks), but were not significantly different in ARES-3A.
- The proportion of responders was statistically significantly greater for asenapine groups compared with placebo in ARES-3B (42% versus 25% at 21 days) and APOLLO-12 (48% versus 34% at 12 weeks), but were not significantly different in ARES-3A.
- Compared with placebo, reductions (improvements) in mean CGI-BP scores were statistically significantly greater for asenapine at 21 days in both ARES-3A and ARES-3B, and at 21 days and 12 weeks in APOLLO-12.
- There were no significant differences between asenapine and placebo on most quality of life measures.

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

- The incidence of serious adverse events was similar across treatment groups in all three trials.
- Across all trials, the frequency of withdrawal due to adverse events was consistently higher for asenapine groups (range 10% to 16%) compared with olanzapine (range 4% to 11%).
- In both ARES trials, extrapyramidal symptoms were more commonly observed in patients treated with asenapine (range 7% to 10%) and olanzapine (range 8% to 9%) compared with placebo-treated patients (range 3% to 4%). In APOLLO-12, the proportion of patients with extrapyramidal symptoms was similar for asenapine and placebo; 10% and 12% respectively.
- Across all trials, both asenapine and olanzapine had numerically greater increases in mean body weight reported compared with placebo; MD: 0.8 kg to 1.6 kg for asenapine and 1.6 kg to 2.4 kg for olanzapine. The proportion of patients with a ≥ 7% increase in body weight was higher for olanzapine groups (range 13% to 19%) compared with asenapine groups (range 6% to 7%).

***Cost and Cost-Effectiveness***

The manufacturer conducted a cost-utility analysis comparing asenapine with olanzapine for patients with manic or mixed episodes associated with bipolar I disorder. The key assumption to support the analysis was equivalent efficacy between asenapine and olanzapine based on a nine-week extension of ARES-3A and ARES-3B combined and a published meta-analysis. As a result, the economic model was focused on the clinical implications of adverse events: extrapyramidal symptom-related events (e.g., akathisia, parkinsonism, hypertonia), weight gain (7% or greater increase in body weight), and the incidence of the long-term complications resulting from weight gain (e.g., diabetes, hypertension, coronary heart disease, and stroke). The manufacturer reported that asenapine is dominant over olanzapine (less expensive and better safety profile).

CDR identified the following limitations with the manufacturer's submission: the model does not consider efficacy outcomes despite evidence that suggests that asenapine and olanzapine may not be equivalent; and, only olanzapine was considered as a comparator despite the availability of other treatments.

The daily cost of asenapine (10 mg twice daily, $2.86) is higher than quetiapine (400 mg to 800 mg, $1.32 to $2.64), risperidone (2 mg to 6 mg, $0.61 to $1.82), lithium (900 mg to 2,100 mg, $0.13 to $0.31) and divalproex sodium (750 mg to 2,000 mg, $0.39 to $1.04); within the range of olanzapine (5 mg to 20 mg, $0.90 to $3.59); and, lower than aripriprazole (15 mg, $4.50) and ziprasidone (40 mg to 80 mg twice daily, $3.78).

**Other Discussion Points:**

- Although none of the included trials was powered to compare asenapine with olanzapine, between-treatment differences for a number of outcomes favoured olanzapine.
- Despite the lack of RCT evidence for the superiority or non-inferiority of asenapine compared with other atypical antipsychotic agents used in bipolar I disorder, based on patient group input, the Committee considered that the lower weight gain observed with asenapine compared with olanzapine may be an advantage.

**Patient Input Information:**
The following is a summary of information, relevant to both conditions, that was provided by four patient groups that responded to the CDR Call for Patient Input:

- Patient groups stated that, for patients with either condition, a number of day-to-day responsibilities (e.g., school or job attendance, driving) are difficult or impossible.
- Patient groups indicated that weight gain associated with current treatments negatively impacts self-esteem and medication adherence, and has important physical health implications. In addition, sleepiness was considered to have a deleterious effect on quality of life.
- Two patient groups, that focused their comments on the bipolar indication, suggested that it would be valuable to have another treatment option with similar effectiveness and no worse side effects compared with currently available treatments.

**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. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

**May 16, 2012 Meeting**

**Regrets:**
None

**Conflicts of Interest:**
None

**About this Document:**
CDEC 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 CDEC made its recommendation. 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 has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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