



## FINAL CDEC RECOMMENDATION

### LURASIDONE

(Latuda — Sunovion Pharmaceuticals Canada Inc.)

Indication: Acute Treatment of Schizophrenia

#### **Recommendation:**

The Canadian Drug Expert Committee (CDEC) recommends that lurasidone not be listed.

#### **Reason for the Recommendation:**

There is insufficient evidence from randomized controlled trials (RCTs) to establish the comparative efficacy of lurasidone relative to other less costly antipsychotics for the acute treatment of schizophrenia.

#### **Background:**

Lurasidone (Latuda) is an atypical antipsychotic with a Health Canada indication for the acute treatment of schizophrenia. Lurasidone is available in 40 mg, 80 mg, and 120 mg film-coated tablets. The product monograph recommends a starting dose of 40 mg once daily and states that patients should be treated with the lowest effective dose that provides optimal clinical response and greatest tolerability, which is expected to be 40 mg or 80 mg once daily for most patients.

#### **Summary of CDEC Considerations:**

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind RCTs of lurasidone, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group submissions regarding important outcomes and issues for patients and caregivers. The manufacturer submitted a confidential price for lurasidone.

#### **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:

- Patient groups stated that the symptoms of schizophrenia interfere with the daily activities of employment, education, socialization, and maintenance of relationships with family and friends.

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- Patient groups noted that there is a significant emotional burden in caring for someone with schizophrenia.
- Patients groups indicated that the current treatments available are limited by side effects such as weight gain, extrapyramidal symptoms, drowsiness, lethargy, and the potential onset of metabolic disorders (e.g., type 2 diabetes mellitus).

### **Clinical Trials**

The systematic review included nine RCTs investigating the efficacy and safety of lurasidone for the treatment of schizophrenia. Seven of the trials were placebo-controlled, acute treatment trials of six-weeks duration designed to assess the efficacy of various doses of lurasidone ranging from 20 mg to 160 mg daily (studies: 6 [N = 149], 196 [N = 180], 229, [N = 500], 231 [N = 478], 233 [N = 488], 2 [N = 460], and 49 [N = 356]). Four of the acute treatment trials (studies 2, 49, 231, and 233) included the following active comparators to verify assay sensitivity: risperidone, haloperidol, olanzapine, and quetiapine extended-release (XR). However, these trials were not designed to assess the comparative efficacy of lurasidone and the active comparators. The manufacturer classified two of these trials (studies 2 and 49) as failed trials because the active comparator failed to differentiate from placebo on one or more of the key efficacy outcomes. One 52-week RCT compared lurasidone with risperidone (study 237; N = 629) in stable patients and one three-week RCT compared lurasidone with ziprasidone (study 254; N = 307) in stable patients.

Limitations of the available evidence include the lack of adequately designed trials to evaluate the comparative efficacy of lurasidone against other atypical antipsychotic agents and the high rates of premature discontinuation in nearly all included studies. More than 30% of patients discontinued early in eight of the nine trials and more than 50% withdrew from studies 6, 49, and 237, including 70% in the placebo group of study 6. The high discontinuation rates could have compromised the comparability of study groups and potentially limited the validity of study results, particularly in studies 6 and 237.

### **Outcomes**

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

- Positive and Negative Syndrome Scale (PANSS) — a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia that consists of three subscales (positive, negative, and general psychopathology).
- Brief Psychiatric Rating Scale derived (BPRSd) — 18 ordered categorical items (from “not present” to “extremely severe,” on a seven-point scale), each developed to assess patient symptomatology in a relatively discrete symptom area. The BPRSd is primarily focused on positive symptoms of schizophrenia.
- The Clinical Global Impression of Severity (CGI-S) — measures the global severity of illness at a given point in time by rating the patient’s illness on a seven-point scale ranging from one (no symptoms) to seven (very severe).
- Serious adverse events and adverse events including extrapyramidal symptoms and weight changes.

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The PANSS was assessed as a primary or secondary outcome in all of the included trials; and it was the primary outcome in studies 2, 229, 231, and 233. Change from baseline PANSS scores at six weeks was assessed as a primary or secondary end point in all of the acute treatment trials. Change from baseline in BPRSd scores at six weeks was assessed as the primary end point in studies 6, 196, and 49. Adverse events were the primary outcome in studies 237 and 254. Time to relapse was assessed as a secondary outcome in study 237.

CDR conducted meta-analyses to assess the efficacy outcomes and change in body weight reported in the seven acute treatment trials. The failed trials, 2 and 49, were excluded from the reference case meta-analyses of efficacy outcomes; however, sensitivity analyses were conducted by including these studies. In the meta-analysis for change in body weight, all six-week studies were pooled.

### Results

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

- In the meta-analysis of non-failed acute-treatment trials, the weighted mean differences (WMDs) in change from baseline in PANSS total score relative to placebo was  $-6.2$  (95% CI,  $-11.1$  to  $-1.3$ ) for 40 mg lurasidone,  $-8.9$  (95% CI,  $-12.2$  to  $-5.7$ ) for 80 mg lurasidone,  $-6.7$  (95% CI,  $-10.9$  to  $-2.5$ ) for 120 mg lurasidone, and  $-16.2$  (95% CI,  $-21.1$  to  $-11.2$ ) for 160 mg lurasidone. The inclusion of the failed studies (2 and 49) in the meta-analyses did not appreciably alter the effect sizes, although the estimate for lurasidone 40 mg was no longer statistically significant.
- Relative to placebo, lurasidone-treated patients were more likely to demonstrate an improvement of  $\geq 30\%$  in PANSS total score. The relative risk (RR) of achieving  $\geq 30\%$  improvement in PANSS was 1.32 (95% CI, 1.07 to 1.62) for 40 mg lurasidone, 1.48 (95% CI, 1.20 to 1.84) for 80 mg lurasidone, 1.27 (95% CI, 1.03 to 1.57) for 120 mg lurasidone, and 2.09 (95% CI, 1.54 to 2.84) for 160 mg lurasidone.
- Among the non-failed trials, the differences in CGI-S between lurasidone 40 mg, 80 mg, 120 mg, and 160 mg versus placebo were  $-0.4$  (95% CI,  $-0.7$  to  $-0.1$ ),  $-0.5$  (95% CI,  $-0.6$  to  $-0.3$ ),  $-0.4$  (95% CI,  $-0.6$  to  $-0.1$ ), and  $-0.8$  ( $-1.1$  to  $-0.6$ ) respectively.
- In the two stable treatment trials (studies 254 and study 237), there were no statistically significant differences between lurasidone and ziprasidone (80 mg twice daily) or risperidone (2 mg/day to 6 mg/day) in change from baseline total PANSS scores.
- Lurasidone failed to demonstrate non-inferiority to risperidone for time to relapse in study 237. There was no statistically significant difference between lurasidone (40 mg to 120 mg) and risperidone (2 mg to 6 mg) for time to relapse (hazard ratio = 1.30; 95% CI, 0.87 to 1.96); however, the non-inferiority criterion (i.e., upper limit of 1.6 for the 95% CI) was exceeded.

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

- Based on pooled results from the seven acute treatment trials, the proportion of patients who experienced serious adverse events with lurasidone 40 mg to 160 mg in the acute treatment trials ranged from 3.2% to 6.2%, compared with 5.6% in the pooled placebo group. The most common serious adverse events among lurasidone-treated patients were related to the worsening of the patients' condition. Among the active comparators, serious

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adverse events were most frequent with haloperidol (6.9%) and least frequent with quetiapine XR (2.5%).

- In the 52-week study 237, the incidence of serious adverse events with flexibly dosed lurasidone (11%) was similar to that of flexibly dosed risperidone (10%).
- Akathisia and parkinsonism were the most frequently reported extrapyramidal symptoms for lurasidone-treated patients. In the acute treatment trials, the proportion of patients experiencing akathisia and parkinsonism increased with higher doses of lurasidone up to 120 mg (akathisia ranged from 11% with 40 mg to 22% with 120 mg and parkinsonism ranged from 4% with 40 mg to 9% with 120 mg). The 160 mg dose of lurasidone was associated with a lower incidence of akathisia (7.4%) and parkinsonism (6.6%).
- In meta-analyses of change from baseline in body weight, only lurasidone 80 mg demonstrated a statistically significant increase compared with placebo (WMD = 0.59 kg; 95% CI, 0.27 to 0.91). Among the active comparators, olanzapine and quetiapine XR were associated with statistically significant increases in body weight when compared with placebo (mean difference = 3.53 kg and 1.96 kg respectively). A weight gain of at least 7% occurred in a higher proportion of patients treated with olanzapine (34%) and quetiapine XR (15%) compared with lurasidone (4% to 9% across doses of 40 mg to 160 mg).

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

The manufacturer submitted a cost-minimization analysis comparing lurasidone with aripiprazole, ziprasidone, quetiapine, risperidone, and olanzapine. The clinical evidence used to support the assumption of similar clinical efficacy and safety was based on a naive indirect comparison of information obtained from product monographs. In the absence of robust comparative head-to-head trial information, or a formal indirect comparison, it is unclear whether the requirements of similar clinical efficacy and safety required for the conduct of a cost-minimization analysis were met.

At recommended doses, the daily cost of lurasidone (40 mg to 120 mg; [confidential price removed at manufacturer's request]) is lower than aripiprazole (10 mg to 30 mg daily; \$4.01 to \$6.53); comparable with ziprasidone (20 mg to 80 mg twice daily; \$3.40 to \$3.89) and generic olanzapine (5 mg to 20 mg daily; \$0.90 to \$7.42); and, more expensive than generic risperidone (2 mg to 6 mg, \$0.61 to \$1.82) and generic quetiapine (300 mg to 800 mg daily, \$0.97 to \$2.59). The confidential price was used by the Committee in making the listing recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

### **Other Discussion Points:**

The Committee noted the following:

- The Health Canada indication for lurasidone is only for the acute treatment of schizophrenia, and the product monograph states that the efficacy of lurasidone for use longer than six weeks has not been systematically evaluated in controlled studies.
- The cost of a 160 mg daily dose of lurasidone would be twice the cost of the 40 mg, 80 mg, or 120 mg dosages.

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**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

**Regrets:**

November 21, 2012: None

January 16, 2013: 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 and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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

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