



## CDEC FINAL RECOMMENDATION

### LURASIDONE RESUBMISSION

(Latuda — Sunovion Pharmaceuticals Canada Inc.)

Indication: Schizophrenia

#### **Recommendation:**

The Canadian Drug Expert Committee (CDEC) recommends that lurasidone be listed for the management of the manifestations of schizophrenia if the following clinical criteria are met:

#### **Clinical Criteria:**

- Patient has a contraindication to less expensive antipsychotic agents, or
- Patient has failed a trial of less expensive antipsychotics because of intolerance or lack of response.

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

1. The revised Health Canada-approved indication for lurasidone is for the “management of the manifestations of schizophrenia” and is no longer restricted to the “acute treatment of schizophrenia.”
2. A network meta-analysis relying on indirect comparisons failed to demonstrate a difference in the clinical benefit of lurasidone compared with aripiprazole and ziprasidone for the Positive and Negative Syndrome Scale (PANSS) and all-cause discontinuations.
3. At the resubmitted price, lurasidone (\$██████) is less costly than aripiprazole (10 mg to 15 mg daily; \$4.13 to \$4.78 per day) and ziprasidone (40 mg to 80 mg twice daily; \$3.97 per day).

#### **Background:**

Lurasidone is an atypical antipsychotic drug indicated for the management of the manifestations 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 tolerability, which is expected to be 40 mg or 80 mg once daily for most patients.

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### Submission History

Lurasidone was previously reviewed for the treatment of acute schizophrenia by CDEC and received a recommendation of “do not list” (see Notice of CDEC Final Recommendation, January 23, 2013). The reason for the recommendation was a lack of evidence to establish the comparative efficacy of lurasidone relative to other less costly antipsychotic drugs for the acute treatment of schizophrenia.

The original Common Drug Review (CDR) report included nine randomized controlled trials (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, non-inferiority 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.

CDEC considered the following outcomes during their deliberations: PANSS, Brief Psychiatric Rating Scale derived (BPRSd), The Clinical Global Impression of Severity (CGI-S), serious adverse events, and adverse events. 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.

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.

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) in this study 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.

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 as the doses of lurasidone increased up to 120 mg

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(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). 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). 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).

Although not included in the CDR systematic review of lurasidone, the following extension studies were summarized and appraised by CDR and discussed by CDEC: Study 234, Study 229E, Study 231E, and Study 199. Study 234 was a 12-month, double-blind extension of Study 233.

This resubmission is based on a new price (reduced price compared with the original submission). In addition, the manufacturer provided an indirect comparison of lurasidone against aripiprazole and ziprasidone; an open-label study of patients switched to lurasidone from another antipsychotic drug; and published versions of Studies 234 and 231E.

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

No new RCTs meet the inclusion of the CDR systematic review. CDEC considered the following information prepared by the CDR:

- the final CDR clinical and pharmacoeconomic review reports from the initial lurasidone submission
- a critique of the manufacturer's pharmacoeconomic evaluation
- a critical appraisal of the manufacturer's submitted indirect comparison
- a summary and critical appraisal of a recently published network meta-analysis
- a summary of the following additional clinical information provided by the manufacturer — an open-label study of patients switched to lurasidone from another antipsychotic drug and the publication of Study 234, an open-label extension of Study 233 — that was reviewed as a Supplemental Issue in the initial CDR review
- patient group-submitted information about outcomes and issues important to patients.

### **Patient Input Information**

The following is a summary of key information provided by three 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, the patient groups noted that there is a considerable emotional burden in caring for someone with schizophrenia.
- 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).
- There is a need for additional antipsychotic treatment options for individuals with schizophrenia. Patient groups indicated that many antipsychotic medications have similar

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efficacy on average; 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.

### **Outcomes**

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

- PANSS — a 30-item clinician-rated instrument for assessing the symptoms of schizophrenia that consists of three subscales (positive, negative, and general psychopathology).
- 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.

### **Manufacturer's Indirect Direct Comparison**

- The manufacturer submitted three indirect treatment comparisons to assess the comparative efficacy of lurasidone versus ziprasidone and aripiprazole:
  - Lurasidone (40 mg to 120 mg once daily) versus ziprasidone (40 mg to 80 mg once daily) using risperidone (2 mg to 6 mg once daily or 3 mg to 5 mg once daily) as the common comparator
  - Lurasidone (40 mg once daily) versus aripiprazole (15 mg to 30 mg once daily) using olanzapine (10 mg to 20 mg once daily or 15 mg once daily) as the common comparator
  - Lurasidone (120 mg once daily) versus aripiprazole (15 mg to 30 mg once daily) using olanzapine as the common comparator (10 mg to 20 mg once daily or 15 mg once daily).
- The manufacturer reported that the indirect comparisons demonstrated that there were no statistically significant differences for the following end points:
  - Lurasidone versus ziprasidone: CGI-S and the Montgomery-Asberg Depression Scale (MADRS)
  - Lurasidone versus aripiprazole: PANSS total score, PANSS positive score, PANSS negative score, and CGI-S

### **Network Meta-analysis**

The CDR systematic literature review identified a network meta-analysis (Leucht et al. 2013) that compared the safety and efficacy of 15 orally administered antipsychotic drugs (lurasidone, amisulpride, aripiprazole, asenapine, chlorpromazine, clozapine, haloperidol, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, zotepine) and placebo for the treatment of schizophrenia.

- There were no statistically significant differences in PANSS total score between lurasidone and aripiprazole, haloperidol, quetiapine, ziprasidone, chlorpromazine, or asenapine. However, lurasidone demonstrated statistically significantly lower efficacy than clozapine, olanzapine, risperidone, and paliperidone.
- Compared with aripiprazole, ziprasidone and placebo, the standardized mean difference (SMD) for change from baseline in PANSS total score was reported as follows:
  - Lurasidone versus aripiprazole: 0.10 (95% credible interval [CrI], -0.05 to 0.25)
  - Lurasidone versus ziprasidone: 0.07 (95% CrI, -0.09 to 0.22)
  - Lurasidone versus placebo: -0.33 (95% CrI, -0.45 to -0.21).

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- Compared with aripiprazole, ziprasidone and placebo, the odds ratio for all-cause discontinuation was reported as follows:
  - Lurasidone versus aripiprazole: 1.25 (95% CrI, 0.95 to 1.67)
  - Lurasidone versus ziprasidone: 1.06 (95% CrI, 0.81 to 1.43)
  - Lurasidone versus placebo: 0.77 (95% CrI, 0.61 to 0.96).
- Changes in body weight (SMD) were also similar with lurasidone compared with aripiprazole, ziprasidone, and placebo:
  - Lurasidone versus aripiprazole: -0.07 (95% CrI, -0.23 to 0.10)
  - Lurasidone versus ziprasidone: 0.00 (95% CrI, -0.16 to 0.16)
  - Lurasidone versus placebo: 0.10 (95% CrI, -0.02 to 0.21).
- Olanzapine, quetiapine, and risperidone were associated with significantly more weight gain than lurasidone.

### Extension Study

- Study 234 was a 12-month, double-blind, extension study comparing lurasidone 40 mg with 160 mg per day versus quetiapine XR 200 mg to 800 mg per day. The study was the extension of Study 233 (PEARL-3), a six-week, double-blind, placebo-controlled trial that compared lurasidone 80 mg, lurasidone 160 mg, and quetiapine XR 600 mg with placebo.
  - The primary efficacy end point of Study 234 was time to relapse. The relapse hazard ratio comparing lurasidone versus quetiapine was 0.73 (95% CI, 0.41 to 1.30) (a hazard ratio of < 1 favours lurasidone), which satisfied the manufacturer's predefined non-inferiority margin (i.e., upper bound of the 95% CI was less than 1.93).
  - Lurasidone was favoured over quetiapine XR for change in PANSS total score (mean difference -6.7 [95% CI, -11.7 to -1.7]).
  - There was no statistically significant difference between lurasidone and quetiapine XR for changes in CGI-S (mean difference -0.2 [95% CI, -0.4 to 0.1]) or MADRS (mean difference -1.3 [95% CI, -3.3 to 0.7]).
  - Approximately 50% of patients in both treatment groups discontinued the study.
  - Adverse events occurred in a similar proportion of patients across treatment groups, although the frequency of akathisia was higher for patients treated with lurasidone continuously or switched from placebo to lurasidone compared with quetiapine XR.

### Cost and Cost-Effectiveness

Lurasidone is available as 40 mg, 80 mg, and 120 mg tablets at a price of ██████ regardless of strength, or ██████. The manufacturer submitted a cost-minimization analysis comparing lurasidone with other atypical antipsychotic drugs available in Canada and considered only drug acquisition costs. The manufacturer focused on comparing lurasidone with aripiprazole and ziprasidone, based on an assumption of similar efficacy and metabolic effects. While no differences in efficacy between lurasidone and all other oral atypical antipsychotic drugs were observed in a network meta-analysis, the absence of head-to-head trials and limitations with the indirect comparison make the assumption of equivalent efficacy uncertain.

At the submitted price, lurasidone (\$█████) is less costly than aripiprazole (10 mg to 15 mg daily; \$1,509 to \$1,746 per year) and ziprasidone (40 mg to 80 mg twice daily; \$1,448 per year), irrespective of dose. By contrast, lurasidone is more costly than quetiapine (\$352 to \$705) and risperidone (\$443 to \$665), irrespective of dose (based on Ontario Drug Benefit Formulary



prices). When compared with other atypical antipsychotic drugs, whether lurasidone is less or more expensive depends on dosing.

### Other Discussion Points:

- In the initial CDR review of lurasidone, the Health Canada-approved indication for the drug was restricted to the “acute treatment of schizophrenia;” however, schizophrenia is a chronic illness and patients typically require long-term treatment. The Health Canada-approved indication for the current CDR review of lurasidone is for the “management of the manifestations of schizophrenia.” CDEC noted that lurasidone is unlikely to be restricted to acute treatment in clinical practice.
- Study 234 was an extension phase of Study 233 and not all patients who completed the initial phase consented to participate in the extension phase. Hence, the randomization that was performed for the initial phase (i.e., Study 233) may have been compromised in Study 234. In addition, there were large proportions of early discontinuations in both the initial phase (approximately 29%) and extension phase (approximately 50%), which could potentially obscure true differences between treatments; thus, increasing the probability of demonstrating non-inferiority. These issues make it difficult to interpret the results of Study 234.
- 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; therefore, the potential cost-savings of the resubmitted price would be lost if the dose exceeds 120 mg per day.
- CDEC noted the following with respect to how the evidence addressed the patient group concerns:
  - Lurasidone appears to have a small advantage as compared with some atypical antipsychotic drugs with respect to weight gain. People taking lurasidone gained less weight when compared with those taking olanzapine, quetiapine, and risperidone. Weight gain was similar with lurasidone compared with aripiprazole, ziprasidone, and placebo.
  - Lurasidone is associated with significant extrapyramidal symptoms, especially akathisia and parkinsonism, and the likelihood of these occurring increases as doses of lurasidone increase.
  - The network meta-analysis suggested that there was no significant difference between lurasidone and several atypical antipsychotic drugs for improving the positive and negative symptoms of schizophrenia; however, lurasidone was considered less effective than clozapine, olanzapine, risperidone, and paliperidone. Lurasidone represents another treatment option for some people with schizophrenia.

### Research Gaps:

CDEC noted the lack of evidence regarding the long-term efficacy and safety of lurasidone compared with other atypical antipsychotic drugs.

**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.

**November 20, 2013 Meeting****Regrets:**

One CDEC member could not attend the meeting.

**Conflicts of Interest:**

None

**About This Document:**

CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmaco-economic 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 requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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