Drug Coverage Decision for BC PharmaCare

About PharmaCare BC PharmaCare is a publicly funded drug plan that helps B.C. residents pay for most prescription drugs and pharmacy services, and some medical devices and supplies.

Details of Drug Reviewed

Drug	**lurasidone**
Dosage form(s)	20 mg, 40 mg, 60 mg, 80 mg, and 120 mg tablets
Manufacturer	Generics
Submission type	**Ministry Initiated**
Use reviewed	For the management of schizophrenia and for the acute management of depressive episodes associated with bipolar I disorder
Canada's Drug and Health Technology Agency (CADTH) recommendation	**For schizophrenia:** CADTH recommended: **to Reimburse with clinical criteria and/or conditions**. Visit the CRR website for more details. **For acute management of depressive episodes associated with bipolar I disorder:** CADTH did not review.
Drug Benefit Council (DBC)	**For the management of schizophrenia:** TheDBC met on February 17, 2014. The DBC considered various inputs including: the final review completed by CADTH completed on December 20, 2013, which included clinical and pharmacoeconomic evidence review material, Clinical Practice Reviews from two Specialists, Manufacturer comments; responses to Patient Input Questionnaires from 1 patient, 5 caregivers, and 1 patient group, and a Budget Impact Analysis. **For the acute management of depressive episodes associated with bipolar I disorder:**

	The DBC met on April 3, 2023. The DBC considered various input, including the Therapeutics Initiative Drug Assessment Working Group (TI DAWG) April 2022 Final Report, "Lurasidone monotherapy for bipolar I depression in adults: A systematic review and appraisal"; the TI DAWG April 2022 Final Report, "Lurasidone acute and maintenance adjunctive therapy for bipolar I depression in adults: A systematic review and appraisal"; and the TI DAWG September 2022 Final Report, "Lurasidone monotherapy and adjunctive therapy to lithium or valproate for bipolar I depression in children aged 10-17 years: A systematic review and appraisal." The DBC also considered a Clinical Practice Review from a specialist and a Budget Impact Assessment. The Ministry received no responses to Your Voice patient input questionnaire from patients, caregivers, or patient groups.
Drug Coverage Decision	**Limited Coverage benefit** for the management of schizophrenia and for the acute management of depressive episodes associated with bipolar I disorder
Date	**March 7, 2024** (This Drug Decision Summary supersedes the listing decisions for lurasidone dated September 19, 2013, and September 16, 2014).
Reasons	**For the management of schizophrenia:** • The drug coverage decision is consistent with the CDEC and DBC recommendations. • On September 16, 2014, based on clinical considerations and the submitted product price, the Ministry made the decision not to list lurasidone (Latuda®), as the drug was not cost-effective and did not offer value for money compared to other covered antipsychotic drugs. • At the time, PharmaCare covered many safe and effective antipsychotic alternatives which appeared to be adequately meeting most patient needs. • Generic versions of lurasidone are now available, and the cost of the generics addresses the cost value concerns compared to other covered antipsychotic drugs. **For the acute management of depressive episodes associated with bipolar I disorder:** • The drug coverage decision is consistent with the DBC recommendation. • Results from four randomized controlled trials (RCTs) provided weak support for efficacy of 6 weeks of lurasidone monotherapy and adjunctive therapy with lithium or valproate in adults with bipolar I depression and a modest reduction in depressive symptoms. • Results from one RCT provided weak support for efficacy of 6 weeks of lurasidone monotherapy in children aged 13 to 17 years and a statistically significant reduction in one efficacy rating scale. • There are no studies of lurasidone as adjunctive therapy to lithium or valproate in the paediatric population. • Generic versions of lurasidone are now available, and the cost of the generics addresses the cost value concerns compared to other covered drugs.

Other information	None

The drug review process in B.C.

A manufacturer submits a request to the Ministry of Health (the Ministry).

An independent group called the Drug Benefit Council (DBC) gives advice to the Ministry by considering:

- whether the drug is safe and effective
- advice from a national group called Canada's Drug and Health Technology Agency (CADTH)
- what the drug costs and whether funding it provides good value to the province
- ethical considerations of covering and not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes a BC PharmaCare coverage decision by taking into account:

- existing BC PharmaCare policies, programs and resources
- the evidence-informed advice of the DBC
- drugs already covered by BC PharmaCare that treat similar medical conditions
- the overall cost of covering the drug

Visit BC PharmaCare and Drug reviews for more information.

Appendix

Drug Benefit Council (DBC)

Recommendation and Reasons for Recommendation

FINAL

Lurasidone (Latuda® and generics)

Sunovion Pharmaceuticals Canada Inc. and generic manufacturers

Description:

Drug review of **lurasidone (Latuda® and generics)** for the following indications:

> As monotherapy or as adjunctive therapy with lithium or valproate for the acute management of depressive episodes associated with bipolar 1 disorder.

> As monotherapy or as adjunctive therapy for the acute management of depressive episodes associated with bipolar 1 disorder in adolescent (13 to 17 years) patients.

Health Canada has granted lurasidone (Latuda®) a Notice of Compliance (NOC) for the treatment of depressive episodes associated with bipolar 1 disorder. However, the lurasidone product monograph specifies that for the adult indication "the efficacy of lurasidone for the long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled studies," and, for the children and adolescents indications, "the safety and efficacy of lurasidone 20 to 80 mg/day for the treatment of bipolar depression in children and adolescents (10 to 17 years) was evaluated in a 6-week, placebo-controlled clinical study in 343 children and adolescents" and that "lurasidone is not indicated for the treatment of depressive episodes in bipolar 1 disorder in patients less than 13 years of age due to insufficient safety and efficacy data."

lurasidone (generics)

Although the DBC has reviewed lurasidone for the treatment of schizophrenia, the DBC has not reviewed lurasidone for depressive episodes associated with bipolar 1 disorder. The Special Authority (SA) department has received an increased volume of requests for lurasidone to treat depressive episodes associated with bipolar I disorder; therefore, the Ministry has initiated an evidence review and commissioned the Therapeutics Initiative (TI) to complete a clinical evidence review.

The Ministry asked the DBC to consider the following questions:

1. Based on the evidence provided, what is your recommendation to the British Columbia Ministry of Health (the Ministry) regarding reimbursement of lurasidone for the treatment of depressive episodes associated with bipolar 1 disorder?
2. If PharmaCare were to provide reimbursement for lurasidone for the treatment of depressive episodes associated with bipolar 1 disorder, what coverage criteria should be considered?

In their review, the DBC considered the following reviews: the TI Drug Assessment Working Group (DAWG) April 2022 Final Report, "Lurasidone monotherapy for bipolar 1 depression in adults: A systematic review and appraisal"; the TI DAWG April 2022 Final Report, "Lurasidone acute and maintenance adjunctive therapy for bipolar 1 depression in adults: A systematic review and appraisal"; and the TI DAWG September 2022 Final Report, "Lurasidone monotherapy and adjunctive therapy to lithium or valproate for bipolar 1 depression in children aged 10-17 years: A systematic review and appraisal." The DBC received no Patient Input Questionnaire responses from patients, caregivers, or patient groups. The DBC also considered a Clinical Practice Review from a specialist and a Budget Impact Assessment.

Dosage Forms:

Latuda® and generic versions of lurasidone are available as 20 mg, 40 mg, 60 mg, 80 mg and 120 mg film-coated tablets.

Recommendations:

1. The Drug Benefit Council (DBC) recommends that lurasidone be reimbursed as follows:

- As monotherapy in adults with bipolar type 1 disorder: Limited Coverage with the following criteria:
  Patients experiencing a major depressive episode of ≥ 4 weeks and < 12 months as defined by DSMIV criteria.

- As adjunct therapy to lithium or valproate in adults with bipolar type 1 disorder: Limited Coverage with the following criteria:
  Patients experiencing a major depressive episode of ≥ 4 weeks and < 12 months as defined by DSMIV criteria and who had an inadequate response to a minimum 28-day trial with lithium or valproate.

- As monotherapy in children and adolescents aged 13-17 with bipolar type 1 disorder:
  Patients experiencing a major depressive episode of ≥ 4 weeks and < 12 months duration as defined by DSMIV criteria, a Children's Depression Rating Scale (CDRS) score of ≥ 45 (≥ 40 indicates depression) at screening and baseline and a Mania Rating Scale (YMRS) score of ≤ 15 with the elevated mood item score ≤ 2.

- As adjunct therapy in children and adolescents aged 13-17: Do Not List.

Reasons for the Recommendation:

1. Summary

- Results from two randomized controlled trials (RCTs) provided weak support for efficacy of 6 weeks of lurasidone monotherapy in adults with bipolar 1 depression and a modest reduction in depressive symptoms.
- Similarly, results from two RCTs provided weak support for efficacy of 6 weeks of lurasidone adjunctive therapy with lithium or valproate in adults with bipolar 1 depression and a reduction in depressive symptoms.
- Results from one RCT provided weak support for efficacy of 6 weeks of lurasidone monotherapy in children aged 13 to 17 years and a statistically significant reduction in one efficacy rating scale.
- There are no studies of lurasidone as adjunctive therapy to lithium or valproate in the paediatric population.
- The RCTs were too small and too short in duration (6 weeks) to systematically evaluate harms.
- At manufacturer list prices, the average daily cost of generic lurasidone is comparable to comparator drugs used to treat bipolar I disorder.

2. Clinical Efficacy

As monotherapy in adults:

- Two RCTs (Loebel 2014; Kato 2020) provide weak support for a causal association between 6 weeks of lurasidone monotherapy in adults with bipolar 1 depression and a modest reduction in depressive symptoms as measured by the primary outcome, Montgomery-Asberg Depression Rating Scale (MADRS).
- The risk of bias for both studies, which are almost identical in study design, was assessed as low in 5 of 7 domains, but high in others due to conflict of interest and lack of transparency of study participants included in calculations. The minimally clinically important difference (MCID) for MADRS was met; however, this has only been validated for unipolar depression and not in bipolar 1 depression.

- Statistically significant improvements were also reported using validated tools for assessing quality of life, functionality, and anxiety, but attrition bias and lack of knowledge of a MCID negate drawing scientifically and clinically valid conclusions from these measurements.

As adjunct therapy to lithium or valproate in adults:

- Two RCTs (Loebel 2014a; Suppes 2016) provide weak support for a causal association between 6 weeks of lurasidone adjunctive therapy in adults with bipolar 1 depression and a reduction in depressive symptoms as measured by the primary outcome, MADRS. The lack of a valid MCID for the MADRS in bipolar depression means the clinical significance is uncertain.
- Statistically significant improvements were also reported using validated tools for assessing quality of life, functionality and anxiety, but attrition bias and lack of knowledge of a MCID negate drawing scientifically and clinically valid conclusions from these measurements.
- One RCT (Calabrese 2017) of adjunctive lurasidone for maintenance treatment in bipolar 1 disorder did not find a statistically significant difference in the primary endpoint, probability of recurrence of any mood episode. A role for lurasidone in maintenance phase treatment has not been validated through RCT evidence.

As monotherapy in children and adolescents aged 13-17:

- One RCT (DelBello 2017) provides weak support for a causal association between 6 weeks of lurasidone monotherapy in children aged 13 to 17 years and a reduction in the study's primary outcome Children's Depression Rating Scale–Revised (CDRS-R), which was statistically significant. The MCID for CDRS-R is unknown, however was judged to be clinically significant by FDA reviewers.
- Secondary outcome measures improved in DelBello 2017 included: Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q), Children's Global Assessment Scale (CGAS), a measure of functionality, and Clinical Global Improvement, Bipolar Version, Severity of Illness score (Depression) (CGI-BP-S).

As adjunct therapy in children and adolescents aged 13-17:

- There are no studies of lurasidone as adjunctive therapy to lithium or valproate in the paediatric population.

3. Safety

As monotherapy in adults:

- Harm data from the lurasidone monotherapy phase III RCTs over the 6-week period contribute little to understanding of harm from lurasidone.
- Higher doses of lurasidone were not more efficacious than lower doses. Moreover, the higher doses were associated with higher frequency of total adverse events and akathisia.
- The RCTs were too small and too short to evaluate serious adverse events like deaths, suicide and hospitalizations.

As adjunct therapy to lithium or valproate in adults:

- Adverse events are known to increase with dose. There was a statistically significant more akathisia (restlessness) with lurasidone in the 3 RCTs, however the full range of harms has not been quantitatively evaluated comprehensively.

As monotherapy in children and adolescents aged 13-17:

- The RCTs were too small and too short to evaluate serious adverse events like deaths, suicide and hospitalizations. Antipsychotics have a significant harm profile with potentially serious adverse events, both fatal and non-fatal including mania and extrapyramidal symptoms.
- Harms data from the one lurasidone monotherapy RCT in the paediatric population over the 6-week period contribute little to understanding of overall harm from lurasidone. Regulatory safety data provides a better overview of known harms than RCT reports, however data for lurasidone from the paediatric population are very limited, with harms data from adult populations also limited and of uncertain applicability to the pediatric population.

4. Economic Considerations

- At manufacturer list prices, the average daily cost of generic lurasidone is comparable to or less than comparator drugs also used to treat bipolar I disorder.
- Listing generic lurasidone as a benefit could potentially result in a cost savings to PharmaCare depending on uptake.

Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

FINAL

lurasidone hydrochloride (Latuda™)

Sunovion Pharmaceuticals Canada Inc.

Description:

Drug review of **lurasidone hydrochloride (Latuda™)** for the following Health Canada approved indication:

For the management of the manifestations of schizophrenia.

In their review, the DBC considered the following: the final review completed by the Common Drug Review (CDR) completed on December 20, 2013, which included clinical and pharmacoeconomic evidence review material, Clinical Practice Reviews from two Specialists, Manufacturer comments; responses to Patient Input Questionnaires from 1 patient, 5 caregivers, and 1 patient group, and a Budget Impact Analysis.

Dosage Forms:

Latuda™ is available as lurasidone hydrochloride 40 mg, 80 mg and 120 mg film-coated tablets.

Recommendations:

lurasidone (generics)

The Drug Benefit Council (DBC) recommends that **lurasidone hydrochloride (Latuda™)** be listed for the management of the manifestations of schizophrenia if the following clinical criteria are met:

Clinical Criteria:

- The patient has a contraindication to less expensive antipsychotic agents; or
- The patient has failed a trial of less expensive antipsychotics because of intolerance or lack of response.

Reasons for the Recommendation:

5. Summary

- 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.
- At the resubmitted price, lurasidone is less costly than aripiprazole and ziprasidone.

6. Clinical Efficacy

- The Common Drug Review (CDR) previously reviewed lurasidone for the treatment of acute schizophrenia and issued a recommendation of "do not list" on 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 resubmission is based on a revised indication (for the management of the manifestations of schizophrenia rather than the previous acute treatment of schizophrenia), a new price (reduced compared with the original submission), and new clinical trial evidence that includes 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 two previously unpublished trials. No new randomized controlled trials (RCTs) meet the inclusion criteria of the CDR systematic review.
- Outcomes defined a priori in the CDR systematic review protocol included the following: PANSS; Brief Psychiatric Rating Scale derived (BPRSd); Clinical Global Impressions - Severity (CGI-S); and serious adverse events and adverse events including extrapyramidal symptoms and weight changes.
- The manufacturer submitted three indirect treatment comparisons to assess the comparative efficacy of lurasidone versus ziprasidone and aripiprazole: lurasidone (40 mg to 120 mg) versus ziprasidone using risperidone 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; and 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 between lurasidone and ziprasidone in the CGI-S and the Montgomery-Asberg Depression Scale (MADRS) end points; and between lurasidone and aripiprazole in the PANSS total score, PANSS positive score, PANSS negative score, and CGI-S end points
- The CDR systematic literature review also identified a network meta-analysis comparing 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.
- The network meta-analysis found 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.
- Changes in body weight were similar with lurasidone compared with aripiprazole, ziprasidone, and placebo. Olanzapine, quetiapine, and risperidone were associated with significantly more weight gain than lurasidone.
- The CDR also considered 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 (Study 234). 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 (a hazard ratio of < 1 favours lurasidone), which satisfied the manufacturer's predefined non-inferiority margin.
- Lurasidone was favoured over quetiapine XR for change in PANSS total score. There was no statistically significant difference between lurasidone and quetiapine XR for changes in CGI-S or MADRS.
- 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 (Study 233) may have been compromised in Study 234. In addition, there were large proportions of early discontinuations in both the initial phase and extension phase, which could obscure true differences between treatments and increase the probability of demonstrating non-inferiority. These issues make it difficult to interpret the results of Study 234.

7. Safety

- In meta-analyses of change from baseline in body weight, only lurasidone 80 mg demonstrated a statistically significant increase compared with placebo. Among the active comparators, olanzapine and quetiapine XR were associated with statistically significant increases in body weight when compared with placebo.
- In the 12-month, double-blind extension study (Study 234), approximately 50% of patients in both lurasidone and quetiapine treatment groups discontinued the study. Adverse events occurred in a similar proportion of patients, although the frequency of akathisia was higher for patients treated with lurasidone continuously or switched from placebo to lurasidone compared with quetiapine.

8. Economic Considerations

- The manufacturer submitted a cost-minimization analysis comparing lurasidone with other atypical antipsychotic drugs available in Canada that 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 and ziprasidone, but more costly than quetiapine and risperidone, irrespective of dose. When compared with other atypical antipsychotic drugs, whether lurasidone is less or more expensive depends on dosing.
- The cost of a 160 mg daily dose of lurasidone is twice the cost of the 40 mg, 80 mg, or 120 mg dosages; therefore, the potential cost-savings would be lost if the dose exceeds 120 mg per day.

9. Of Note

- 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.
- The DBC noted there is a lack of evidence regarding the long-term efficacy and safety of lurasidone compared with other atypical antipsychotic drugs.
- Patient input from patients, caregivers and patient groups indicated the symptoms of schizophrenia significantly interfere with the daily activities of employment, education, socialization, and maintenance of relationships with family and friends, and quality of life.
- Current treatments for schizophrenia 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). Patients expect a treatment to offer reduced symptoms, improved quality of life, and fewer adverse events

lurasidone (generics)

- Patient groups expressed a desire for additional antipsychotic treatment options, indicating that many antipsychotic medications have similar efficacy but there is variability in individual patient response.