

Latuda (Lurasidone HCl) Receives 2 New Indications for Use in Bipolar Depression as Monotherapy and as Adjunctive Therapy with Lithium or Valproate

By Loretta Fala, Medical Writer

Bipolar disorder is a disruptive, long-term illness associated with mood swings ranging from the lows of depression to the highs of mania, and in some cases, symptoms of depression and mania at the same time (ie, mixed episodes).¹ The symptoms of bipolar disorder may vary from person to person. Mood swings associated with bipolar disorder have the potential to cause substantial difficulties in relationships, work, or school. Moreover, manic episodes can be severe and, in some cases, even harmful.¹

According to the National Institute of Mental Health, an estimated 2.6% of the US adult population—approximately 5.7 million people—are affected by bipolar disorder.² The median age of onset for bipolar disorder is 25 years.² According to the Centers for Disease Control and Prevention, in 2011, patients with bipolar disorder had a 39.1% inpatient hospitalization rate compared with a 4.5% rate for patients with other behavioral healthcare diagnoses.³ Overall, bipolar disorder is the most expensive behavioral health diagnosis, attributed mostly to indirect costs, including lost productivity, absenteeism, and presenteeism (ie, attending work while sick).³

The comorbid conditions associated with bipolar disorder include anxiety, substance abuse, panic disorder, and eating disorders, among others. The risk of suicide is increased in patients with bipolar disorder, particularly in those who also have anxiety and substance abuse.⁴

The total economic burden of bipolar disorder, including direct and indirect costs, in the United States was estimated to be \$45 billion in 1991.^{5,6} A 2009 analysis estimated that the total costs of bipolar disorder were dramatically higher, totaling \$151 billion in direct and indirect costs.⁷ Of this total, bipolar I disorder accounted for \$30.7 billion, and bipolar II disorder accounted for \$120.3 billion.⁷

Bipolar disorder requires lifelong treatment, which may include medication, psychological counseling or therapy, and education and support groups.¹ The aim of initial treatment is to balance moods immediately, and once symptoms are stabilized, maintenance therapy is

used to manage bipolar disorder on a long-term basis. Failure to adhere to maintenance treatment increases the risk for relapse and the escalation of minor mood changes into full-blown episodes of mania or depression.¹ Early diagnosis and management may help to improve outcomes for patients and to reduce associated health-care costs.

Medications used to treat bipolar disorder include lithium, anticonvulsants, antipsychotics, antidepressants, benzodiazepines, and a combination of olanzapine and fluoxetine. These agents have class-specific adverse effects. Finding an appropriate treatment for an individual patient generally involves a trial-and-error approach and an adjustment to a new medication. In addition, some medications can take weeks or even months to manifest the full therapeutic effect.¹

“Patients with bipolar disorder spend the majority of their symptomatic time in the depressed phase of the illness. This phase most commonly results in impaired function, a remarkable decrease in quality of life and may lead to increased risk for attempted suicide,” said Joseph Calabrese, MD, Professor of Psychiatry and Director of the Mood Disorders Program, University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, OH. “Unfortunately, there are very few treatments specifically approved to treat the symptoms of bipolar depression, which represents a very large unmet medical need for patients and their families.”

A New Atypical Antipsychotic Agent for the Treatment of Bipolar Depression

In June 2013, lurasidone hydrochloride (HCl; Latuda; Sunovion Pharmaceuticals), an oral atypical antipsychotic, was approved by the US Food and Drug Administration (FDA) for 2 new indications—as monotherapy, and as adjunctive therapy with lithium or with valproate for the treatment of adult patients with major depressive episodes associated with bipolar I disorder (bipolar depression). Latuda was previously approved by the FDA in 2010 for the treatment of patients with schizophrenia.⁸

Table 1

Lurasidone HCl Monotherapy: Primary Efficacy Results for Studies in Depressive Episodes Associated with Bipolar I Disorder (MADRS Scores)

Treatment group	Primary efficacy measure: MADRS		
	Mean baseline score (SD)	LS mean change from baseline (SE)	Placebo-subtracted difference ^a (95% CI)
Lurasidone HCl (20-60 mg daily) ^b	30.3 (5)	-15.4 (0.8)	-4.6 (-6.9 to -2.3)
Lurasidone HCl (80-120 mg daily)	30.6 (4.9)	-15.4 (0.8)	-4.6 (-6.9 to -2.3)
Placebo	30.5 (5)	-10.7 (0.8)	—

^aDifference (drug minus placebo) in LS mean change from baseline.
^bTreatment group significantly superior to placebo.
 NOTE: Bipolar I disorder is also referred to as bipolar depression.
 CI indicates confidence interval, unadjusted for multiple comparisons; HCl, hydrochloride; LS, least-squares; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation; SE, standard error.
 Source: Latuda (lurasidone hydrochloride) tablets prescribing information; 2013.

The approval of lurasidone HCl was supported by 2 clinical trials, one that evaluated its efficacy as monotherapy, and another that evaluated its efficacy as adjunctive therapy in adults with depressive episodes associated with bipolar depression.^{8,9}

Mechanism of Action

The mechanism of action of lurasidone HCl for the treatment of bipolar depression and schizophrenia is unknown. Its efficacy may be mediated through a combination of central dopamine D₂ and serotonin type 2 (5-HT_{2A}) receptor antagonism. Lurasidone HCl is an antagonist with high affinity binding at the D₂ receptors and the 5-HT serotonin receptors 5-HT_{2A} and 5-HT₇ receptors.⁸

In short-term, placebo-controlled trials of patients with bipolar depression and schizophrenia, no postbaseline QT prolongations exceeding 500 msec were reported in patients treated with lurasidone HCl or placebo.⁸

Dosing

For the treatment of bipolar depression, the recommended starting oral dose of lurasidone HCl as monotherapy or as adjunctive therapy with either lithium or valproate is 20 mg daily, with no dose titration required; the recommended dose for lurasidone HCl is 20 mg daily to 120 mg daily.⁸ The maximum recommended dose of lurasidone HCl, as monotherapy or as adjunctive therapy with lithium or valproate, is 120 mg daily. Lurasidone HCl should be taken with food (at least 350 calories): adminis-

tration with food substantially increases the absorption of lurasidone HCl. Lurasidone HCl is available as tablets in 20-mg, 40-mg, 60-mg, 80-mg, and 120-mg strengths.⁸

In patients with moderate and severe renal impairment, the recommended starting dose of lurasidone HCl is 20 mg daily, and the maximum recommended dose is 80 mg daily. In patients with moderate and severe hepatic impairment, the recommended starting dose is 20 mg daily. The maximum recommended dose is 80 mg daily for patients with moderate hepatic impairment and 40 mg daily for patients with severe hepatic impairment.⁸

With the concomitant use of a moderate cytochrome (CY) P3A4 inhibitor (eg, diltiazem), the dose of lurasidone HCl should be reduced to half of the original dose level. The recommended starting dose is 20 mg daily, and the maximum recommended dose is 80 mg daily.

With the concomitant use of a moderate CYP3A4 inducer, it may be necessary to increase the dose of lurasidone HCl.

Lurasidone HCl should not be used concomitantly with a strong CYP3A4 inducer (eg, rifampin, avasimibe, St John's wort, phenytoin, carbamazepine). Grapefruit and grapefruit juice should be avoided by patients taking lurasidone HCl, because the juice may inhibit the CYP3A4 enzyme and alter the concentrations of lurasidone HCl.⁸

Clinical Studies

Lurasidone HCl as Monotherapy

The efficacy of lurasidone HCl as monotherapy was demonstrated in a 6-week, randomized, double-blind, placebo-controlled trial of 485 adult patients who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* criteria for major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features.⁸ These patients ranged in age from 18 to 74 years, with a mean age of 41.5 years. The patients were randomized to receive 1 of 2 flexible-dose ranges of lurasidone HCl (20-60 mg daily or 80-120 mg daily) or to placebo.⁸

The Montgomery-Åsberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with total scores ranging from 1 (no depressive features) to 60 (maximum score), was used as the primary rating instrument to measure depressive symptoms in this study. The primary end point was the change from baseline in MADRS score at week 6. The Clinical Global Impression-Bipolar-Severity of Illness scale (CGI-BP-S), a clinician-rated scale that measures the patient's current illness state on a 7-point scale, with a higher score associated with greater illness severity, served as the secondary rating instrument.⁸

Based on this clinical trial, lurasidone HCl was found to be superior to placebo for the low-dose range

(20-60 mg daily) and the high-dose range (80-120 mg daily) in reducing the MADRS and CGI-BP-S scores at week 6 (Table 1). The high-dose range did not show additional efficacy, on average, compared with the low-dose range.⁸

Lurasidone HCl as Adjunctive Therapy with Lithium or Valproate

The efficacy of lurasidone HCl as an adjunctive therapy with lithium or valproate was demonstrated in a 6-week, randomized, double-blind, placebo-controlled trial of 340 adult patients who met the DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder, with or without rapid cycling, and without psychotic features. These patients ranged in age from 18 to 72 years, with a mean age of 41.7 years. Patients who remained symptomatic after treatment with lithium or valproate were randomized to receive lurasidone HCl at flexible doses of 20 mg to 120 mg daily, or to placebo.⁸

To assess depressive symptoms in this study, the MADRS was used as the primary rating instrument. The primary end point was the change from baseline in MADRS score at week 6. The key secondary instrument was the CGI-BP-S scale. In this study, lurasidone HCl as an adjunctive therapy with lithium or valproate was superior to placebo at reducing MADRS and CGI-BP-S scores at week 6 (Table 2).⁸

Safety

The most frequently observed adverse reactions (incidence $\geq 5\%$ and at least twice the rate for placebo) associated with the use of lurasidone HCl as monotherapy for bipolar depression (daily doses ranging from 20-120 mg) reported in clinical trials were akathisia, extrapyramidal symptoms (ie, bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, Parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus), somnolence, nausea, vomiting, diarrhea, and anxiety.

At daily doses ranging from 20 mg to 120 mg as adjunctive therapy with lithium or valproate for bipolar depression, the most frequent adverse reactions (incidence $\geq 5\%$ and at least twice the rate of placebo) were akathisia and somnolence.⁸

Contraindications

Lurasidone HCl is contraindicated in patients with a known hypersensitivity to lurasidone HCl or any components in the formulation. Other contraindications for lurasidone HCl include concomitant use with a strong CYP3A4 inhibitor (eg, ketoconazole) or a strong CYP3A4 inducer (eg, rifampin).⁸

Table 2 Lurasidone HCl Adjunctive Therapy with Lithium or Valproate: Primary Efficacy Results for Studies in Depressive Episodes Associated with Bipolar I Disorder (MADRS Scores)

Treatment group	Primary efficacy measure: MADRS		
	Mean baseline score (SD)	LS mean change from baseline (SE)	Placebo-subtracted difference ^a (95% CI)
Lurasidone HCl (20-120 mg daily) ^b + lithium or valproate	30.6 (5.3)	-17.1 (0.9)	-3.6 (-6 to -1.1)
Placebo + lithium or valproate	30.8 (4.8)	-13.5 (0.9)	—

^aDifference (drug minus placebo) in LS mean change from baseline.

^bTreatment group statistically significantly superior to placebo.

NOTE: Bipolar I disorder is also referred to as bipolar depression.

CI indicates confidence interval, unadjusted for multiple comparisons; HCl, hydrochloride; LS, least-squares; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation; SE, standard error.

Source: Latuda (lurasidone hydrochloride) tablets prescribing information; 2013.

Warnings and Precautions

Boxed warning. The prescribing information for lurasidone HCl includes a boxed warning stating that elderly patients with dementia-related psychosis who are treated with antipsychotic drugs have an increased risk of death. Lurasidone HCl is not approved for the treatment of patients with dementia-related psychosis. The boxed warning also states that there is an increased risk of suicidal thinking and suicidal behavior in children, adolescents, and young adults taking antidepressants, and patients should be monitored for worsening and emergence of suicidal thoughts and behaviors when taking lurasidone HCl.⁸

Neuroleptic malignant syndrome (NMS). NMS is a potentially fatal symptom complex that has been reported with the use of antipsychotic drugs, including lurasidone HCl. The management of NMS should include immediate discontinuation of lurasidone HCl or other antipsychotic drugs not essential to concurrent therapy. Patients should be monitored carefully.⁸

Tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient taking lurasidone HCl, drug discontinuation should be considered if clinically appropriate. However, some patients may require treatment with lurasidone HCl despite the presence of tardive dyskinesia.

Metabolic changes. Atypical antipsychotic drugs have been associated with metabolic changes, including hyperglycemia, dyslipidemia, and weight gain, that may increase cardiovascular and cerebrovascular risk. Pa-

tients should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. Glucose should be monitored regularly in patients with diabetes or who are at risk for diabetes. Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Weight gain has been observed with the use of atypical antipsychotics. The clinical monitoring of weight is recommended.

Hyperprolactinemia. Prolactin elevations may occur with use of lurasidone HCl and other dopamine D₂ receptor antagonists.

Leukopenia, neutropenia, and agranulocytosis. Complete blood counts should be performed in patients with a preexisting low white blood cell count or a history of leukopenia or neutropenia. If a clinically significant decline in white blood cells occurs in the absence of other causative factors, the discontinuation of lurasidone HCl should be considered.

The approval of lurasidone HCl for bipolar depression adds a new treatment option for patients suffering from this serious illness.

Orthostatic hypotension and syncope. Dizziness, tachycardia or bradycardia, and syncope may occur with the use of lurasidone HCl, especially early in treatment. In patients with known cardiovascular or cerebrovascular disease, and in antipsychotic-naïve patients, a lower starting dose and slower titration should be considered.⁸

Use in Specific Populations

Pregnancy. Lurasidone HCl should only be used during pregnancy if the potential benefit justifies the potential risk.⁸

Nursing mothers. Lurasidone HCl should be discontinued by nursing mothers or nursing should be discontinued while taking lurasidone HCl. The risk of drug discontinuation to the mother should be considered.⁸

Conclusion

Bipolar depression is a lifelong illness associated with serious morbidity and a heavy economic toll. In June 2013, the FDA approved 2 new indications for the oral atypical antipsychotic lurasidone HCl for the treatment of depressive episodes associated with bipolar depression; the drug was approved as monotherapy, and as adjunctive therapy with lithium or valproate. Previously, this drug was approved by the FDA for the treatment of schizophrenia in 2010. The approval of lurasidone HCl for bipolar depression adds a new treatment option for patients suffering from this serious illness.

In 2 trials, lurasidone HCl demonstrated significant improvements in depressive symptoms after 6 weeks compared with placebo, as monotherapy, and as adjunctive therapy with lithium or valproate, in patients with depressive episodes associated with bipolar depression.

In clinical trials of patients with bipolar depression, the most common adverse reactions in patients receiving lurasidone HCl as monotherapy were akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety. In patients receiving lurasidone HCl as adjunctive therapy with lithium or valproate, the most common adverse reactions were akathisia and somnolence. ■

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