Current PSYCHIATRY

Lurasidone for schizophrenia

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In October 2010, the FDA approved lurasidone for the acute treatment of schizophrenia at a dose of 40 or 80 mg/d administered once daily with food (***Table 1***).

A new atypical antipsychotic offers once-daily dosing and is well tolerated and considered weight neutral

Table 1

Lurasidone: Fast facts

Brand name: Latuda
Indication: Schizophrenia in adults
Approval date: October 28, 2010
Availability date: February 2011
Manufacturer: Sunovion Pharmaceuticals, Inc.
Dosing forms: 40 mg and 80 mg tablets
Recommended dosage: Starting dose: 40 mg/d. Maximum dose: 80 mg/d

How it works

Although the drug's exact mechanism of action is not known, it is thought that lurasidone's antipsychotic properties are related to its antagonism at serotonin 2A (5-HT2A) and dopamine D2 receptors.[1]

Similar to most other atypical antipsychotics, lurasidone has high binding affinity for 5-HT2A and D2. Lurasidone has also high binding affinity for 5-HT7, 5-HT1A, and α2C-adrenergic receptors, low affinity for α-1 receptors, and virtually no affinity for H1 and M1 receptors (***Table 2, page 68***). Activity on 5-HT7, 5-HT1A, and α2C-adrenergic receptors is believed to enhance cognition, and 5-HT7 is being studied for a potential role in mood regulation and sensory processing.[2,3] Lurasidone's low activity on α-1, H1, and M1 receptors suggests a low risk of orthostatic hypotension, H1-mediated sedation and weight gain, and H1- and M1-mediated cognitive blunting.

Pharmacokinetics

Lurasidone is absorbed in the gastrointestinal tract. It reaches maximum concentration (Cmax) in 1 to 3 hours. Cmax doubles when lurasidone is administered with food (≥350 calories), but absorption is independent of the meal's fat content.[4] After absorption, the drug is highly bound (99%) to serum proteins (albumin and α-1-glycoprotein). The elimination half-life is 18 hours and steady-state concentration is reached within 7 days.[1] Lurasidone is eliminated predominantly through cytochrome P450 (CYP) 3A4 metabolism in the liver.

Efficacy

Lurasidone's efficacy for treatment of acute schizophrenia was established in four 6-week, randomized placebo-controlled clinical trials.[1] The patients were adults (mean age: 38.8; range: 18 to 72) who met DSM-IV-TR criteria for schizophrenia, didn't abuse drugs or alcohol, and had not taken any investigational drug for ≥1 month. Symptoms were measured on the Positive and Negative Syndrome Scale (PANSS); Brief Psychiatric Rating Scale as derived from the PANSS (BPRSd); and the Clinical Global Impressions-Severity scale (CGI-S).

In the first clinical trial, 145 patients were randomized to lurasidone, 40 mg/d or 120 mg/d, or placebo. Treatment with

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Table 2

Lurasidone receptor binding profile and receptor-related effects

	Ki (nM)*	Effects associated with activity on the receptor
D2	0.994	Antipsychotic effects. Akathisia (15%), parkinsonism (11%), dystonia (5%), hyperprolactinemia (8.3% for women, 1.9% for men)
5-HT2A	0.47	Antipsychotic effects. Improves extrapyramidal symptoms
5-HT7	0.495	Antipsychotic effects. Improves cognition, mood
5-HT1A	6.38	Improves cognition, mood. Nausea (12%), vomiting (8%)
α-1	48	Orthostatic hypotension (5%), sedation (22%)
α-2C	10.8	Improves cognition
H1	>1000	No significant adverse effects mediated through H1 receptor because of low binding affinity
M1	>1000	No significant adverse effects mediated through M1 receptor because of low binding affinity

*Ki dissociation constant; the lower the number, the higher affinity of the compound for the receptor

Source: Adapted from reference 1, expert opinion, and lurasidone data on file, 2008

Clinical Point

Lurasidone appears to have a rapid onset of action and provides sustained improvement of symptoms

either dose of lurasidone was superior to treatment with placebo on the BPRSd (Least Squares Mean [LSM] difference from placebo in change from baseline: -5.6 on lurasidone 40 mg/d, -6.7 on lurasidone 120 mg/d) and CGI-S.[1,5]

The second trial randomized 180 patients to lurasidone, 80 mg/d, or placebo. Lurasidone, 80 mg/d, was superior to placebo as measured on the BPRSd (LSM difference

from placebo in change from baseline: -4.7 on lurasidone 80 mg/d) and CGI-S.[1,6]

The third trial randomized 489 patients to lurasidone, 40 mg/d, 80 mg/d, 120 mg/d, or placebo. All lurasidone arms were superior to placebo on PANSS (LSM difference from placebo in change from baseline: -2.1 on 40 mg/d, -6.4 on 80 mg/d, and -3.5 on 120 mg/d) and CGI-S scores. This study also showed that lurasidone appears to have a rapid onset of action (day 3 to 4) and provides sustained improvement of symptoms.[1]

In the fourth trial, 473 individuals were randomized to lurasidone, 40 mg/d or 120 mg/d, olanzapine, 15 mg/d, or placebo. Olanzapine and both dosages of lurasidone were superior to placebo in improving PANSS scores (LSM difference from placebo in change from baseline: -9.7 on lurasidone 40 mg/d, -7.5 on lurasidone 120 mg/d, and -12.6 on olanzapine 15 mg/d) and CGI-S.[1,7] Both doses of lurasidone were not superior to olanzapine but had less negative impact on lipid profile, weight gain, and glycemia.

Tolerability

Tolerability information is extracted from a clinical study database consisting of 2,096 patients with schizophrenia who participated in premarketing clinical trials and were exposed to single or multiple doses of lurasidone, 20 mg, 40 mg, 80 mg, or 120 mg.[1] Overall, lurasidone was well tolerated. The rate of discontinuation from clinical trials because of adverse effects was 9.4% for lurasidone vs 5.9% for placebo. Somnolence, akathisia, nausea, parkinsonism, and agitation were the most commonly reported adverse reactions; somnolence and akathisia appear dose-related. Other adverse effects associated with lurasidone were nausea, vomiting, dyspepsia, dystonia, dizziness, insomnia, agitation, and anxiety (***Table 2***).

Metabolic changes (hyperlipidemia, hyperglycemia, and increased body weight) associated with cardiovascular risk in patients treated with atypical antipsychotics were studied in short-term placebo-controlled trials. Lurasidone is considered to be weight-neutral and does not have significant effects on serum lipids or glucose.[2] As is the case with other D2 antagonists, lurasidone is associated with increased prolactin, which appears to be greater in females and is dose-dependent. Lurasidone is not associated with significant QTc prolongation, seizures, transaminases increase, or changes in serum chemistry, hematology, or urinalysis.

Contraindications

Lurasidone is contraindicated in patients with known sensitivity to lurasidone hydrochloride. Because of the risk for pharmacokinetic drug-drug interactions, lurasidone is contraindicated for patients who are taking strong CYP3A4 inhibitors (eg, ketoconazole) or inducers (eg, rifampin).

Similar to other medications in its class, lurasidone carries a "black-box" warning of

Related Resource

- Citrome L. Lurasidone for schizophrenia: a review of the efficacy and safety profile for this newly approved second-generation antipsychotic. Int J Clin Pract. 2010 Epub ahead of print.

Drug Brand Names

Ketoconazole • Nizoral
Lurasidone • Latuda
Olanzapine • Zyprexa
Rifampin • Rifadin

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

Lurasidone is associated with increased prolactin, which appears to be dose-dependent

Bottom Line

Lurasidone, 40 mg/d or 80 mg/d, provides control of psychotic symptoms in patients with acute schizophrenia and appears to have a metabolically neutral profile. The drug does not require initial dose titration and should be given with food that provides ≥350 calories to improve medication absorption.

increased mortality in elderly patients with dementia-related psychosis and it is not FDA-approved for treating this condition. Animal teratogenicity studies using lurasidone, 25 mg/kg/d and 50 mg/kg/d, did not show adverse effects during organogenesis, and lurasidone is classified as pregnancy category B (animal studies failed to demonstrate risk to the fetus and there are no adequate and well-controlled studies in pregnant women, or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester). The use of lurasidone in geriatric and pediatric populations was not studied.[1]

Clinical Point

Lurasidone does not require initial dose titration and should be given with food to improve medication absorption

Dosing

Lurasidone is manufactured as 40 mg and 80 mg tablets. The recommended starting dose is 40 mg/d and the maximum recommended dose is 80 mg/d.[1] In clinical trials, lurasidone, 120 mg/d, was associated with increased incidence of adverse effects without added benefit.

Lurasidone doesn't require initial dose titration and should be given with food that provides ≥350 calories to improve medication absorption. Dose adjustment is recommended for use in patients with moderate or severe renal or hepatic impairment and when coadministered with CYP3A4 moderate inhibitors; the dose in these patients should not exceed 40 mg/d.

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