

## Lurasidone

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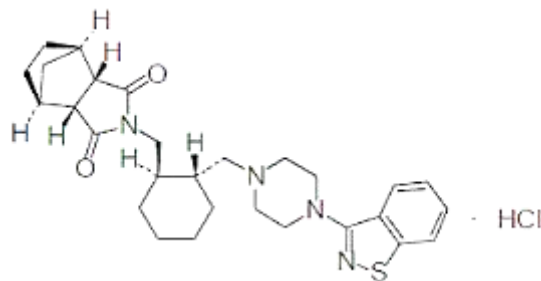
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**Composition:** Lurasidone Hydrochloride

**Strengths:** 20 mg, 40 mg, 60 mg, 80 mg and 120 mg film-coated tablets.



### Class

Lurasidone is a benzisothiazol derivative second-generation antipsychotic and has a complex multi-ring structure that is minimally soluble in water. Chemically, it is structurally related to perospirone and ziprasidone and other benzisothiazoles including the benzisoxazole derivatives risperidone, its active metabolite paliperidone, and iloperidone.

### Pharmacodynamic properties

Lurasidone is antagonist at following receptors: D<sub>2</sub>, 5HT<sub>7</sub> and 5HT<sub>2A</sub>. It is a partial agonist at 5HT<sub>1A</sub> receptor but this effect is only 33% that of serotonin. In comparison to other atypical antipsychotics it has the highest affinity for the 5-HT<sub>7</sub> receptor and its potent 5-HT<sub>7</sub> receptor antagonism, might be beneficial for mood and cognition. Also the lack of affinity for the dopamine D<sub>1</sub> and D<sub>4</sub> receptor might also contribute to its cognitive enhancing effect. It has moderate affinity for α<sub>2C</sub>-adrenergic receptors and low affinity for α<sub>1</sub>-adrenergic receptors so less chances of orthostatic hypotension. It has minimal affinity for 5-HT<sub>2C</sub> receptors and it has negligible affinity for histamine H<sub>1</sub> and muscarinic receptors, which are linked to sedation and weight gain and have negative cognitive effects.

### Other effects

It is known to cause weight gain and increase plasma glucose levels but is much less compared to other atypical antipsychotics. The levels of total cholesterol and triglycerides level dropped in patients taking lurasidone. Prolactin levels also rises with lurasidone but this effect is dose related and gender based. It has no effect on ECG QTc interval and increase in suicidal behaviours.

### Pharmacokinetic properties

It is rapidly absorbed in the stomach and reaches peak concentrations within 1.5–3 hours (T<sub>max</sub>) after single and multiple oral doses. It is more effectively absorbed when taken with food and a meal of approximately 350 calories maximizes and stabilizes absorption of the drug. No alteration is observed with the fat content of the meal. It is highly plasma protein bound (99.8% is bound to albumin and  $\alpha$ -1-glycoprotein). It is metabolized predominantly by the cytochrome P450 isozyme 3A4 and broken down by oxidative N-dealkylation, hydroxylation of norbornane ring, and S-oxidation. There are two nonmajor, active metabolites (ID-14283 and ID-14326), two major, nonactive metabolites (ID-20219 and ID-20220), and a non major, non active metabolite (ID-11614). The half-life of lurasidone is 18 hours for a 40 mg oral dose, so it can be taken once daily. Steady state is achieved within 5 to 7 days. The mean terminal half-life at steady state in patients with schizophrenia ranges 28.8 and 37.4 hours. The majority of the metabolic remnants of lurasidone end up in the feces (80%), with a small fraction in the urine (9%). Smoking is not expected to have an effect on lurasidone pharmacokinetics as it is not a substrate for CYP1A2.

### Tolerability

The most common adverse effects with Lurasidone compared with placebo are –

- 1) Nausea (16.7% vs 3.3%)
- 2) Vomiting (11.1% vs 5.6%)
- 3) Dyspepsia (11.1% vs 3.3%)
- 4) Somnolence (11.1% vs 3.3%)
- 5) Constipation (11.1% vs 5.6%)
- 6) Sedation (10.0% vs 4.4%)
- 7) Insomnia (10.0% vs 3.3%)
- 8) Akathisia (8.9% vs 3.3%)
- 9) Anxiety (6.7% vs 1.1%)

Other side effects include tremor, headache, dry mouth and diarrhoea. Rare side effects are orthostatic hypotension and seizures in predisposed cases.

### Indications

It is indicated for the treatment of –

- 1) Acute schizophrenia;
- 2) Acute mania;
- 3) Bipolar depression;
- 4) Cognitive dysfunction with schizophrenia;
- 5) Sleep problems related with psychosis and depression;
- 6) Treatment resistant depression;
- 7) Behavioural disturbances in children and adolescents;
- 8) Behavioural disturbances in dementia.

It is US Food and Drug Administration for the acute treatment of adults with schizophrenia (October 2010) and bipolar 1 depression (June 2013). There is evidence of increased mortality in elderly patients with dementia related psychosis with use of lurasidone (4.5% vs 2.6% in placebo), so needs to be used carefully.

### **Contradictions**

It is contraindicated in any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone. It is contraindicated with strong CYP3A4 inhibitors (e.g., ketoconazole) and strong CYP3A4 inducers (e.g., rifampin).

### **Pregnancy and lactation**

No adequate data is available.

### **Dosage and administration**

Usual dose range is 40-80mg/day. Also, lurasidone dose should not exceed 40 mg/d when coadministered with a moderate CYP3A4 inhibitor such as diltiazem. In patients with renal impairment start with 20mg/day and maximum upto 80mg/day for creatinine clearance of <50mg/min. For hepatic impairment patients with a Child-Pugh Class B, starting dose is 20 mg/day with a maximum dose of 80 mg/day; Child-Pugh Class C patients should start at 20 mg/day with a maximum dose of 40 mg/day. Dosing of lurasidone need not be modified for elderly patients with psychosis (ages 65–85 years).

### **Suggested References and Further Reading**

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Conflict of Interest - Nil