

Lurasidone: A New Antipsychotic For Schizophrenia

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Objectives

- Review the pharmacology and the pharmacokinetics
- Identify the indications, dosing, and administration
- Assess the safety
- Examine recent changes to package insert

Introduction

- New second-generation atypical antipsychotic
- Approved by the FDA in October 2010
- No conflicts of interest to report

Pharmacology/Pharmacokinetics

Mechanism of Action

- Exact mechanism of action is unknown
- Antagonistic effects on dopamine (D_2) and serotonin ($5HT_{2a}$) receptors
- Greater affinity for:
 - $5HT_7$
 - $5HT_{1a}$
 - Alpha_{2c}-adrenergic
- Highest affinity for the $5HT_7$ receptor subtype than any other medication in its class

Latuda (lurasidone HCL) [package insert] Updated April, 2012.
Meyer JM Expert Opin Investig Drugs 2009.
Ishibashi T, JPET 2010.

Mechanism of Action

- Low affinity:
 - Alpha₁-adrenergic receptors
- Almost no affinity for:
 - Histamine H_1 receptors
 - Muscarinic M_1 receptors
- Suggesting a reduced potential for:
 - Orthostasis
 - Weight gain
 - Sedation

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Other Effects?

- Cognitive Effects
 - 5HT₇
 - 5HT_{1a}
 - Alpha_{2c}
- Antidepressant and Anxiolytic Effects
 - 5HT₇
 - 5HT_{1a}
- Sleep
 - 5HT₇

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Ishibashi T. JET 2010.

Pharmacokinetic Properties

- Peak concentrations (T_{max}) in 1-3 hours
- t_{1/2} about 18 hours
- Highly plasma protein bound (99.8%)
- Metabolized mainly in the liver by CYP3A4
- ID-14283:
 - Main active metabolite
 - Comparable pharmacological profile
 - Shorter life (7.48-10 hours) than lurasidone

Latuda (lurasidone HCL) [package insert] Updated April, 2012.

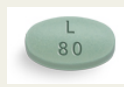
Indications & Dosing/Administration



20 mg



40 mg



80 mg

FDA-Approved Indications

- Treatment of patients with acute schizophrenia
- Efficacy has not been established in controlled studies for more than 6 weeks
- Should periodically re-evaluate the long-term usefulness of the drug for the individual patient

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Potential Off-Label Uses

- Schizoaffective disorder
- Bipolar disorder
- Chronic maintenance treatment of schizophrenia
- Currently being evaluated for the use in bipolar depression
 - PREVAIL 1, 2, 3
 - Monotherapy, add-on therapy, and prophylaxis

Samalin L. Therapeutics and Clinical Risk Management 2011.

Dosing

- Starting dose = 40 mg/daily
- Dosage range = 40 mg/day-160 mg/day
- Moderate and severe renal impairment should not exceed 80 mg/day
- Hepatic impairment:
 - Moderate – should not exceed 80 mg/day
 - Severe – should not exceed 40 mg/day

Latuda (lurasidone HCL) [package insert] Updated April, 2012.

Administration

- Absorption estimated at 9-19%
 - Dose-dependent
- A meal over 350 calories will:
 - Increase the mean C_{max} about 3-times
 - Increase AUC about 2-times
- Important to provide patient counseling

Latuda (lurasidone HCL) [package insert] Updated April, 2012.

Safety

Adverse Effects

- Commonly Observed Adverse Reactions
 - Somnolence
 - Akathisia
 - Nausea
 - Parkinsonism

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EPS

Adverse Event Term	Percentage of EPS Compared to Placebo					
	placebo (%) N = 709	lurasidone 20mg/day (%) N = 71	lurasidone 40mg/day (%) N = 487	lurasidone 80mg/day (%) N = 538	lurasidone 120mg/day (%) N = 291	lurasidone 160mg/day (%) N = 121
All EPS events	9	10	21	23	39	20
All EPS events, excluding akathisia/restlessness	7	6	14	13	24	14
Akathisia	3	6	11	12	22	7
Dystonia	<1	0	4	5	7	2
Parkinsonism	5	6	9	8	17	11
Restlessness	1	1	3	1	3	2

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Weight Changes Vs. Placebo

- Mean change in weight (kg) from baseline:
 - Placebo = - 0.02 kg
 - Lurasidone:
 - 20 mg/day = - 0.15 kg
 - 40 mg/day = 0.22 kg (~ 0.5 lbs)
 - 80 mg/day = 0.54 kg (~1.2 lbs)
 - 120 mg/day = 0.68 kg (~1.5 lbs)
 - 160 mg/day = 0.60 kg (~1.3 lbs)

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Lipid Changes Vs. Placebo

Mean change from baseline (mg/dL):

Total Cholesterol

- Placebo = - 5.8
- Lurasidone:
 - 20 mg/day = - 12.3
 - 40 mg/day = - 5.7
 - 80 mg/day = - 6.2
 - 120 mg/day = - 3.8
 - 160 mg/day = - 6.9

Triglycerides

- Placebo = - 13.4
- Lurasidone:
 - 20 mg/day = - 29.1
 - 40 mg/day = - 5.1
 - 80 mg/day = - 13.0
 - 120 mg/day = -3.1
 - 160 mg/day = - 10.6

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Glucose Changes Vs. Placebo

- Mean change from baseline (mg/dL):
 - Placebo = 0
 - Lurasidone:
 - 20 mg/day = - 0.6
 - 40 mg/day = 2.6
 - 80 mg/day = - 0.4
 - 120 mg/day = 2.5
 - 160 mg/day = 2.5

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QTc prolongation

- No post-baseline QTc prolongations exceeding 500 msec were reported
- No cases of torsade de pointes
- QTc prolongation evaluated in a study
 - 87 clinically stable patients
 - Patients treated with lurasidone 120mg, 600mg, or ziprasidone 160mg daily
 - No lurasidone treated patients experienced QTc increases greater than 60 msec from baseline.

Latuda (lurasidone HCL) [package insert] Updated April, 2012.

Drug Interactions

Coadministered Drug	Lurasidone dose	Effect on lurasidone C _{max}	Effect on lurasidone AUC	Recommendation
Ketoconazole (strong CYP3A4 inhibitor) 400mg/day x 5 days	10mg single dose	6.9-times lurasidone alone	9-times lurasidone alone	Should not be coadministered with lurasidone
Diltiazem (moderate CYP3A4 inhibitor) 240mg/day x 5 days	20mg single dose	2.1-times lurasidone alone	2.2-times lurasidone alone	Lurasidone dose should not exceed 80 mg/day if coadministered
Rifampin (strong CYP3A4 inducer) 600mg/day x 8 days	40mg single dose	1/7 th of lurasidone alone	1/5 th of lurasidone alone	Should not be coadministered with lurasidone
Lithium 600mg BID x 8 days	120mg/day x 8 days	0.9-times lurasidone alone	1.1-times lurasidone alone	No dose adjustment required

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Conclusions/Summary

- Potential Advantages:
 - Well tolerated and favorable metabolic profile
 - No signs of glucose elevation or lipid changes
 - Small increase in weight gain
 - Good cardiovascular tolerability
 - No hypotension
 - No widening the QT interval
 - Once daily dosing, no initial dose titration

Conclusions/Summary

- Potential Disadvantages :
 - Lacks long-term efficacy trials
 - Side effects
 - Dose dependent EPS
 - Cost of medication
 - \$18.46 a tablet
 - \$6,737.90 per year
 - Must be taken with a meal over 350 calories
 - No comparative studies

McKesson Online Ordering System. Accessed April 10, 2012.

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Question 1

- Lurasidone has higher affinity than any other medication in its class for what receptor subtype?

- A. M₁
- B. 5HT₇
- C. 5HT_{2a}
- D. H₁
- E.

- Answer: B

Question 2

- Lurasidone is currently marketed as 40, 80, and 120 mg strength tablets?

- A. True
- B. False

- Answer: B

Question 3

- Lurasidone is FDA-approved for what indication?

- A. Bipolar Mania
- B. Bipolar Depression
- C. Schizoaffective Disorder
- D. Acute Schizophrenia

- Answer: D

Question 4

- Lurasidone should be administered with a meal over 350 calories?

- A. True
- B. False

- Answer: A