Brand Name: Latuda®

Generic Name: Lurasidone

Manufacturer[1,2,3]: Sunovion Pharmaceuticals Inc.

Drug Class[1,2]: Atypical Antipsychotic

Uses:

Labeled Uses[1,2,3]: Treatment of schizophrenia
Unlabeled Uses: Not applicable

Mechanism of Action[1,2,3]:

The exact mechanism of action is unknown, but is thought to be mediated primarily through mixed serotonin-dopamine antagonism. Its effect on schizophrenia is believed to be the result of a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism. Lurasidone exhibits high affinity for D_2, 5-HT_{2A}, and 5-HT_7 receptors; moderate affinity for $alpha_{2C}$-adrenergic receptors; and is a partial agonist for 5-HT_{1A} receptors. The combined antagonism of serotonin and dopamine is thought to improve the negative symptoms of psychoses and reduce the incidence of extrapyramidal side effects in comparison to typical antipsychotics. Antipsychotics with a high affinity for serotonin receptors are thought to be more effective for treating the negative symptoms of schizophrenia than those with primarily dopaminergic modulation.

Pharmacokinetics[1,2,3]:

T_{max}	1 – 3 hours
V_d	6173 L
$t_{½}$	18 hours
Clearance	3902 mL/min
Protein binding	99%
Bioavailability	9 – 19%

Absorption: Steady-state concentrations are reached within 7 days. The mean C_{max} and AUC are approximately 3-times and 2-times higher, respectively, when taken with food.

Metabolism: Lurasidoneis primarily metabolized through hepatic CYP3A4. Main metabolic pathways include oxidative N-dealkylation, hydroxylation, and S-oxidation. There are two active metabolites and two major inactive metabolites.

Elimination: Following a single dose, total excretion in urine and in feces combined was approximately 89% (feces ~80%; urine ~9%).

Efficacy:

Meltzer HY, Cucchiaro J, Silva R, Ogasa M, Phillips D, Xu J, Kalali AH, Schweizer E, Pikalov A, Loebel A. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. *The American Journal of Psychiatry*.AJP in Advance.2011 June 15: 1-11.

Study Design: Prospective, randomized, multicenter, double-blind, parallel- and olanzapine controlled design study

Description of Study:*Methods:* 478 acutely ill schizophrenic patientsat 25 sites were randomly assigned to receive 6 weeks of double-blind treatment with once-daily doses of 40 mg or 120 mg of lurasidone, 15 mg of olanzapine or placebo.Efficacy was assessed using the PANSS total and subscale scores, the CGI-S, and the Montgomery-Åsberg Depression Rating Scale (MADRS). Safety evaluations included vital signs, weight, laboratory tests, 12-lead ECG, and reported adverse events.The primary efficacy measure was the change from baseline in PANSS total score at week 6, and the key secondary efficacy measure was the change from baseline in CGI-S score at week 6. *Outcome Results:*The change from baseline to week 6 in PANSS total score was significantly greater for the lurasidone 40 mg (-25.7; adjusted p=0.002), lurasidone 120 mg (–23.6; adjusted p=0.022), and the olanzapine group (-28.7, p<0.001) compared with the placebo group (–16.0). Treatment with both doses of lurasidone or with olanzapine was also associated with significantly greater improvement at week 6 on PANSS positive and negative subscale scores, and CGI-S score compared with placebo. The incidence of akathisia was higher with 120 mg of lurasidone (22.9%) than with 40 mg of lurasidone (11.8%), olanzapine (7.4%), or placebo (0.9%). The proportion of patients experiencing ≥7% weight gain was 5.9% for the lurasidone groups combined, 34.4% for the olanzapine group, and 7.0% for the placebo group.

Limitations: The validity of the modified PANSS cognitive subscale is not well established. There were multiple dropouts in the study. Standard Error (SE) was used to report variability. Many of the authors were employed by the manufacturer.

Conclusion: The study showed that lurasidone was an effective treatment for patients with acute schizophrenia, supported by significant improvements in PANSS total score and CGI score; lurasidone was not found to be superior to olanzapine and olanzapine had more defined responders on efficacy measures at Week 6. Safety assessments indicated a higher frequency of adverse events associated with 120 mg/day of lurasidone compared with 40 mg/day. These findings provide support for the daily dose range of 40 – 80 mg for lurasidone recommended by the U.S. FDA.

Nakamura M, Ogasa M, Guarino J, Phillips D, Severs J, Cucchiaro J, Loebel A. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *The Journal of Clinical Psychiatry*. 2009 June; 70(6): 829-36.

Study Design: Randomized, multicenter, double-blind, parallel-controlled group study design

Description of Study:*Methods:* 180 patients meeting study entry criteria were randomly assigned to six weeks of double-blind treatment 80 mg of lurasidone or placebo. The primary efficacy measure was the Brief Psychiatric Rating Scale derived from the Positive and Negative Syndrome Scale (BPRSd) extracted from the PANSS. Secondary efficacy measures included the PANSS total and positive, negative, general psycopathology, and cognitive subscales; the CGI-S; and the MADRS. *Outcome Results:* Significant improvements were seenwith lurasidone,

compared to placebo, on the BPRSd (Least Squares Mean (SE) Change = -8.9 (1.3) vs. -4.2 (1.4); p=0.0018). Improvements were seen with lurasidone on secondary efficacy measures as well, including the PANSS total score (-14.1 (2.1) vs. -5.5 (2.2); p=0.0040), PANSS positive symptoms (-4.3 (0.7) vs. -1.7 (0.7); p=0.0060), PANSS negative symptoms (-2.9 (0.5) vs. -1.3 (0.5); p=0.0250), PANSS general psychopathology (-7.0 (1.1) vs. -2.7 (1.2); p=0.0061), PANSS cognitive (-2.1 (0.4) vs. -0.5 (0.4); p=0.0015), CGI-S (-0.6 (0.1) vs. -0.2 (0.1); p=0.0072), and MADRS (-2.9 (0.8) vs. -0.1 (0.9); p=0.0187) subscales. Treatment was generally well tolerated and was not associated with adverse metabolic changes or ECG parameters. There were no clinically significant differences between lurasidone and placebo in objective measures of extrapyramidal symptoms.

Limitations: Standard Error (SE) was used to report variability. Many of the authors were employed by the manufacturer. Dose-response effects could not be evaluated due to the use of single fixed-dose. No comparator atypical antipsychotic was used, limiting efficacy and tolerability analyses. There was a relatively high discontinuation rate of 42%.

Conclusion: The results of this study suggest that lurasidone is a safe and effective treatment for patients with an acute exacerbation of schizophrenia.

Contraindications:

- **Hypersensitivity to lurasidone[1,2,3]:**Hypersensitivity to lurasidone or any other components of the commercial formulation. Angioedema has been observed with lurasidone use.

- **Potent CYP3A4 inhibitors and inducers[2,3]:** Concomitant use with strong inhibitors or inducers of CYP3A4; lurasidone is primarily metabolized via CYP3A4 and drug interactions have been observed.
    - Chloramphenicol, conivaptan, dalfopristin, delavirdine, indinavir, isoniazid, itraconazole, ketoconazole, metoclopramide, posaconazole, quinupristin, rifampin, ritonavir, telithromycin, tipranavir

- Concurrent use with dopamine or epinephrine as these drugs may enhance the hypotensive effect of lurasidone.

Precautions[1,2,3,4]:

- **Black Box Warning:**Elderly patients with dementia-related psychosis treated with antipsychotic drugsare at an increased risk of death

- **Cerebrovascular Adverse Reactions:**A higher risk of cerebrovascular incidents, including fatalities, has been reported with other atypical antipsychotics.

- **Neuroleptic Malignant Syndrome (NMS):** NMS is a rare but potentially fatal symptom complex associated with the use of antipsychotic drugs. NMS typically manifests as mental status changes, fever, muscle rigidity, and/or autonomic instability. If this reaction is suspected, lurasidone should be discontinued immediately.

- **Tardive Dyskinesia:** A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic medications; risk may be increased in elderly patients, particularly elderly women. Discontinuation of lurasidone should be considered if signs and symptoms appear.

- **Metabolic Changes:** Atypical antipsychotics have been associated with metabolic changes including hyperglycemia and weight gain.
  - **Hyperglycemia and Diabetes Mellitus:** Use with caution in patients with diabetes or other disorders of glucose regulation. Patients with established diabetes mellitus who are started on lurasidone should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.
  - **Weight Gain:** Significant weight gain has been observed with atypical antipsychotic treatment; clinical monitoring of weight is recommended.

- **Hyperprolactinemia:** Lurasidone can elevate prolactin levels due to central dopamine D_2 antagonism which may result in infertility or other endocrine abnormalities.

- **Blood Dyscrasias:** Leukopenia, neutropenia, and agranulocytosis (sometimes fatal) have been reported during treatment with antipsychotic agents. Patients with risk factors (pre-existing low WBC and/or history of drug-induced leukopenia/neutropenia) should have their CBC monitored frequently during the first few months of therapy. Lurasidone should be discontinued at the first sign of drop in WBC if it is likely not attributable to any other cause. Patients with clinically significant neutropenia should be closely monitored for fever and infection and treated promptly if signs and symptoms occur. Lurasidone should be discontinued in patients with severe neutropenia (ANC < 1000/mm^3).

- **Orthostatic Hypotension and Syncope:**Consider monitoring orthostatic vital signs in patients for whom hypotension is of concern. Counsel patients about measures to prevent orthostatic hypotension, such as rising slowly from a seated position. Consider dose reduction if hypotension occurs.

- **Seizures:**Use lurasidone cautiously in patients with seizures, a history of seizures, or with conditions that lower the seizure threshold.

- **Potential for Cognitive and Motor Impairment:**Like other antipsychotics, lurasidone has the potential to impair judgment, thinking, or motor skills. Caution patients about driving or operating heavy machinery until they know how lurasidone affects them.

- **Body Temperature Regulation:**Impaired core body temperature regulation may occur while being treated with lurasidone. Caution patients about strenuous exercise, heat exposure, dehydration, and concomitant medications possessing anticholinergic effects.

- **Suicide:**Patients, caregivers and families should be informed about the risks of antipsychotic drugs causing suicidal thoughts and behaviors. Any emergence or worsening of the signs and symptoms of depression, unusual mood or behavioral changes, emergence of suicidal thoughts,

behavior or thoughts about self-harm should be reported to the healthcare provider immediately.

- **Dysphagia:** Lurasidone should not be used in patients at risk for aspiration pneumonia because esophageal dysmotility and aspiration have been associated with antipsychotic therapy.

- **Parkinson's Disease:**Lurasidone should be avoided in patients with Parkinson's disease unless the benefit of therapy outweighs the risk of motor symptom exacerbation; antipsychotics can worsen the motor symptoms of Parkinson's disease.

- **Use in Patients with Concomitant Illnesses:** Data is limited regarding use of lurasidone in patients with certain concomitant illnesses; patients with a recent history of myocardial infarction or unstable heart disease were excluded from premarketing clinical studies.

- **Pregnancy:** Lurasidone is Pregnancy Category B and no teratogenic or adverse developmental effects were observed in animal studies. Neonates exposed to antipsychotic drugs during the third trimester may be at risk for extrapyramidal and/or withdrawal symptoms following delivery. There are no adequate and well-controlled studies of lurasidone in pregnant women. Women who become pregnant or intend to become pregnant should notify their physician.

- **Lactation:** It is unknown if lurasidone or its metabolites are excreted in human milk.

- **Pediatrics:** Safety and effectiveness in pediatric patients has not been established.

- **Geriatrics:** Clinical studies did not include sufficient numbers of elderly patients to determine a difference in response compared to younger adults. Elderly patients with psychosis (65 to 85) had similar serum concentrations to younger adults; therefore, no dosage adjustments are necessary.

- **Renal Impairment:** Lurasidone should not exceed 40 mg/day in patients with moderate and severe renal impairment (Cl_{Cr} ≥ 10 mL/min to < 50 mL/min).

- **Hepatic Impairment:** Lurasidone should not exceed 40 mg/day in patients with moderate and severe hepatic impairment (Child-Pugh Class B and C).

Adverse Effects[2]:

Occurring in > 10% of patients

Central Nervous System

Somnolence (dose-related: 19% to 23%)

Akathisia (dose-related: 11% to 15%)

Endocrine & Metabolic

Increased fasting glucose (10% to 14%)

Gastrointestinal

Nausea (12%)

Neuromuscular & Skeletal

Extrapyramidal symptoms (24% to 26%)

Parkinsonism (11%)

Occurring in > 1% to < 10% of patients

Cardiovascular

Tachycardia

Central Nervous System

Insomnia (8%)
Agitation (6%)
Anxiety (6%)
Dizziness (5%)
Dystonia (5%)
Fatigue (4%)
Restlessness (3%)

Dermatologic

Pruritus
Rash

Endocrine & Metabolic

Prolactin increased (≥5 x ULN: females: 8%; males: 2%)

Gastrointestinal

Dyspepsia (8%)
Vomiting (8%)
Weight gain (≥7% increase in baseline body weight: 6%)
Salivaryhypersecretion (2%)
Abdominal pain
Appetite decreased
Diarrhea

Neuromuscular & Skeletal

Back pain (4%)
CPK increased

Ocular

Blurred vision

Renal

Creatinine increased (3%)

Drug Interactions[1,2,3,4]:

- Lurasidone is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 enzymes, suggesting that an interaction with inhibitors or inducers of these enzymes is unlikely.

- The manufacturer recommends a maximum daily dose of 40 mg in patients concomitantly taking any of the following medications. If these agents are used, monitor the patient carefully for toxicity and efficacy.
    - Amiodarone, amprenavir, antiparkinsonian agents, aprepitant, atazanavir, bupropion, carbamazepine, clarithromycin, danazol, darunavir, dasatinib, deferasirox, diltiazem, dronedarone, efavirenz, erythromycin, ethanol, fosamprenavir, fosaprepitant, imatinib, lanreotide, lapatinib, lithium, mifepristone, nefazodone, nelfinavir, nilotinib, octreotide, quinine, radiopaque contrast agents, saquinavir, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), sodium phosphate

monobasic monohydrate, sodium phosphate dibasic anhydrous, tamoxifen, tocilizumab, troleandomycin, verapamil, voriconazole, zafirlukast

- Concomitant use of the following drugs may lead to an increased risk of lurasidone-related adverse reactions:
    - Aldesleukin,basiliximab, cimetidine, fluconazole, pantoprazole, ranolazine

- Concomitant use of the following drugs may lead to decreased plasma concentrations of lurasidone and therefore a decrease in its efficacy:
    - Aminoglutethimide, barbiturates, bexarotene, bosentan, carbamazepine, dexamethasone, Echinacea, ethotoin, etravirine, fosphenytoin, metyrapone, modafinil, nevirapine, oxcarbazepine, phenytoin, pioglitazone, primidone, rifabutin, St. John's Wort, topiramate

- Due to the CNS effects of lurasidone, caution should be used if lurasidone is given in combination with other centrally acting medications:
    - Acetylcholinesterase inhibitors, amphetamines, anxiolytics, barbiturates, benzodiazepines, buprenorphine, butorphanol, dronabinol, droperidol, hydroxyzine, hypnotics, methotrimeprazine, methylpheidate, nabilone, nalbuphine, opiate agonists, pentazocine, sedatives, tramadol
    - Patients should be advised to avoid ethanol consumption during treatment to avoid additive CNS depressant effects.

- Lurasidone may enhance the hypotensive effects of alpha blockers and other antihypertensive agents due to the antagonism of alpha-1 adrenergic receptors. If concurrent use is necessary, patients should be counseled on measures to prevent orthostatic hypotension. Close monitoring of blood pressure is recommended until the full effects of the combination therapy are known.

- Caution is recommended with the concurrent use of other drugs that can lower the seizure threshold.
    - Antipsychotics should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours post-procedure.
    - Sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous
    - Bupropion is associated with a dose-related risk of seizures. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this type of combination must be used; the patient should be closely monitored.

- Lurasidone may enhance the QTc-prolonging effect of quinidine and procainamide. Consider treatment alternatives in patients with acute lurasidone overdose. If treatment cannot be avoided, monitor for excessive QTc interval prolongation.

- Caution is recommended with the concurrent use of medications with anticholinergic activity, such as antimuscarinics, as this combination may contribute to heat-related disorders. Monitor patients for heat intolerance, decreased sweating, or increased body temperature.

- In general, antipsychotics can worsen the motor symptoms of Parkinson's disease thereby decreasing the overall effectiveness of antiparkinsonian agents. In addition, Parkinson's treatments like pramipexole, ropinirole, or tolcapone may cause drowsiness which can result in additive CNS effects with lurasidone. Therefore, lurasidone should be avoided in patients receiving medications for Parkinson's disease unless the benefit of lurasidone therapy outweighs the risk of decreased therapeutic response to levodopa or other treatments.

- Grapefruit and grapefruit juice may cause increased blood concentrations of lurasidone. It is advisable for patients to maintain consistency in their intake of grapefruit or grapefruit juice while taking lurasidone.

Dosing/Administration[1,2,3,4]:

- Recommended initial dose is 40 mg orally daily with food (at least 350 calories); initial dose titration is not required
- Maximum recommended dose is 80 mg orally daily.
- Dosage adjustment is recommended in patients with moderate and severe renal impairment (Cr_{Cl}greater than or equal to 10 mL/min to less than 50 mL/min) and inpatients with moderate and severe hepatic impairment (Child-Pugh class B and C). Lurasidone dosage should not exceed 40 mg/day.
- Dosage adjustments are not recommended on the basis of age, gender, and race.
- Safety and efficacy in neonates, infants, children, and adolescents have not been established.

Conclusion:

Lurasidone is an effective option in the treatment of schizophrenia. There is wide inter-patient variability in drug selection for atypical antipsychotics and patient-specific factors should always be taken into consideration.Advantages of lurasidone include: a low propensity for weight gain; dosing does not necessarily require titration; no concern about possible adverse effects of partial agonism of the dopamine D_2 receptor; and there is no effect on the QT interval (5, 6, 7). Potential disadvantages or reasons to avoid its use in certain patients include: the possibility of dose-related extrapyramidal symptoms and akathisia, dose-related somnolence, and cost (5, 6, 7). Another important consideration is that lurasidone must be taken with food (at least 350 calories) due to limitations in absorption.

Recommended References:

(1) Lurasidone. Clinical Pharmacology [Internet Database]. Elsevier / Gold Standard, Inc., 2011. Available at: http://www.clinicalpharmacology.com. Accessed: July 7, 2011.
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(4) Lurasidone. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colorado: Thomson Reuters(Healthcare) Inc. Updated periodically.
(5) Nakamura M, Ogasa M, Guarino J, Phillips D, Severs J, Cucchiaro J, Loebel A. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *The Journal of Clinical Psychiatry*. 2009 June; 70(6): 829 – 36.
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(7) Citrome L. Lurasidone for schizophrenia: a review of the efficacy and safety profile for this newly approved second-generation antipsychotic. *International Journal of Clinical Practice*. 2011 Feb; 65(2): 189 – 210.

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