PEROSPIRONE

**Brands** • Lullan  
*see index for additional brand names*

**Generic?** No

**Class**  
• Neuroscience-based Nomenclature: dopamine and serotonin receptor antagonist (DS-RAn)  
• Atypical antipsychotic (serotonin-dopamine antagonist, second generation antipsychotic)

**Commonly Prescribed for**  
(bold for FDA approved)  
• Schizophrenia (Japan)

**How the Drug Works**  
• Blocks dopamine 2 receptors, reducing positive symptoms of psychosis  
• Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms  
*Interactions at 5HT1A receptors may contribute to efficacy for cognitive and affective symptoms in some patients*

**How Long Until It Works**  
• Psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition and affective stabilization  
• Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients require up to 16–20 weeks to show a good response, especially on cognitive symptoms

**If It Works**  
• Most often reduces positive symptoms in schizophrenia but does not eliminate them  
• Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia  
• Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third  
• Perhaps 5–15% of schizophrenic patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year  
• Such patients are considered super-responders or “awakeners” since they may be well enough to be employed, live independently, and sustain long-term relationships  
• Continue treatment until reaching a plateau of improvement  
• After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis  
• For second and subsequent episodes of psychosis, treatment may need to be indefinite  
• Even for first episodes of psychosis, it may be preferable to continue treatment

**If It Doesn’t Work**  
• Consider trying one of the first-line atypical antipsychotics (e.g., risperidone, olanzapine, quetiapine, aripiprazole, paliperidone, asenapine, iloperidone, lurasidone)  
• If 2 or more antipsychotic monotherapies do not work, consider clozapine  
• If no first-line atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine  
• Some patients may require treatment with a conventional antipsychotic  
• Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection  
• Consider initiating rehabilitation and psychotherapy such as cognitive remediation  
• Consider presence of concomitant drug abuse

**Best Augmenting Combos**  
For Partial Response or Treatment Resistance

• Augmentation of perospirone has not been systematically studied  
• Addition of a benzodiazepine, especially short-term for agitation  
• Addition of a mood-stabilizing anticonvulsant such as valproate, carbamazepine, or lamotrigine may theoretically be helpful in both schizophrenia and bipolar mania  
• Augmentation with lithium in bipolar mania may be helpful
PEROSPIRONE (continued)

**Tests**
* Potential of weight gain, diabetes, and dyslipidemia associated with perospirone has not been systematically studied, but patients should be monitored the same as for other atypical antipsychotics

**Before starting an atypical antipsychotic**
* Weigh all patients and track BMI during treatment
  • Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
* Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
  • Determine if patient is
    • overweight (BMI 25.0–29.9)
    • obese (BMI ≥30)
    • has pre-diabetes (fasting plasma glucose 100–125 mg/dL)
    • has diabetes (fasting plasma glucose >126 mg/dL)
    • has hypertension (BP >140/90 mm Hg)
    • has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
  • Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

**Monitoring after starting an atypical antipsychotic**
* BMI monthly for 3 months, then quarterly
  • Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
* Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained >5% of initial weight
  • Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic
* Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness, and clouding of sensorium, even coma
  • Should check blood pressure in the elderly before starting and for the first few weeks of treatment
  • Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and perospirone should be discontinued at the first sign of decline of WBC in the absence of other causative factors

**SIDE EFFECTS**

**How Drug Causes Side Effects**
* By blocking dopamine 2 receptors in the striatum, it can cause motor side effects
  • By blocking dopamine 2 receptors in the pituitary, it can cause increased prolactin (unusual)
  • Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with some atypical antipsychotics is unknown
  • Receptor binding portfolio of perospirone is not well characterized

**Notable Side Effects**
* Extrapyramidal symptoms, akathisia
* Insomnia
  • Sedation, anxiety, weakness, headache, anorexia, constipation
  • Theoretically, tardive dyskinesia (should be reduced risk compared to conventional antipsychotics)
  • Elevated creatine phosphokinase levels

**Life-Threatening or Dangerous Side Effects**
* Rare neuroleptic malignant syndrome
  • Theoretically, seizures are rarely associated with atypical antipsychotics
  • Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis

**Weight Gain**
* Not well characterized
Sedation

- Occurs in significant minority

What to Do About Side Effects

- Wait
- Wait
- Wait
- For motor symptoms, add an anticholinergic agent
- Reduce the dose
- Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects

- Benztropine or trihexyphenidyl for motor side effects
- Sometimes amantadine can be helpful for motor side effects
- Benzodiazepines may be helpful for akathisia
- Many side effects cannot be improved with an augmenting agent

Long-Term Use

- Long-term studies not reported, but as for other atypical antipsychotics, long-term use for treatment of schizophrenia is common

Habit Forming

- No

How to Stop

- Slow down-titration (over 6–8 weeks), especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- Rapid discontinuation may lead to rebound psychosis and worsening of symptoms
- If antiparkinson agents are being used, they should be continued for a few weeks after perospirone is discontinued

Pharmacokinetics

- Metabolized primarily by CYP450 3A4
- No active metabolites

Drug Interactions

- Ketaconazole and possibly other CYP450 3A4 inhibitors such as nefazodone, fluvoxamine, and fluoxetine may increase plasma levels of perospirone
- Carbamazepine and possibly other inducers of CYP450 3A4 may decrease plasma levels of perospirone

Other Warnings/Precautions

- Not reported

Do Not Use

- If there is a proven allergy to perospirone

DOSING AND USE

Usual Dosage Range

- 8–48 mg/day in 3 divided doses

Dosage Forms

- Tablet 4 mg, 8 mg

How to Dose

- Begin at 4 mg 3 times a day, increasing as tolerated up to 16 mg 3 times a day

Dosing Tips

- Some patients have been treated with up to 96 mg/day in 3 divided doses
- Unknown whether dosing frequency can be reduced to once or twice daily, but by analogy with other agents in this class with half-lives shorter than 24 hours, this may be possible
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose

- Not reported

SPECIAL POPULATIONS

Renal Impairment

- Use with caution

Hepatic Impairment

- Use with caution

Cardiac Impairment

- Use with caution
PEROSPIRONE (continued)

Elderly
- Some patients may tolerate lower doses better
- Although atypical antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events

Potential Advantages
- In Japan, studies suggest efficacy for negative symptoms of schizophrenia

Potential Disadvantages
- Patients who have difficulty complying with three times daily administration

Primary Target Symptoms
- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Affective symptoms (depression, anxiety)
- Cognitive symptoms

Pearls
- Extrapyramidal symptoms may be more frequent than with some other atypical antipsychotics
- Potent 5HT1A binding properties may be helpful for improving cognitive symptoms of schizophrenia in long-term treatment
- Theoretically, should be effective in acute bipolar mania

Children and Adolescents
- Use with caution

Pregnancy
- There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
- Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary

Breast Feeding
- Unknown if perospirone is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk

Recommended either to discontinue drug or bottle feed
- Infants of women who choose to breast feed should be monitored for possible adverse effects

Suggested Reading