Approximately 80% of patients with schizophrenia relapse within 5 years\(^1\) despite the availability and increased use of second-generation antipsychotics. Long-acting depot formulations are a proven, effective treatment option for patients with schizophrenia. In October 2015, another long-acting injectable antipsychotic, aripiprazole lauroxil, was FDA-approved for schizophrenia.\(^2\) Aripiprazole lauroxil is administered IM every 4 to 6 weeks in the deltoid or gluteal region and is available in multiple dosages (Table 1).

**Mechanism of action**

Aripiprazole lauroxil is a prodrug of aripiprazole. Prodrugs are chemical compounds that exert their pharmacological effects after they undergo a biologic transformation and transform into a more active metabolite.\(^3\) The development of prodrugs is an established method used to improve physiochemical or pharmacokinetic properties of the pharmacologically active compound.

After IM injection, aripiprazole lauroxil is most likely converted by an enzyme-mediated hydrolysis to \(N\)-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole. Aripiprazole’s mechanism of action is mediated through a combination of partial agonist activity at D2 and 5-HT1A receptors and antagonistic activity at 5-HT2A receptors.\(^2,4\)

**Dosing and administration**

If your patient has never taken aripiprazole, ensure that she (he) will tolerate the drug by initiating a trial of oral aripiprazole before beginning treatment with aripiprazole lauroxil; establishing tolerability might take as long as 2 weeks because of the half-life of aripiprazole.

Aripiprazole lauroxil can be started at 441 mg, 662 mg, or 882 mg administered monthly; these dosages correspond to 300 mg, 450 mg, and 600 mg of aripiprazole, or 10 mg/d, 15 mg/d, ≥20 mg/d of oral aripiprazole, respectively (Table 2).\(^2\) Aripiprazole lauroxil can be administered either in the deltoid muscle (441 mg only) or gluteal muscle (441 mg, 662 mg, or 882 mg).\(^2,4,5\) Treatment with the 441-mg, 662-mg, or 882-mg dosages can be given every 4 weeks but the 882-mg dosage can be given every 6 weeks and only in the gluteal muscle, which provides greater dosing flexibility compared with extended-release injectable aripiprazole.\(^2,4,5\)

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**Table 1**

**Fast facts about aripiprazole lauroxil**

<table>
<thead>
<tr>
<th>Brand name:</th>
<th>Aristada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication:</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Approval date:</td>
<td>October 5, 2015</td>
</tr>
<tr>
<td>Manufacturer:</td>
<td>Alkermes</td>
</tr>
<tr>
<td>Dosing forms:</td>
<td>441 mg, 662 mg, 882 mg</td>
</tr>
<tr>
<td>Recommended dosage:</td>
<td>441 mg, 662 mg, or 882 mg monthly, or 882 mg every 6 weeks</td>
</tr>
</tbody>
</table>

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Dr. Khan is Professor, Department of Psychiatry, and Dr. Ovais is an observer physician, Saint Louis University School of Medicine, St. Louis, Missouri.

**Disclosures**

Dr. Khan is a speaker for Janssen, Alkermes, and Lundbeck/Otsuka. Dr. Ovais reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.
Supplementation with oral aripiprazole is required for 21 days before the first aripiprazole lauroxil injection. The next injection should not be given earlier than 14 days after the previous dose. When a dose is missed, follow the guidelines outlined in Table 3.

After a single injection, aripiprazole starts to appear in the systemic circulation at Day 5 or Day 6 and continues to be released for another 36 days. Steady-state concentration will be reached after the fourth monthly injection. The termination half-life of aripiprazole lauroxil ranged from 29 to 35 days after each monthly injection.

Packaging. Aripiprazole lauroxil is available as single-dose, pre-filled, color-coded syringes for IM injection at 441 mg (light blue), 662 mg (green), and 882 mg (burgundy); syringes do not require refrigeration (Table 2). The syringe needs to be tapped at least 10 times to dislodge any material that might have settled. Shake the syringe vigorously for at least 30 seconds to ensure a uniform suspension. Shake it again for 30 seconds if the syringe is not used within 15 minutes.

Efficacy
The efficacy of aripiprazole lauroxil for treating patients with schizophrenia has been established, in part, on the basis of efficacy data from clinical trials of oral aripiprazole. In addition, efficacy has been established in a 12-week, multicenter, randomized, placebo-controlled, double-blind, fixed-dose study of 622 individuals age 18 to 70 with schizophrenia. All eligible patients were diagnosed with schizophrenia as defined by DSM-IV-TR criteria and confirmed by the Structured Clinical Interview for DSM-IV Disorders, Clinical Trial Version and were experiencing an acute exacerbation of their illness at the time of the study. To be eligible for the study, participants had to have a Positive and Negative Syndrome Scale (PANSS) total score of 70 to 120 and score of ≥4 for ≥2 of the selected positive items (delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution). Individuals also were required to have a
Clinical Global Impression-Severity scale score of ≥4. Efficacy was assessed using the PANSS and Clinical Global Impression–Improvement scale (CGI-I).

Patients were randomized in a 1:1:1 ratio to receive IM aripiprazole lauroxil, 441 mg, aripiprazole lauroxil, 882 mg, or placebo once monthly in the gluteal region for 12 weeks. The gluteal muscle was selected as the injection site to maintain blinding to the study drug.

After establishing tolerability to oral aripiprazole, participants received oral aripiprazole or placebo daily for the first 3 weeks. The IM injections were administered on Days 1, 29, and 57. Efficacy was measured primarily as change in total PANSS score from the baseline to day 85; secondary efficacy variable was the CGI-I score at day 85. Statistically significant separation in PANSS score was observed in each aripiprazole lauroxil dosage group (441 mg and 882 mg) compared with placebo. Significant improvement in both active treatment groups was observed as early as Day 8 and continued throughout the study (P ≤ .004). The number of patients who improved much or very much on the CGI-I was significantly greater in either aripiprazole lauroxil group, compared with placebo (P < .001).

**Contraindications**

**Allergic reactions.** Patients who are hypersensitive to oral aripiprazole should not receive aripiprazole lauroxil. Hypersensitivity reactions have ranged from pruritus and urticaria to anaphylaxis.

**Drug–drug interactions.** Reduce aripiprazole lauroxil dosage to the next lower dosage when used in combination with a strong CYP3A4 inhibitor.

**Overdose**

No data are available on aripiprazole lauroxil overdose. However, there is one known case of oral aripiprazole overdose in a patient who ingested 1,260 mg of oral aripiprazole (42 times the maximum recommended daily dosage) but recovered completely. Common side effects reported in at least 5% of all overdose cases include vomiting, somnolence, and tremor. If an overdose occurs, call a poison control center immediately.

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**Clinical Point**

Reduce aripiprazole lauroxil dosage to the next lower dosage when used in combination with a strong CYP3A4 inhibitor.

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| Table 4 |

<table>
<thead>
<tr>
<th>Adverse reactions in aripiprazole lauroxil-treated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Akathisia</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Injection site pain</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Increased weight</td>
</tr>
<tr>
<td>Restlessness</td>
</tr>
<tr>
<td>Increased blood creatine phosphokinase</td>
</tr>
</tbody>
</table>

Source: Reference 2
Related Resources


Drug Brand Names

Aripiprazole - Abilify
Aripiprazole extended-release - Abilify Maintena
Aripiprazole lauroxil - Aristada
Carbamazepine - Tegretol
Clarithromycin - Biaxin
Clarithromycin Itraconazole - Sporanox
Fluoxetine - Prozac
Olanzapine - Zyprexa
Paroxetine - Paxil
Quetiapine - Seroquel
Rifampin - Rifadin
Risperidone - Risperdal
Quinidine - Quinidex
Seroquel
Abilify Maintena
Paxil
Risperdal

Acknowledgement

Maaz A. Khan, a student at the University of Oklahoma, Norman, Oklahoma, contributed to this article.

Clinical Point

The overall safety profile of aripiprazole lauroxil is similar to that of oral aripiprazole.

‘Black-box’ warning for patients with dementia

Aripiprazole lauroxil, similar to all other atypical antipsychotics, has a “black-box” warning stating that (1) it is not approved for treating dementia-related psychosis, and (2) it is associated with an increased risk of death with off-label use to treat behavioral problems in older adults with dementia-related psychosis.2 Meta-analysis of 17 placebo-controlled trials in patients taking an atypical antipsychotic (olanzapine, aripiprazole, risperidone, or quetiapine) revealed a risk of death in drug-treated patients 1.6 to 1.7 times that of placebo-treated patients.6

Adverse reactions

The overall safety profile of aripiprazole lauroxil is similar to that of oral aripiprazole. Most commonly observed adverse reaction during clinical trials of aripiprazole lauroxil was akathisia (incidence ≥5% and at least twice rate seen with placebo).2 Other common adverse reactions are shown in Table 4 (page 52).2 Recently, the FDA issued a warning that compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex have been reported with all formulations of aripiprazole.7 According to reports, these urges stopped when the drug was discontinued or the dosage reduced. Although rare, these impulse-control problems could result in harm if they are not recognized. See the full prescribing information for a complete set of adverse reactions.

References


Bottom Line

Aripiprazole lauroxil is a novel, long-acting second-generation antipsychotic that offers flexibility in terms of safe and effective dosing and can be administered in the deltoid (441 mg) or gluteal muscle (626 mg and 882 mg) and at dosing intervals of 4 to 6 weeks. Safety and tolerability profile of aripiprazole lauroxil are similar to that of oral aripiprazole. Aripiprazole lauroxil represents a new treatment option for patients with schizophrenia.