



7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Aripiprazole

Table 1. Clinically important drug interactions with Aripiprazole

Table with 3 columns: Concomitant Drug Name or Drug Class, Clinical Rationale, and Clinical Recommendation. Rows include CYP3A4 inhibitors, CYP3A4 inducers, antihypertensive drugs, benzodiazepines, and 7.2 Drugs Having No Clinically Important Interactions with Aripiprazole.

8.8 Other Specific Populations

No dosage adjustment for aripiprazole is required on the basis of a patient's sex, race, or smoking status [see CLINICAL PHARMACOLOGY (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Aripiprazole is not a controlled substance.

9.2 Abuse and Dependence

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt discontinuation of dosing.

10 VERDOSA

10.1 Human Experience

In clinical trials and in postmarketing experience, adverse reactions of deliberate or accidental overdose with oral aripiprazole have been reported worldwide. These include overdoses with oral aripiprazole alone and in combination with other substances.

10.2 Management of Overdose

No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdose and ECG interval prolongation is present.

10.3 Pharmacokinetics

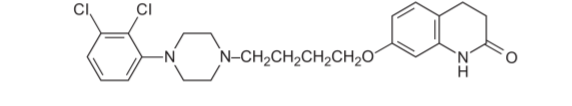
In clinical trials, the terminal elimination half-life of aripiprazole was approximately 15 hours. The mean plasma concentration of aripiprazole was approximately 15 ng/mL at steady state.

10.4 Hematology

There is no information on the effect of hematology in clinical trials with aripiprazole. Hematology is unlikely to be useful in overdose management since aripiprazole is highly protein bound.

11 DESCRIPTION

Aripiprazole is a psychotropic drug that is available as Aripiprazole Orally Disintegrating Tablets. Aripiprazole is 11-(4R,2D)-dichlorophenyl-piperazinebutyl-3,4-dihydrocarbazole. The empirical formula is C<sub>21</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>3</sub> and the molecular weight is 466.29. The chemical structure is shown below.



Aripiprazole Orally Disintegrating Tablets are available in 10 mg and 15 mg strengths. Inactive ingredients include mannitol, aspartame, calcium stearate, croscarmellose, vanillin, silicified microcrystalline cellulose, and lactose monohydrate.

12 CLINICAL PHARMACOLOGY

The mechanism of action of aripiprazole in schizophrenia or bipolar mania is unknown. However, the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D<sub>2</sub> and 5-HT<sub>1A</sub> receptors and antagonist activity at 5-HT<sub>2A</sub> receptors.

12.1 Mechanism of Action

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12.2 Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine D<sub>2</sub> and D<sub>4</sub>, serotonin 5-HT<sub>1A</sub>, and 5-HT<sub>2A</sub> receptors. It also exhibits high affinity for alpha-1 and alpha-2 adrenergic receptors.

12.3 Pharmacokinetics

Aripiprazole activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent to its major metabolite, dehydro-aripiprazole. The pharmacokinetics of aripiprazole are dose-proportional.

ORAL ADMINISTRATION

Aripiprazole is well absorbed after administration of the tablet with peak plasma concentrations occurring within 3 to 5 hours. The absolute oral bioavailability of the tablet formulation is 87%.

8 Nursing Mothers

Aripiprazole is present in human breast milk. Because of the potential for serious adverse reactions in nursing infants from aripiprazole, a decision should be made whether to discontinue nursing or to continue the drug, taking into account the importance of the drug to the mother.

8 Pediatric Use

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in pediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weight [see CLINICAL PHARMACOLOGY (12.3)].

Schizophrenia

Safety and effectiveness in pediatric patients with schizophrenia were established in a 6-week, placebo-controlled clinical trial in 202 pediatric patients aged 13 to 17 years [see DOSAGE AND ADMINISTRATION (2.1), ADVERSE REACTIONS (6.1), and CLINICAL STUDIES (14.1)].

Information describing a clinical study in which efficacy was not demonstrated in patients ages 6 to 17 years is approved for Otsuka America Pharmaceutical, Inc.'s ABILIFY (aripiprazole) product. However, due to Otsuka America Pharmaceutical, Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Aripiprazole in juvenile rats caused mortality, CNS clinical signs, impaired memory and learning, and delayed sexual maturation when administered at oral doses of 10, 20, and 30 mg/kg/day from weaning (21 days old) through maturity (90 days old).

Aripiprazole in juvenile dogs (2 months old) caused CNS clinical signs of tremors, hyperexcitability, and aggression when administered at oral doses of 10, 20, and 30 mg/kg/day from weaning (21 days old) through maturity (90 days old).

Aripiprazole in juvenile monkeys (6 months old) caused CNS clinical signs of tremors, hyperexcitability, and aggression when administered at oral doses of 10, 20, and 30 mg/kg/day from weaning (21 days old) through maturity (90 days old).

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The effects of aripiprazole on the exposures of other drugs are summarized in Figure 3.

Figure 3: The effects of aripiprazole on pharmacokinetics of other drugs

Figure 3 shows the effects of aripiprazole on the pharmacokinetics of other drugs. The graph plots Change Relative to Reference (without interacting drug) on the x-axis (0.5 to 3) and Drug Name on the y-axis.

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An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender, or race.

A large-term trial enrolled 210 treatment-naïve outpatients meeting DSM-IV criteria for schizophrenia who were, by history, symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications and randomized to aripiprazole or placebo for up to 26 weeks of observation for relapse.

Relapse during the double-blind phase was defined as CGI-Improvement score  $\leq 5$  (minimally worse) score  $\geq 5$  (moderately severe) on the hostility or unconcernedness items of the PANSS, or  $\geq 20\%$  increase in the PANSS total score. Patients receiving aripiprazole 15 mg/day experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo (Study 5 Figure 6).

The efficacy of aripiprazole in the treatment of schizophrenia in pediatric patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled trial of outpatients who met DSM-IV criteria for schizophrenia and had a PANSS score  $\geq 20$  at baseline. In this trial (N=302) comparing two fixed doses of aripiprazole (10 or 30 mg/day) to placebo, aripiprazole 15 mg/day was found to be superior to placebo in the primary outcome measure of the study (Study 6 in Table 16), the primary outcome measure of the study. The 30 mg/day dosage was not shown to be more efficacious than the 10 mg/day dose. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

Figure 7: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse (Bipolar Study 7)

Figure 7 shows the Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse (Bipolar Study 7). The graph plots Proportion with Relapse on the y-axis (0 to 1) and Days from Randomization on the x-axis (0 to 180).

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Perforation

15 mm

297 mm

210 mm

### MEDICATION GUIDE

## Aripiprazole (AR-i-PIP-ra-zole) Orally Disintegrating Tablets

Read this Medication Guide before you start taking aripiprazole and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

**What is the most important information I should know about aripiprazole?**  
(For other side effects, also see **“What are the possible side effects of aripiprazole?”**).

Serious side effects may happen when you take aripiprazole, including:

- **Increased risk of death in elderly patients with dementia-related psychosis:** Medicines like aripiprazole can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia).  
Aripiprazole is not approved for the treatment of patients with dementia-related psychosis.
- **Risk of suicidal thoughts or actions:** Antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions:
  1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
  2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
  3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
    - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
    - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
    - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

**Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:**

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

**What else do I need to know about antidepressant medicines?**

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child’s healthcare provider for more information.

**What is aripiprazole?**  
**Aripiprazole is a prescription medicine used to treat:**

- schizophrenia
- manic or mixed episodes that happen with bipolar I disorder

It is not known if aripiprazole is safe or effective in children:

- under 13 years of age with schizophrenia
- under 10 years of age with bipolar I disorder

**Who should not take aripiprazole?**  
Do not take aripiprazole if you are allergic to aripiprazole or any of the ingredients in aripiprazole. See the end of this Medication Guide for a complete list of ingredients in aripiprazole.

**What should I tell my healthcare provider before taking aripiprazole?**  
Before taking aripiprazole, tell your healthcare provider if you have or had:

- diabetes or high blood sugar in you or your family; your healthcare provider should check your blood sugar before you start aripiprazole and also during therapy.
- seizures (convulsions).
- low or high blood pressure.
- heart problems or stroke.
- pregnancy or plans to become pregnant. It is not known if aripiprazole will harm your unborn baby.
- breast-feeding or plans to breast-feed. Aripiprazole can pass into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you receive aripiprazole.
- low white blood cell count.
- phenylketonuria. Aripiprazole Orally Disintegrating Tablets contain phenylalanine.
- any other medical conditions.

**Tell your healthcare provider about all the medicines that you take,** including prescription and over-the-counter medicines, vitamins and herbal supplements.

Aripiprazole and other medicines may affect each other causing possible serious side effects. Aripiprazole may affect the way other medicines work, and other medicines may affect how aripiprazole works.

Your healthcare provider can tell you if it is safe to take aripiprazole with your other medicines. Do not start or stop any medicines while taking aripiprazole without talking to your healthcare provider first. Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

**How should I take aripiprazole?**

- Take aripiprazole exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking aripiprazole yourself.
- Aripiprazole can be taken with or without food.
- If you miss a dose of aripiprazole, take the missed dose as soon as you remember. If it is almost time for the next dose, just skip the missed dose and take your next dose at the regular time. Do not take two doses of aripiprazole at the same time.
- If you have been prescribed Aripiprazole Orally Disintegrating Tablet, take it as follows:

Perforation

15 mm

297 mm

210 mm

20007492

- o Do not open the blister until ready to take the orally disintegrating tablet.
- o To remove one orally disintegrating tablet, open the package and peel back the foil on the blister to expose the tablet.
- o Do not push the tablet through the foil because this could damage the tablet.
- o Immediately upon opening the blister, using dry hands, remove the tablet and place the entire Aripiprazole Orally Disintegrating Tablet on the tongue.
- o Tablet disintegration occurs rapidly in saliva. It is recommended that Aripiprazole Orally Disintegrating Tablet be taken without liquid. However, if needed, it can be taken with liquid.
- o Do not attempt to split the Aripiprazole Orally Disintegrating Tablet.
- If you take too much aripiprazole, call your healthcare provider or poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.

**What should I avoid while taking aripiprazole?**

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how aripiprazole affects you. Aripiprazole may make you drowsy.
- Avoid getting over-heated or dehydrated.
  - o Do not over-exercise.
  - o In hot weather, stay inside in a cool place if possible.
  - o Stay out of the sun. Do not wear too much or heavy clothing.
  - o Drink plenty of water.

**What are the possible side effects of aripiprazole?**

**Aripiprazole may cause serious side effects, including:**

- See **“What is the most important information I should know about aripiprazole?”**
- **Stroke in elderly people (cerebrovascular problems) that can lead to death**
- **Neuroleptic malignant syndrome (NMS).** Tell your healthcare provider right away if you have some or all of the following symptoms: high fever, stiff muscles, confusion, sweating, changes in pulse, heart rate, and blood pressure. These may be symptoms of a rare and serious condition that can lead to death. Call your healthcare provider right away if you have any of these symptoms.
- **Uncontrolled body movements (tardive dyskinesia).** Aripiprazole may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop receiving aripiprazole. Tardive dyskinesia may also start after you stop receiving aripiprazole.
- **Problems with your metabolism such as:**
- **High blood sugar (hyperglycemia) and diabetes.** Increases in blood sugar can happen in some people who take aripiprazole. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes), your healthcare provider should check your blood sugar before you start aripiprazole and during your treatment.

**Call your healthcare provider if you have any of these symptoms of high blood sugar while taking aripiprazole:**

- ▶ feel very thirsty
- ▶ need to urinate more than usual
- ▶ feel very hungry
- ▶ feel weak or tired
- ▶ feel sick to your stomach
- ▶ feel confused, or your breath smells fruity
- o **increased fat levels (cholesterol and triglycerides) in your blood.**
- o **weight gain.** You and your healthcare provider should check your weight regularly.

- **Orthostatic hypotension (decreased blood pressure).** Lightheadedness or fainting when rising too quickly from a sitting or lying position.
- **Low white blood cell count**
- **Seizures (convulsions)**
- **problems with control of your body temperature especially when you exercise a lot or are in an area that is very hot. It is important for you to drink water to avoid dehydration.** See “What should I avoid while receiving aripiprazole?”
- **difficulty swallowing that can cause food or liquid to get into your lungs.**

**The most common side effects of aripiprazole in adults include:**

- nausea
- vomiting
- constipation
- headache
- blurred vision
- dizziness
- anxiety
- insomnia
- restlessness
- inner sense of restlessness/need to move (akathisia)
- upper respiratory illness

**The most common side effects of aripiprazole in children include:**

- feeling sleepy
- headache
- vomiting
- fatigue
- increased or decreased appetite
- insomnia
- nausea
- stuffy nose
- weight gain
- uncontrolled movement such as restlessness, tremor, muscle stiffness

- increased saliva or drooling

These are not all the possible side effects of aripiprazole. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store aripiprazole?**

- Store aripiprazole at 20° to 25°C (68° to 77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

Keep aripiprazole and all medicines out of the reach of children.

**General information about the safe and effective use of aripiprazole.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use aripiprazole for a condition for which it was not prescribed. Do not give aripiprazole to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about aripiprazole. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about aripiprazole that was written for healthcare professionals.

**What are the ingredients in aripiprazole orally disintegrating tablets?**

**Active ingredient:** aripiprazole

**Inactive ingredients:** mannitol, aspartame, calcium stearate, crospovidone, vanilla, silicified microcrystalline cellulose, and lactose monohydrate. Colorants include iron oxide red.

**Additional pediatric use information is approved for Otsuka America Pharmaceutical, Inc.’s ABILIFY® (aripiprazole) product. However, due to Otsuka America Pharmaceutical, Inc.’s marketing exclusivity rights, this drug product is not labeled with that information.**

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Manufactured by:  
Alembic Pharmaceuticals Limited  
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