

Texas Vendor Drug Program

Drug Use Criteria: Atypical Antipsychotics (long-acting injectable)

Publication History

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Notes: Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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TEXAS
Health and Human
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Social Services*

1 Dosage

1.1 Adults

Long-acting injectable (LAI) second generation (atypical) antipsychotics are FDA-approved drugs to treat psychiatric disorders. All of the LAI atypical antipsychotics are used to treat schizophrenia. Invega Sustenna® has an additional indication for treating schizoaffective disorder. Both Abilify Maintena® and Risperdal Consta® have an additional indication for treating bipolar I disorder.¹⁻¹² Recommended treatment dosages for LAI atypical antipsychotics are summarized in Table 1.

Table 1. Adult LAI Atypical Antipsychotic Recommended Dosages¹⁻¹²

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
Schizophrenia, bipolar I disorder (maintenance therapy)	Aripiprazole (Abilify Maintena®)	300 mg, 400 mg intramuscular (IM) injection	400 mg IM once monthly
Schizophrenia	Aripiprazole lauroxil (Aristada®)	441 mg, 662 mg, 882 mg, 1064 mg IM injection	1064 mg IM every two months
Schizophrenia	Olanzapine (Zyprexa® Relprevv™)	210 mg, 300 mg, 405 mg IM injection	300 mg IM every two weeks
Schizophrenia, schizoaffective disorder	Paliperidone palmitate (Invega Sustenna®)	39 mg, 78 mg, 117 mg, 156 mg, 234 mg IM injection	234 mg IM once monthly
Schizophrenia in patients who have been treated on Invega Sustenna® for at least four months	Paliperidone palmitate (Invega Trinza®)	273 mg, 410 mg, 546 mg, 819 mg IM injection	819 mg IM once every 3 months

Treatment Indication	Drug Name	Available Dosage Strengths	Maximum Recommended Dosage
Schizophrenia, bipolar I disorder (maintenance therapy)	Risperidone (Risperdal Consta®)	12.5 mg, 25 mg, 37.5 mg, 50 mg IM injection	50 mg IM every 2 weeks

Abilify Maintena® dosages must be modified in patients prescribed CYP3A4 or CYP2D6 inhibitors, or in those patients identified as CYP poor metabolizers. Abilify Maintena® should be avoided in patients prescribed CYP3A4 inducers concurrently.¹⁻⁵ Recommended Abilify Maintena® dosages when prescribed concurrently with CP450-modifying medications are summarized in Table 2.

Table 2. Cytochrome P450-Associated Dosage Changes for Aripiprazole (Abilify Maintena®) (Adults) ¹⁻⁵

Factors	Dosage Adjustment
Abilify Maintena® 300 mg intramuscular administration	
Strong CYP3A4 or CYP2D6 inhibitor (greater than 14 days)	Reduce to 200 mg
CYP3A4 and CYP2D6 inhibitor together (greater than 14 days)	Reduce to 160 mg
CYP3A inducer (greater than 14 days)	Avoid use
Abilify Maintena® 400 mg intramuscular administration	
Strong CYP3A4 or CYP2D6 inhibitor (greater than 14 days)	Reduce to 300 mg
CYP3A4 and CYP2D6 inhibitor together (greater than 14 days)	Reduce to 200 mg
CYP3A inducer (greater than 14 days)	Avoid use
Abilify Maintena® in CYP2D6 poor metabolizers	
Known CYP2D6 poor metabolizers	Reduce to 300 mg
Known CYP2D6 poor metabolizer taking a CYP3A4 inhibitor	Reduce to 200 mg

Aristada® dosages must be modified in patients prescribed CYP3A4 or CYP2D6 inhibitors as well as CYP3A4 inducers concurrently.^{1-4, 6} Recommended Aristada® dosages when prescribed concurrently with CP450-modifying medications are summarized in Table 3.

Table 3. Cytochrome P450-Associated Dosage Changes for Aripiprazole Lauroxil (Aristada®) (Adults) ^{1-4, 6}

Factors	Dosage Adjustment
Strong CYP3A inhibitor	Reduce Aristada® dose to the next lowest strength; if patient is taking 441 mg, no dosage adjustment required
Strong CYP2D6 inhibitor	Reduce Aristada® dose to next lowest strength; if patient is taking 441 mg, no dosage adjustment required
Known CYP2D6 poor metabolizer taking a strong CYP3A inhibitor	If patient is taking 662 or 882 mg, reduce the dose to 441 mg; if patient is taking 441 mg, no dosage adjustment required
Known CYP2D6 poor metabolizer taking a strong CYP2D6 inhibitor	No dose adjustment needed
Both a strong CYP2D6 inhibitor and CYP3A inhibitor	Avoid using in patients who are taking 662 or 882 mg; if patient is taking 441 mg, no dosage adjustment needed
CYP3A4 inducers	No dose adjustment is needed for the 662 mg or 882 mg dosages; if patient is taking 441 mg, increase dose to 662 mg

1.2 Pediatrics

Safety and efficacy of LAI atypical antipsychotics for use in children younger than 18 years of age have not been established.¹⁻¹⁰

2 Duration of Therapy ¹⁻¹²

If the patient is tolerating the LAI atypical antipsychotic, then there is no basis for limiting treatment length for approved psychiatric disorders as schizophrenia, schizoaffective disorder, and bipolar I disorder are chronic, lifelong diseases.

3 Duplicative Therapy

Co-administration of two or more LAI atypical antipsychotics is not justified due to limited additional therapeutic benefit and increased risk of adverse effects.¹⁻¹²

Patient profiles containing concomitant prescriptions for two or more LAI atypical antipsychotics will be reviewed.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for LAI atypical antipsychotics are summarized in Table 6. Only those drug-drug interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed:

Table 6. Select LAI Atypical Antipsychotic Drug-Drug Interactions^{4-10, 13}

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
Aripiprazole	Citalopram	Increased risk of QT prolongation and serotonin syndrome because aripiprazole is a partial agonist of 5-HT1A and citalopram is a selective serotonin reuptake inhibitor	Avoid use	Major (DrugReax) 2-major (CP)
Aripiprazole	Strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole)	Increased risk of aripiprazole overexposure because aripiprazole is metabolized by CYP3A4	Monitor patient closely and adjust aripiprazole dosages as needed	Major (DrugReax) 3-moderate (CP)
Long-acting injectable atypical antipsychotics (LAI AAs)	CNS depressants	Increased risk of respiratory and central nervous system depression due to additive pharmacologic effects.	Use cautiously together; observe patients for enhanced CNS adverse effects	Major (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
LAI AAs	Metoclopramide	Increased risk of extrapyramidal reactions or neuroleptic malignant syndrome	Avoid use	Contraindicated (DrugReax) 1-severe,2-major (CP)
LAI AAs	QT interval-prolonging medications (e.g. posaconazole)	Increased risk of QT interval prolongation	Avoid use; if combined use necessary, administer cautiously together and monitor closely	Contraindicated (DrugReax) 1-severe,2-major,3-moderate (CP)
Olanzapine	Agents that lower seizure threshold (e.g. clomipramine)	Increased seizure risk because psychotropic drugs may reduce the seizure threshold	Use caution when administered concomitantly	Major (DrugReax) 3-moderate (CP)
Atypical antipsychotics	CYP3A4 and CYP1A2 inducers (e.g. carbamazepine)	Concomitant use can lead to decreased serum concentrations of atypical antipsychotics	Monitor treat efficacy and adjust atypical antipsychotic dosages as needed	Major (DrugReax) 2-major (CP)
Olanzapine (CYP1A2 substrate)	CYP1A2 inhibitor (e.g. fluvoxamine)	Increased olanzapine serum concentrations	Monitor patient closely and adjust olanzapine dosages as needed	Major (DrugReax) 2-major (CP)
Risperidone	Serotonergic agents (e.g. linezolid)	Increased risk of serotonin syndrome	Monitor patients for serotonin syndrome	Major (DrugReax) 2-major (CP)
Risperidone Olanzapine	Lithium	Increased extrapyramidal symptoms; encephalopathy and brain damage have occurred in case reports due to unknown mechanism	Monitor patients closely for symptoms and monitor lithium levels	Major (DrugReax) 2-major (CP)

5 References

1. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at www-micromedexsolutions-com.libproxy.uthscsa.edu/ (cited: Sept. 10, 2019).
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at clinicalpharmacology-ip.com.ezproxy.lib.utexas.edu/. Accessed September 10, 2019.
3. Facts and Comparisons eAnswers [database online]. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; Sept. 10, 2019.
4. AHFS Drug Information 2019. Jackson, WY: Teton Data Systems, Version 8.10.1, 2019. Stat!Ref Electronic Medical Library. Available at online-statref-com.libproxy.uthscsa.edu/. Accessed Sept. 10, 2019.
5. Aripiprazole intramuscular extended-release injection (Abilify Maintena®) package insert. Otsuka America Pharmaceutical, Inc., Feb. 2019.
6. Aripiprazole lauroxil intramuscular extended-release injection (Aristada®) package insert. Alkermes, Inc., Aug. 2019.
7. Olanzapine extended release injectable suspension (Zyprexa® Relprevv™) package insert. Eli Lilly and Company, Jan. 2018.
8. Paliperidone palmitate extended-release injection suspension (Invega® Sustenna®) package insert. Janssen Pharmaceuticals, Jan. 2019.
9. Paliperidone palmitate extended release suspension (Invega Trinza®) package insert. Janssen Pharmaceuticals, Jan. 2019.
10. Risperidone long-acting injection (Risperdal Consta®) package insert. Janssen Pharmaceuticals, Inc., Jan. 2019.
11. Correll CU, Citrome L, Haddad PM, et al. The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. *J Clin Psychiatry*. 2016; 77(suppl 3): 1-24.
12. Llorca PM, Abbar M, Courtet P, et al. Guidelines for the use and management of long-acting injectable antipsychotics in serious mental illness. *BMC Psychiatry*. 2013; 13: 340.