

Atypical Antipsychotic Long-Acting Injectable (LAI) Review (Aripiprazole, Paliperidone, Risperidone)

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN
Pharmacist Executives

Background: In 2021, 20.4% of Veterans diagnosed with schizophrenia treated in VA received at least a single dose of a long-acting injectable antipsychotic medication. The 2023 VA/DoD Clinical Practice Guideline for Management of First-Episode Psychosis and Schizophrenia suggests offering long-acting injectable antipsychotics to improve medication adherence in individuals with schizophrenia as a “new-added” recommendation.

Thus far, 2023 has seen the approval of three new dosage forms of atypical antipsychotic long-acting injectable agents, included in this review. The LAIs have unique and varied preparation and administration techniques (e.g., duration the product must be shaken, injection speed, injection location, refrigeration requirements).

Formulary status of available LAIs is either PA-F with CFU or non-formulary. The goal of this review is to provide an overview of this class of medication for the Committee to review. Comparative information is summarized in the tables below.

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Table 1. Aripiprazole LAIs ¹⁻⁴

	Aripiprazole Maintena	Aripiprazole Aristada	Aripiprazole Asimtufii
How supplied (Formulary Status)	300mg, 400mg (PA-F with CFU)	441mg, 662mg, 882mg, 1064mg (PA-F with CFU)	720mg, 960mg (PA-F with CFU)
Administration, intramuscular (IM)	Deltoid or gluteal	Deltoid (441mg only) or gluteal	Gluteal
Indication	Schizophrenia in adults Maintenance monotherapy treatment of bipolar I disorder in adults	Schizophrenia in adults	Schizophrenia in adults Maintenance monotherapy treatment of bipolar I disorder in adults
Schedule	Monthly	Monthly, q6wks, q 2 months	Q 2 months
Oral overlap	Yes, 14 days	Yes, 21 days unless used with Initio (675mg+30mg oral dose)	Yes, 14 days
Conversions	15mg oral – 300mg IM monthly 20mg oral – 400mg IM monthly	10mg oral – 441mg IM monthly 15mg oral – 662mg IM monthly, 882mg q6wks, or 1064mg q2months IM 20mg oral – 882 mg IM monthly	400mg IM qmonth – 960mg q2months
Refrigeration required	No	No	No
Reconstitution/shake	Room temperature/ 20 seconds (pre-filled syringe) 30 seconds (vial)	Tap 10x + shake 30 seconds (syringe)	Tap 10x + shake 10 seconds (syringe)

Table 2. Paliperidone LAIs ⁵⁻⁷

	Paliperidone Sustenna	Paliperidone Trinza	Paliperidone Hafyera
How supplied (Formulary Status)	39mg, 78mg, 117mg, 156mg, 234mg (PA-F with CFU)	273mg, 410mg, 546mg, 819mg (PA-F with CFU)	1092mg, 1560mg (PA-F with CFU)
Administration, intramuscular (IM)	Deltoid or gluteal	Deltoid or gluteal	Gluteal
Indication	<ul style="list-style-type: none"> • Schizophrenia in adults. • Schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants 	<ul style="list-style-type: none"> • Schizophrenia after they have been adequately treated with PP1M for at least four months. 	<ul style="list-style-type: none"> • Schizophrenia after they have been adequately treated with PP1M for at least four months • OR after PP3M for at least one 3-month cycle
Schedule	Monthly	Q3 months	Q6 months
Oral overlap	No	No	No
Conversions	12mg pali/6mg risp ~ 234mg IM; 9mg pali/4mg risp~156mg IM; 6mg pali/3mg risp ~117mg IM; 3mg pali/2mg risp ~ 39-78mg IM	78mg PP1M = 273mg; 117mg PP1M = 410mg; 156mg PP1M = 546mg; 234mg PP1M = 819mg	156mg PP1M = 1092mg; 234mg PP1M = 1560mg; 546mg PP3M = 1092mg; 819mg PP3M = 1560mg
Refrigeration required	No	No	No
Shake	10 seconds	15 seconds	15 + 15 seconds

Table 3. Risperidone LAIs ⁸⁻¹¹

	Risperidone Consta	Risperidone Perseris	Risperidone Rykindo	Risperidone Uzedy
How supplied (Formulary Status)	12.5mg, 25mg, 37.5mg, 50mg (PA-F with CFU)	90mg, 120mg (NF)	12.5mg, 25mg, 37.5mg, 50mg (NF)	50mg, 75mg, 100mg, 125mg, 150mg, 200mg, 250mg (NF)
Administration, intramuscular (IM)	Deltoid or gluteal	Subcutaneous, abdomen	Gluteal	Subcutaneous, abdomen or upper arm
Indication	Schizophrenia Monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder	Schizophrenia	Schizophrenia Monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder	Schizophrenia
Schedule	Q2weeks	Q4weeks	Q2weeks	Q4 or q8 weeks
Oral overlap	21 days	No	7 days	No
Conversions	2mg po ~ 25mg IM; 4mg po ~ 37.5mg IM; 6mg po ~ 50 mg IM	3mg po = 90mg SQ 4mg po = 120mg SQ	2mg po ~ 25mg IM; 4mg po ~ 37.5mg IM; 6mg po ~ 50 mg IM	2mg po = 50mg monthly or 100mg q2months; 3mg po = 75mg monthly or 150mg q2months; 4mg po = 100mg monthly or 200 mg q2months, 5mg po = 125mg monthly or 250mg q2months
Refrigeration required	Yes	Yes	Yes	Yes
Shake	10 seconds	5 + 55 cycles	30 + 20-30 seconds	Flick 3x

Proposed Place in Therapy and Formulary Considerations

Schizophrenia is a neurodevelopmental disorder with a typical age of onset in the late adolescence or early adulthood with prevalence peaking at age 40. The prevalence is estimated at approximately 1% of the population and is one of the top 15 leading causes of disability worldwide. In FY 2021, VA provided health care for approximately 74,000 Veterans with schizophrenia with 20.4% of these individuals receiving at least a single dose of a long-acting injectable antipsychotic medication. LAIs may improve medication adherence and decrease hospitalizations compared to their oral counterparts. The 2023 VA-DoD CPG for Schizophrenia makes a “Strong For” recommendation that antipsychotic medication be prescribed for the maintenance treatment of schizophrenia. This recommendation also states medication choice should be based upon patient-specific characteristics, patient preferences, and medication side effect profiles. However, patient preferences for these agents vary significantly. Logistical considerations include route of administration, oral overlap requirements, staff education for administration (e.g., duration the product must be shaken, injection speed, injection location), refrigeration requirements, and cost.

There are three aripiprazole LAI dosage forms, with similar indications and routes of administration. None require refrigeration but all require oral overlap for 14-21 days and must be shaken prior to administration. No oral overlap is required for Aristada when Initio (675mg) is administered with a 30 mg oral dose. Aristada represents 41% market share among aripiprazole LAIs, has a high PADR approval rate, and is the least expensive LAI among the aripiprazole products. To avoid oral overlap, Aristada should be administered with Initio for maximum benefit, and may be administered monthly or q2months (1064mg only). Reported ADEs among the aripiprazole LAI dosage forms are low, pharmacologically expected, and similar among the products.

There are three paliperidone LAI dosage forms, with similar indications and routes of administration. None require refrigeration and importantly, do not require oral overlap. All syringes require shaking. Administration schedule ranges from monthly to q3months or q6months. Among the paliperidone LAI products, Sustenna is the most widely used and the products as a class, represents 51% market share in units purchased. PADR approval is high. Paliperidone is “flat priced” but is among the most expensive LAI. Reported ADEs are low, and pharmacologically expected. As paliperidone is the metabolite of risperidone.

Risperidone LAIs are available in four different dosage forms, two IM, and two subcutaneous. The availability of a subcutaneously administered LAI, offering an alternative to intramuscular, is relatively recent. All require refrigeration. Administration schedules range from q2 to q8wk. Oral overlap is required for the two intramuscular LAIs (7-21 days) but is not required for the subcutaneous LAIs. All require some form of shaking prior to administration. Risperidone Consta is the main LAI used among the risperidone LAI products and represents an 18% market share in purchased units. PADR approval rate is high. Reported ADEs are low, pharmacologically expected, and similar to paliperidone. The two subcutaneously administered risperidone LAI products are non-formulary.

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