Clinical Policy Title:	Long Acting Injectable Antipsychotics
Policy Number:	RxA.655
Drug(s) Applied:	aripiprazole extended release (Abilify Maintena®), aripiprazole lauroxil (Aristada®), aripiprazole lauroxil (Aristada Initio®), olanzapine pamoate (Zyprexa Relprevv™), paliperidone palmitate (Invega Sustenna®), paliperidone palmitate (Invega Trinza®), risperidone microspheres (Risperdal Consta®), risperidone subcutaneous (Perseris™)
Original Policy Date:	9/4/2020
Last Review Date:	9/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Long-acting injectable (LAI) antipsychotics are a pharmacologic strategy for treating patients with schizophrenia and bipolar I disorder who relapse due to nonadherence to antipsychotic medication. Rather than the daily pill-taking required with oral antipsychotics, LAI antipsychotics are administered by injection at two to four-week intervals.

As with oral antipsychotics, dosing of the LAI antipsychotics is optimized when clinical effectiveness is achieved while minimizing size effects.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
aripiprazole extended release (Abilify Maintena®)	• Treatment of schizophrenia in adults • Maintenance monotherapy treatment of bipolar I disorder in adults	160 mg-400 mg monthly (no sooner than 26 days after the previous injection)	400 mg every 4 weeks
aripiprazole lauroxil (Aristada®, Aristada Initio®)	• Aristada®: ○ Treatment of schizophrenia in adults • Aristada Initio®: ○ In combination with oral aripiprazole, is indicated for the initiation of Aristada® when used for the treatment of schizophrenia in adults	Aristada®: Intramuscularly every 4 weeks (441, 662, 882 mg) Every 6 weeks (882 mg only) Every 2 months (1064 mg only) Aristada Initio®: One time dose of 675 mg injection and one 30 mg dose of oral aripiprazole in conjunction with the first Aristada injection	Aristada®: 882 mg every 4 weeks Aristada Initio®: 675 mg one time dose

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
olanzapine pamoate (Zyprexa Relprevv™)	• Treatment of schizophrenia	150 to 405 mg every 2 to 4 weeks	300 mg every 2 weeks
paliperidone palmitate (Invega Sustenna®, Invega Trinza®)	• Invega Trinza®: ○ Treatment of schizophrenia in patients after they have been adequately treated with Invega Sustenna® • Invega Sustenna®: ○ Treatment of schizophrenia in adults. ○ Treatment of schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants.	Invega Sustenna®: 39 to 234 mg every 4 weeks Invega Trinza®: 273 to 819 mg every 12 weeks	Invega Sustenna®: 234 mg every 4 weeks Invega Trinza®: 819 mg every 12 weeks
risperidone microspheres (Risperdal Consta®)	• Treatment of schizophrenia • Monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder	12.5 to 50 mg every 2 weeks*	50 mg every 2 weeks
risperidone subcutaneous (Perseris™)	• Treatment of schizophrenia in adults	90 to 120 mg every 4 weeks[±]	120 mg every 4 weeks

*Severe impairment (Child-Pugh class C) and Severe impairment (CrCl <30 mL/minute): 0.5 mg twice daily orally for 1 week then 1 mg twice daily or 2 mg once daily for 1 week; if tolerated, begin 25 mg IM every 2 weeks; continue oral dosing for 3 weeks after the first IM injection. An initial IM dose of 12.5 mg may also be considered.
[±]Hepatic and Renal Impairment (Subcutaneous): Initiate with oral dosing (titrate up to 3 mg/day); if tolerated and effective, beginning 90 mg once monthly can be considered.

Dosage Forms

- Abilify Maintena®: 300 mg, and 400 mg; single-dose pre-filled dual chamber syringe, single-dose vial
- Aristada®: 441 mg, 662 mg, 882 mg or 1064 mg; single-dose pre-filled syringe
- Aristada Initio®: 675 mg; single-dose pre-filled syringe
- Zyprexa Relprevv™: 210 mg/vial, 300 mg/vial, and 405 mg/vial
- Invega Sustenna®: 39 mg/0.25 mL, 78 mg/0.50 mL, 117 mg/0.75 mL, 156 mg/1.00 mL, or 234 mg/1.50 mL; injectable suspension
- Invega Trinza®: 273 mg/0.875 mL, 410 mg/1.315 mL, 546 mg/1.75 mL, or 819 mg/2.625 mL; injectable suspension
- Risperdal Consta®: 12.5 mg, 25 mg, 37.5 mg, and 50 mg; vial kits
- Perseris™: 90 mg and 120 mg; injectable suspension

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Schizophrenia (must meet all):

1. Diagnosis of schizophrenia;
2. Age ≥ 18 years;
3. Prescribed by or in consultation with a psychiatrist;
4. History of non-adherence to oral antipsychotic therapy; (see Appendix D)
5. Must meet (a, b, c, or d):
   a. If request is for Abilify Maintena®, Aristada®, or Aristada Initio®: Established tolerability with oral aripiprazole;
   b. If request is for Risperdal Consta® or Perseris™: Established tolerability with oral risperidone;
   c. If request is for Zyprexa Relprevv™: Established tolerability with oral olanzapine;
   d. If request is for Invega Sustenna® or Invega Trinza®: Established tolerability with oral paliperidone or risperidone.
6. If Invega Trinza® is requested, adequate treatment has been established with Invega Sustenna® for ≥ 4 months;
7. If Aristada Initio® is requested, it is used in conjunction with Aristada® and an oral one time 30 mg dose of aripiprazole.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

B. Bipolar I Disorder (must meet all):

1. Diagnosis of bipolar I disorder;
2. Request is for one of the following: Abilify Maintena® or Risperdal Consta®;
3. Age ≥ 18 years;
4. Prescribed by or in consultation with a psychiatrist;
5. History of non-adherence to oral antipsychotic therapy;
6. Must meet (a or b):
   a. If request is for Abilify Maintena®: Established tolerability with oral aripiprazole;
   b. If request is for Risperdal Consta®: Established tolerability with oral risperidone.

Approval Duration

Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Schizophrenia (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;

Approval Duration
Commercial: 12 months
Medicaid: 12 months

B. Bipolar I Disorder (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
LAI: Long-acting injectable

APPENDIX B: Therapeutic Alternatives
Not applicable.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Known hypersensitivity to the active ingredient.

- Boxed Warning(s):
  - All products: Increased mortality in elderly patients with dementia-related psychosis;
  - Zyprexa Relprevv™: Post- injection delirium/sedation syndrome.

APPENDIX D: General Information
Oral Antipsychotics

Typical/First Generation Antipsychotics	Atypical/Second Generation Antipsychotics
• Chlorpromazine • Fluphenazine • Haloperidol (Haldol®) • Loxapine • Perphenazine • Pimozide • Thioridazine • Thiothixene	• Aripiprazole (Abilify®) • Saphris® • Rexulti® • Vraylar® • Clozapine (Clozaril®) • Fanapt® • Latuda® • Olanzapine (Zyprexa®)

• Trifluoperazine	• Olanzapine/fluoxetine (Symbyax®) • Paliperidone (Invega®) • Quetiapine (Seroquel®) • Risperidone (Risperdal®) • Ziprasidone (Geodon®)

References

1. Abilify Maintena® Prescribing Information. Tokyo, Japan: Otsuka Pharmaceutical Co.; June 2020. Available at: https://www.otsuka-us.com/sites/g/files/qhldwo3326/files/media/static/Abilify-M-PI.pdf. Accessed on July 08, 2021.
2. Aristada® Prescribing Information. Waltham, MA: Alkermes Inc.; March 2021. Available at: https://www.aristada.com/downloadables/ARISTADA-PI.pdf. Accessed on July 08, 2021.
3. Aristada Initio® Prescribing Information. Waltham, MA: Alkermes Inc.; March 2021. Available at: https://www.aristada.com/downloadables/ARISTADA-INITIO-PI.pdf . Accessed on July 08, 2021.
4. Zyprexa Relprevv™ Prescribing Information. Indianapolis, IN: Eli Lilly and Company; February 2021. Available at: http://pi.lilly.com/us/zyprexa_relprevv.pdf. Accessed on July 08, 2021.
5. Invega Sustenna® Prescribing Information. Titusville, NJ: Janssen Pharmaceutical; February 2021. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVEGA+SUSTENNA-pi.pdf. Accessed on July 08, 2021.
6. Invega Trinza® Prescribing Information. Titusville, NJ: Janssen Pharmaceutical; February 2021. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVEGA+TRINZA-pi.pdf. Accessed on July 08, 2021.
7. Risperdal Consta® Prescribing Information. Titusville, NJ: Janssen Pharmaceutical; February 2021. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/RISPERDAL+CONSTA-pi.pdf. Accessed on July 08, 2021.
8. Perseris™ Prescribing Information. North Chesterfield, VA: Indivior Inc; December 2019. Available at: https://www.perserishcp.com/prescribing-information.pdf. Accessed on July 08, 2021.
9. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at: http://www.clinicalpharmacology-ip.com/. Accessed July 08, 2021.
10. UpToDate. [database online]. Waltham, MA: Wolters Kluwer; 2020. Available at: Uptodate.com/contents/pharmacotherapy-for-schizophrenia-long-acting-injectable-antipsychotic-drugs. Accessed July 08, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	9/4/2020	09/14/2020
Policy was reviewed: 1. Dosing Information dosing regimen for Abilify Maintena was updated from " 200 to 400 mg every 4 weeks" to "160 mg-400 mg monthly (no sooner than 26 days after the previous injection)". 2. Dosing Information maximum dose for Aristada was updated to include "Aristada Initio®: 675 mg one time dose".	07/08/2021	09/14/2021

3. Dosing Information was updated to include footnotes regarding hepatic and renal impairment, "*Severe impairment (Child-Pugh class C) and Severe impairment (CrCl <30 mL/minute): 0.5 mg twice daily orally…" and "±Hepatic and Renal Impairment (Subcutaneous): Initiate with oral dosing…". 4. Statement about provider sample ''The provision of provider samples does not guarantee coverage…" was added to Clinical Policy. 5. Continued Therapy Approval Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 6. Continued Therapy Approval Criteria II.B.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 7. Appendix D was updated to remove inactive/unavailable drugs Thorazine, Prolixin, Loxitane, Trilafon, Orap, Mellaril, Navane, Stelazine, asenapine maleate, brexpiprazole, cariprazine, iloperidone, and lurasidone. 8. References were reviewed and updated.		