Clinical Policy: Olanzapine Long-Acting Injection (Zyprexa Relprevv)

Reference Number: ERX.SPA.180
Effective Date: 12.01.17
Last Review Date: 08.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Olanzapine (Zyprexa Relprevv®) is a long-acting atypical antipsychotic.

FDA Approved Indication(s)
Zyprexa Relprevv is indicated for the treatment of schizophrenia.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Zyprexa Relprevv is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Schizophrenia (must meet all)**:**

1. Diagnosis of schizophrenia;
2. Prescribed by or in consultation with a psychiatrist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. The requested product was initiated in an inpatient setting during a recent (within 60 days) hospital admission;
   b. History of non-adherence to oral antipsychotic therapy (*see Appendix D for examples*), and both of the following (i and ii):
      i. Failure of an aripiprazole long-acting injection (i.e., Abilify Maintena®, Aristada® ± Aristada Initio™ - preferred products) and Risperdal Consta®, unless contraindicated or clinically significant adverse effects are experienced;
      ii. Established tolerability with oral olanzapine;
5. Dose does not exceed 405 mg every 4 weeks or 300 mg every 2 weeks.

Approval duration:
Commercial – Length of Benefit
Medicaid – 6 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Schizophrenia (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, or documentation supports one of the following (a or b):
   a. Member is currently receiving Zyprexa Relprevv for schizophrenia, and has received this medication for at least 30 days;

b. Therapy was initiated in an inpatient setting during a recent (within 60 days) hospital admission;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 405 mg every 4 weeks or 300 mg every 2 weeks.

Approval duration:
Commercial – Length of Benefit
Medicaid – 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents;
B. Dementia-related psychosis;
C. Alzheimer's disease.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
olanzapine (Zyprexa®)	5 to 10 mg PO QD	20 mg/day
Risperdal Consta (risperidone)	Adults: 25 mg IM (deep gluteal or deltoid injection) once every 2 weeks; some adult patients not responding to the 25 mg dose may benefit from 37.5 mg or 50 mg IM once every 2 weeks	50 mg every 2 weeks
Abilify Maintena (aripiprazole monohydrate)	The recommended starting and maintenance dose is 400 mg IM monthly (no sooner than 26 days after the previous injection). Dose can be reduced to 300 mg in patients with adverse reactions. • Used in combination with oral aripiprazole for the first 14 consecutive days. Known CYP2D6 poor metabolizers: Recommended starting and maintenance dose is 300 mg IM monthly as a single injection.	400 mg/month
Aristada (aripiprazole lauroxil)	*Initiation Method 1*: Administer one IM injection of Aristada Initio 675 mg (deltoid or gluteal muscle) and one dose of oral aripiprazole 30mg in conjunction with the first Aristada injection. • First Aristada injection may be started on same day or up to 10 days after administration of Aristada Initio	882 mg/month

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	• Avoid injection of both Aristada and Aristada Initio into the same deltoid or gluteal muscle. *Initiation Method 2:* Used in combination with oral aripiprazole for the first 21 consecutive days. Depending on individual patient's needs, treatment can be initiated at a dose of 441 mg, 662 mg, or 882 mg IM administered monthly; 882 mg administered every 6 weeks; or 1,064 mg administered every 2 months. Dose adjustments are required for 1) known CYP2D6 poor metabolizers and 2) for patients taking CYP3A4 inhibitors, CYP2D6 inhibitors, or CYP3A4 inducers for more than 2 weeks.	
Aristada Initio (aripiprazole lauroxil)	Schizophrenia *(therapy initiation only)* Single dose of 675 mg IM injection, in combination with a single dose of 30 mg oral aripiprazole, to initiate Aristada treatment or to re-initiate Aristada treatment. Aristada may be started at the same time or within 10 days of Aristada Initio/oral aripiprazole.	675 mg once

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): patients are at risk for severe sedation (including coma) or delirium after each injection and must be observed for at least 3 hours in a registered facility with ready access to emergency response services

Appendix D: Examples of Oral Antipsychotics – Generic (Brand)

Typical/First Generation Antipsychotics†	Atypical/Second Generation Antipsychotics
• Chlorpromazine (Thorazine®) • Fluphenazine (Prolixin®) • Haloperidol (Haldol®) • Loxapine (Loxitane®) • Perphenazine (Trilafon®) • Pimozide (Orap®) • Thioridazine (Mellaril®) • Thiothixene (Navane®) • Trifluoperazine (Stelazine®)	• Aripiprazole (Abilify®)* • Asenapine maleate (Saphris®) • Brexpiprazole (Rexulti®) • Cariprazine (Vraylar®) • Clozapine (Clozaril®) • Iloperidone (Fanapt®) • Lumateperone (Caplyta®) • Lurasidone (Latuda®) • Olanzapine (Zyprexa®)* • Olanzapine/fluoxetine (Symbyax®) • Paliperidone (Invega®)* • Quetiapine (Seroquel®) • Risperidone (Risperdal®)* • Ziprasidone (Geodon®)

†*Most typical/first generation antipsychotics are available only as generics in the U.S.*
**Long-acting injectable formulation available*

Appendix E: General Information

- Zyprexa Relprevv is available only through a restricted distribution program called Zyprexa Relprevv Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment. Adverse events with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, have been reported following injections of Zyprexa Relprevv. The goal of the Zyprexa Relprevv Patient Care Program is to mitigate the risk of negative outcomes associated with Zyprexa Relprevv post-injection delirium/sedation syndrome.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Schizophrenia	IM: 150 mg/2 weeks, 300 mg/4 weeks, 210 mg/2 weeks, 405 mg/4 weeks, or 300 mg/2 weeks Zyprexa Relprevv should be administered by a healthcare professional.	405 mg every 4 weeks or 300 mg every 2 weeks

VI. Product Availability

Powder for suspension: 210 mg, 300 mg, 405 mg

VII. References

1. Zyprexa Relprevv Prescribing Information. Indianapolis, IN: Lilly USA, LLC; October 2019. Available at https://www.zyprexarelprevvprogram.com/public/Default.aspx. Accessed March 22, 2021.
2. Kim B, Lee SH, Yang YK, et al. Review Article: Long-acting injectable antipsychotics for first-episode schizophrenia: The pros and cons. Schizophr Res Treatment. August 14, 2012; 2012: 560836. doi:10.1155/2012/560836.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2021. Available at: http://www.clinicalpharmacology-ip.com/. Accessed March 22, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q17 Annual Review Policy split from ERX.SPMN.192 Long-acting injectable antipsychotics. Converted to new template. Added age restriction as safety and effectiveness have not been established in patients < 18 years. Added max dose. Increased all approval durations to length of benefit. Added dementia-related psychosis and Alzheimer's disease as indications/diagnoses for which coverage is not authorized per PI.	10.02.17	11.17
3Q 2018 annual review: no significant changes; references reviewed and updated.	05.02.18	08.18
3Q 2019 annual review: initial and continued therapy criteria were revised to allow approval for members who initiate therapy during a recent inpatient visit, without the requirement to step through oral agents; added Medicaid line of business with 6/12 month approval durations; references reviewed and updated.	05.31.19	08.19
3Q 2020 annual review: no significant changes; references reviewed and updated.	05.12.20	08.20
Aripiprazole long-acting injectable added as a trial requirement and restricted, along with risperidone, to cases of oral therapy non-adherence.	09.17.20	11.20
3Q 2021 annual review: no significant changes; references reviewed and updated.	03.22.21	08.21

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.