Clinical Policy: Paliperidone Long-Acting Injection (Invega Sustenna, Invega Trinza)

Reference Number: ERX.SPA.178
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
Paliperidone (Invega Sustenna®, Invega Trinza®) is an atypical antipsychotic.

FDA Approved Indication(s)
Invega Sustenna is indicated:
- For the treatment of schizophrenia in adults
- For the treatment of schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants

Invega Trinza is indicated for the treatment of schizophrenia in patients after they have been adequately treated with Invega Sustenna (1-month paliperidone palmitate extended-release injectable suspension) for at least 4 months.

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 Invega Sustenna and Invega Trinza are **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 one of the following (i or ii):
      i. If Invega Trinza is requested, adequate treatment has been established with Invega Sustenna for at least the last 4 months;
      ii. If Invega Sustenna is requested, all of the following (a, b, and c):
         a) 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;
         b) Established tolerability with oral paliperidone or oral risperidone;
         c) No known hypersensitivity to paliperidone or risperidone;
5. Dose does not exceed (a or b):
   a. Invega Sustenna: 234 mg per month;
   b. Invega Trinza: 819 mg every 3 months.

Approval duration:

Commercial – Length of Benefit
Medicaid – 6 months

B. Schizoaffective Disorder (must meet all)**:**
1. Diagnosis of schizoaffective disorder;
2. Request is for Invega Sustenna;
3. Prescribed by or in consultation with a psychiatrist;
4. Age ≥ 18 years;
5. Member meets one of the following (a or b):
   a. History of non-adherence to oral antipsychotic therapy (*see Appendix D for examples*) and has established tolerability with oral risperidone or paliperidone;
   b. Therapy was initiated in an inpatient setting during a recent (within 60 days) hospital admission;
6. Dose does not exceed 234 mg per month.

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

C. 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. All Indications in Section I (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 the requested agent for a covered indication, and has received this medication for at least 30 days;
   b. Therapy was initiated in an inpatient setting for a covered indications 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 the following (a or b):
   a. Invega Sustenna: 234 mg per month;
   b. Invega Trinza: 819 mg every 3 months.

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.

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
paliperidone (Invega®)	Schizophrenia and schizoaffective disorder Adults: initially, 6 mg PO QD Recommended dose: 3-12 mg/day	12 mg/day
risperidone (Risperdal®)	Schizophrenia Adults: initially, 2 mg/day PO (as a single dose) or 1 mg PO BID; adjust as tolerated to the recommended target dose of 4 to 8 mg/day Effective dose range: 4 to 16 mg/day	16 mg/day
Risperdal Consta® (risperidone)	Schizophrenia 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
Invega Sustenna® (paliperidone)	See Section V Dosage and Administration	See Section V Dosage and Administration
Abilify Maintena® (aripiprazole monohydrate)	Schizophrenia 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)	Schizophrenia *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 • 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	882 mg/month

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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): known hypersensitivity to paliperidone, risperidone, or to any excipients.
- Boxed warning(s): increased risk of death in elderly patients with dementia-related psychosis treated with antipsychotic drugs

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*

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Paliperidone (Invega Sustenna)	Schizophrenia	Initial: 234 mg IM on day 1 and 156 mg one week later (day 8), both administered in the deltoid muscle Maintenance*: 39-234 mg IM monthly in either the deltoid or gluteal muscle	234 mg/month
	Schizoaffective disorder	Initial: 234 mg IM on day 1 and 156 mg one week later (day 8), both administered in the deltoid muscle Maintenance*: 78-234 mg IM monthly in either the deltoid or gluteal muscle	234 mg/month
Paliperidone (Invega Trinza)	Schizophrenia	Invega Trinza is to be used only after Invega Sustenna (1-month paliperidone palmitate extended-release injectable suspension) has been established as adequate treatment for at least four months.	819 mg every 3 months

Drug Name	Indication	Dosing Regimen	Maximum Dose
		Initiate Invega Trinza when the next 1-month paliperidone palmitate dose is scheduled with an Invega Trinza dose based on the previous 1-month injection dose, using the equivalent 3.5-fold higher dose as shown: If the last dose of Invega Sustenna is: / Initiate Invega Trinza at the following dose: 78 mg / 273 mg 117 mg / 410 mg 156 mg / 546 mg 234 mg / 819 mg Following the initial Invega dose, Invega Trinza should be administered IM every 3 months. Invega Trinza may be administered up to 7 days before or after the monthly time point of the next scheduled paliperidone palmitate 1-month dose.	

**Administered 5 weeks after the first injection*

VI. Product Availability

Drug Name	Availability
Paliperidone (Invega Sustenna)	Extended-release injectable suspension: 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/1 mL, or 234 mg/1.5 mL
Paliperidone (Invega Trinza)	Extended-release injectable suspension: 273 mg/0.875 mL, 410 mg/1.315 mL, 546 mg/1.75 mL, or 819 mg/2.625 mL

VII. References

1. Invega Sustenna Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; February 2021. Available at https://www.invegasustennahcp.com/. Accessed March 19, 2021.
2. Invega Trinza Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; February 2021. Available at https://www.invegatrinzahcp.com/. Accessed March 19, 2021.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2021. Available at: http://www.clinicalpharmacology-ip.com/. Accessed March 19, 2021. Ac
4. 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.

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. Re-auth: Removed requirement that member should re-establish treatment with Invega Sustenna for 4 months before reinitiating Invega Trinza if > 9 months have elapsed since specialist is involved in care. Added dementia-related psychosis as an indication for which coverage is not authorized per PI.	09.29.17	11.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2018 annual review: no significant changes; references reviewed and updated.	05.01.18	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
For Invega Trinza requests, required Invega Sustenna history edited to indicate transition continuity; aripiprazole long-acting injectable added as a trial requirement and restricted, along with risperidone, to cases of oral therapy non-adherence; hypersensitivity contraindication added for risperidone and paliperidone.	09.17.20	11.20
3Q 2021 annual review: no significant changes; references reviewed and updated.	03.19.21	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.