Paliperidone Palmitate (INVEGA HAFYERA)
National Drug Monograph
November 2021

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

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Paliperidone palmitate extended-release injectable suspension (PP6M) is long-acting injectable antipsychotic. Its mechanism of action is unknown but thought to be mediated through dopamine D2 and serotonin 5HT2a receptor antagonism.

Indication(s) Under Review in This Document

- PP6M, an every-six-month injection, is an atypical antipsychotic indicated for the treatment of schizophrenia in adults after they have been adequately treated with:
    - A once-a-month paliperidone palmitate extended-release injectable suspension (e.g., INVEGA SUSTENNA) for at least four months OR
    - An every-three-month paliperidone palmitate extended-release injectable suspension (e.g., INVEGA TRINZA) for at least one three-month cycle.

Dosage Form(s) Under Review

- Extended-release injectable (IM gluteal only) suspension: 1,092 mg/3.5 mL or 1,560 mg/5 mL single-dose prefilled syringes.

Clinical Evidence Summary

Efficacy Considerations

- The efficacy and safety of PP6M for the treatment of schizophrenia in 702 adult patients who had previously been stabilized on either paliperidone palmitate 1-month (PP1M) for at least 4 months or paliperidone palmitate 3-month (PP3M) for at least one 3-month injection cycle was evaluated in a phase 3, randomized, double-blind, active-controlled, interventional, parallel-group, multicenter, non-inferiority study (NCT03345342, Table 1 and 2) to evaluate time to relapse in adults with a DSM-5 diagnosis of schizophrenia.

- Patients were young (approximately 41 years of age), white (74%) males (69%), with a mean age of onset of schizophrenia approximately 28 years of age. Most had not been previously hospitalized (58%).
- The mean score at baseline for the Positive and Negative Syndrome Scale (PANSS) was 52 and the mean score for the Clinical Global Impressions-Severity (CGI-S) scale was 3, indicating mildly ill subjects.
- PP6M demonstrated non-inferiority to PP3M on the primary endpoint of time to first relapse at the end of the 12-month double blind phase in the intent to treat (ITT) analysis.
- 7.5% of patients in the PP6M treatment group and 4.9% of patients in the PP3M treatment group experienced a relapse event. The Kaplan-Meier estimated difference (PP6M – PP3M), 2.9% (95% CI: -1.1 to 6.8). The median time to relapse (median survival time refers to the time at which the cumulative survival function equals 0.5 or [50%]), was not estimable in either the PP6M or the PP3M group due to the low rates of relapses in the study.
- The safety profile of PP6M was consistent with previous studies of PP1M and PP3M.

Table 1. Key Inclusion and Exclusion Criteria[1,3,4]

Inclusion
• Age 18-70
• Diagnosis of schizophrenia (DSM-5) for ≥ 6 months before screening
• Receiving treatment with PP1M, PP3M, risperidone LAI, or any oral antipsychotic
• Total PANSS score < 70 at screening and at randomization
Exclusion
• Receiving involuntary treatment
• Unstable medical conditions
• History of NMS or TD
• History of unresponsiveness or intolerance to risperidone or paliperidone
• Suicide attempt ≤ 12 months before screening or imminent risk of suicide or violent behavior
• DSM-5 diagnosis of moderate or severe substance use disorder (except nicotine and caffeine) ≤ 6 months of screening
• Treatment with LAI antipsychotic other than risperidone or paliperidone with ≤ 6 months of screening

DSM-5, Diagnostic and Statistical Manual, 5th edition; LAI, long-acting injectable, PANSS, Positive and Negative Syndrome Scale; NMS, Neuroleptic malignant syndrome; TD, tardive dyskinesia

Table 2. Outcome Measures [1,3,4]

Primary

- Time to first relapse in double-blind phase defined as:
  - Psychiatric hospitalization
  - Increase in PANSS score by: 25% if at randomization > 40, 10 points if at randomization ≤ 40
  - Suicidal/homicidal ideation and aggressive behavior
  - Deliberate self-injury or violent behavior resulting in suicidal or clinically significant injury
  - Specific PANSS items score ≥ 5 or ≥ 6, if maximum score at randomization was ≤ 3 or 4 respectively

Secondary

- Change from baseline in:
  - PANSS Total and Subscale score
  - CGI-S score
  - PSP score
- Percentage of patients who met criteria for symptomatic remission

PANSS, Positive and Negative Syndrome Scale; CGI-S, Clinical Global Impression-Severity; PSP, Personal and Social Performance

Safety Considerations

Table 4. Adverse Events with ≥2% Incidence in PP6M Treated Patients[1]

	PP3M N=224 %	PP6M N=478 %
Diarrhea	1	2
Injection site reaction	5	11
Upper respiratory tract infection	13	12
UTI	1	3
Weight increased	8	9
Back pain	1	3
Musculoskeletal pain	1	3
Extrapyramidal symptoms	9	11
Headache	5	7
Anxiety	0	3

Other warnings / precautions:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis
- Neuroleptic Malignant Syndrome
- QT Prolongation
- Tardive Dyskinesia
- Metabolic Changes
- Orthostatic Hypotension and Syncope
- Falls
- Leukopenia, Neutropenia, and Agranulocytosis
- Hyperprolactinemia
- Potential for Cognitive and Motor Impairment
- Seizures

Drug Interactions: Avoid using strong CYP3A4 and/or P-gp inducers during a dosing interval for PP6M. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended-release tablets.

Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure.

Renal Impairment (CrCl < 90 ml/min): Not recommended

Other Therapeutic Options

Table 8.

Drug	Formulary status	Clinical Guidance/ Indication	Other Considerations
Paliperidone palmitate (Sustenna)	PA-F with CFU	Schizophrenia and schizoaffective d/o	Administered IM monthly (deltoid initial 2 injections, then deltoid or gluteal)
Paliperidone palmitate (Trinza)	PA-F with CFU	Schizophrenia	Administered IM every 3 months (deltoid or gluteal)
Risperidone (Consta)	PA-F with CFU	Bipolar disorder and schizophrenia	Administered IM biweekly (deltoid or gluteal)

Projected Place in Therapy

- Schizophrenia is a chronic and debilitating mental disorder characterized by alterations in thought processes, perceptions, emotional responsiveness, and social interactions. It affects

approximately one percent of the general population and is one of the top 15 leading causes of disability worldwide.[5,6]

- Antipsychotics are the current pharmacologic standard of care for the management of patients with schizophrenia.
- First line antipsychotic agents on the VA National Formulary include the long-acting injectables [aripiprazole (Ability Maintena, Aristada, Aristada Initio), fluphenazine decanoate, haloperidol decanoate, risperidone (Consta), and paliperidone palmitate (Sustenna, Trinza)].
- PP6M is similar to other long-acting dosage forms of paliperidone on the formulary, save an extended dosing interval (6 months vs 3 months vs monthly)
- Results from study NCT03345342 demonstrated that PP6M is non-inferior to PP3M on the primary endpoint of time to first relapse at the end of the 12-month double blind phase in the intent to treat (ITT) analysis. The safety profile of PP6M was consistent with previous studies of PP1M and PP3M.
- PP6M is an option for patients with schizophrenia who have been stabilized on PP1M or PP3M, have normal renal function (CrCl > 90 ml/min), and are not receiving a strong CYP3A4 and/or P-gp inducers during a dosing interval.

References

1. INVEGA HAFYERA (paliperidone palmitate) extended-release injectable suspension [prescribing information]. Janssen Pharmaceuticals, Inc. Titusville, NJ. 2021.
2. NDA 207946/S-010. Supplement approval letter. Department of Health and Human Services. Food and Drug Administration, Silver Spring, MD 20993. August 30, 2021.
3. A Study of Paliperidone Palmitate 6-Month Formulation - Full Text View - ClinicalTrials.gov
4. https://clinicaltrials.gov/ct2/show/NCT03345342?term=NCT03345342&draw=2&rank=1
5. Schizophrenia. National Institute of Mental Health. https://www.nimh.nih.gov/health/statistics/schizophrenia.shtml. Accessed 10/21/21.
6. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017 Sep 16;390(10100):1211-1259.

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