Paliperidone palmitate (Invega Hafyera™) Drug Bulletin

October 2021

Nonproprietary Name	paliperidone palmitate
Brand Name	Invega Hafyera
Manufacturer	Janssen
FDA Approval Date	August 30, 2021
Market Availability Date	September 14, 2021
Indication	Treatment of schizophrenia in adults after they have been adequately treated with: • A once-a-month paliperidone palmitate extended-release (PP1M) injectable suspension (e.g., Invega Sustenna®) for ≥ 4 months OR • An every-3-month paliperidone palmitate extended-release (PP3M) injectable suspension (e.g., Invega Trinza®) for ≥ one 3-month cycle
Dosage Form	Extended-release (ER) suspension for intramuscular (IM) injection: 1,092 mg/3.5 mL and 1,560 mg/5 mL prefilled syringes
Dosage	• Administered once every 6 months IM into the gluteal muscle by a healthcare professional • Initial dose is based on the previous PP1M (Invega Sustenna) or PP3M (Invega Trinza) dose • When switching from a PP1M product to Invega Hafyera, the first dose of Invega Hafyera should be administered when the next PP1M dose is scheduled (1 week before or after the scheduled PP1M dose is acceptable); the last two PP1M doses should be the same immediately prior to switching to Invega Hafyera; if the last PP1M dose is 156 mg or 234 mg, then the first dose of Invega Hafyera should be 1,092 mg or 1,560 mg, respectively; there are no equivalent doses of Invega Hafyera for 39 mg, 78 mg, or 117 mg doses of a PP1M product • When switching from a PP3M product to Invega Hafyera, the first Invega Hafyera dose should be administered when the next PP3M dose is scheduled (2 weeks before or after the scheduled PP3M dose is acceptable); if the last PP3M dose is 546 mg or 819 mg, then the first dose of Invega Hafyera should be 1,092 mg or 1,560 mg, respectively; there are no equivalent doses of Invega Hafyera for 273 mg or 410 mg doses of a PP3M product • If needed, dosage adjustment can be made every 6 months between the dose of 1,092 mg to 1,560 mg based on the patient's response and tolerability • Invega Hafyera doses may be given up to 2 weeks before or 3 week after the scheduled 6-month dose in order to avoid missed doses; if a dose is missed, restart therapy with a PP1M product as instructed in the product label

CLINICAL CONSIDERATIONS

- Paliperidone palmitate ER (Invega Hafyera) is an atypical antipsychotic. Paliperidone palmitate is hydrolyzed to paliperidone, the major active metabolite of risperidone.[1] Paliperidone is an antagonist at the central dopamine D_2 and serotonin $5HT_{2A}$ receptors, *in vitro.*
- A single dose of Invega Hafyera provides paliperidone over a 6-month period.[2] Doses of 1,092 mg and 1,560 mg deliver paliperidone total exposure within the exposure range for corresponding doses of injectable PP1M (156 mg and 234 mg, respectively) and PP3M (546 mg and 819 mg, respectively), and once-daily doses of paliperidone extended-release oral tablets.
- Safety[3]
  - Contraindications – Paliperidone palmitate ER (Invega Hafyera) is contraindicated in patients with known hypersensitivity to any component of the product or to risperidone. Hypersensitivity reactions have been reported in patients treated with risperidone and in patients treated with paliperidone.
  - Warnings – increased mortality (boxed warning) and risk of cerebrovascular adverse events (e.g., stroke) in elderly patients with dementia-related psychosis; neuroleptic malignant syndrome (discontinue therapy if suspected); QT prolongation (avoid use in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias); tardive dyskinesia (periodically assess need for continued therapy); metabolic changes (e.g., weight gain hyperglycemia, diabetes mellitus, dyslipidemia); orthostatic hypotension and syncope (use with caution in predisposed patients); increased risk of falls (assess fall risk periodically); leukopenia, neutropenia, and agranulocytosis (monitor as appropriate, discontinue Invega Hafyera if severe neutropenia occurs); hyperprolactinemia; cognitive and motor impairment potential; seizures (use cautiously in patients with a history of seizures or other conditions that have the potential for lower seizure threshold); dysphagia (use cautiously in patients with risk of aspiration pneumonia); priapism; disrupted body temperature regulation.
  - Common adverse reactions – Invega Hafyera versus PP3M (Invega Trinza), respectively: upper respiratory tract infection (12% versus 13%), injection site reaction (11% versus 5%), weight gain (9% versus 8%), headache (7% versus 5%), and extrapyramidal symptoms (7% versus 5%).
  - Drug Interactions – Use caution with concomitant use of centrally active drugs and alcohol which may affect central nervous system (CNS) effects of paliperidone; monitor orthostatic vital signs in patients predisposed for hypotension if concurrently used with other drugs that induce orthostatic hypotension; avoid concomitant use with strong inducers of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, or St. John's wort) since this may decrease paliperidone exposure; paliperidone may antagonize effect of levodopa and other dopamine agonists (monitor/manage as clinically indicated).
  - Special Populations
    - Pregnancy – Use during the third trimester of pregnancy may increase the risk for extrapyramidal and/or withdrawal symptoms of neonate following delivery. Enrollment

of pregnant patients in the pregnancy exposure registry is encouraged. In addition, paliperidone may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential.

- Pediatrics – Safety and efficacy have not been established in patients < 18 years of age.
- Geriatric – Clinical studies did not include a sufficient number of patients ≥ 65 years of age to assess their response compared to younger individuals.
- Renal Impairment – Invega Hafyera is not recommended in patients with renal impairment (any severity).
- Hepatic Impairment – No dosage adjustment is required with mild or moderate hepatic impairment; it has not been studied with severe hepatic impairment.
- Patients with Parkinson's disease or Lewy Body Dementia may have increased sensitivity to paliperidone and increased risk of adverse effects.

- Clinical Trial[4,5]: A 12-month, multicenter, randomized, double-blind, phase 3, non-inferiority trial compared IM treatment with every-6-month paliperidone palmitate (Invega Hafyera; PP6M) and every-3-month paliperidone palmitate (Invega Trinza; PP3M). A total of 702 patients 18 to 70 years with schizophrenia who had previously received stable treatment with either once-monthly paliperidone palmitate (PP1M) 156 mg or 234 mg for at least 4 months or PP3M 546 mg or 819 mg for at least one 3-month injection cycle entered the double-blind period of the trial. Patients were randomized to PP6M (plus matching placebo injections; n=478) or PP3M (n=224). Relapse was defined as psychiatric hospitalization, increase in Positive and Negative Syndrome Scale [PANSS] total score, increase in individual PANSS item scores, deliberate self-injury, violent behavior, or suicidal/homicidal behavior. In the study, 7.5% and 4.9% of patients in the PP6M and PP3M treatment groups, respectively, experienced a relapse event (Kaplan-Meier estimated difference, 2.9%; 95% confidence interval [CI], -1.1 to 6.8), demonstrating non-inferiority (< 10% of the upper bound of the 95% CI) of PP6M compared to PP3M. Safety profiles were similar between the groups.
- Goals of treatment of schizophrenia are to stabilize the patient (reduce acute symptoms), return to baseline functioning, prevent recurrence of symptoms, and maximize functioning and quality of life. The American Psychiatric Association (APA) suggests use of a long-acting injectable (LAI) antipsychotic for patients who prefer this therapy or for patients with a history of uncertain or poor adherence.[6] With the exception of clozapine, no antipsychotic has demonstrated superior efficacy when compared to other agents within the class.
- Invega Hafyera is an LAI atypical antipsychotic. It is the first and only LAI to allow for twice-yearly doses for the treatment of schizophrenia in adults – the fewest doses of any LAI available. Other LAI atypical antipsychotics for schizophrenia with maintenance IM dosing ranging from every 2 weeks to every 3 months include aripiprazole ER (Abilify Maintena® [once monthly]), aripiprazole lauroxil ER (Aristada® [every 1 or 2 months or every 6 weeks]), olanzapine ER (Zyprexa® Relprevv™ [every 2 or 4 weeks]), paliperidone palmitate (Invega Sustenna [once monthly], Invega Trinza every 3 months]), and risperidone (Risperdal Consta® [every 2 weeks], Perseris® [once monthly]).[7,8,9,10,11]

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Antipsychotics
Clinical Edit	**Initial Approval Criteria** ▪ Patient is ≥ 18 years of age; **AND** ▪ Patient has a diagnosis of schizophrenia; **AND** ▪ Patient must be established on Invega Sustenna® for ≥ 4 months OR Invega Trinza® for at least one 3-month cycle with adequate response and acceptable tolerance; **AND** ▪ If switching from Invega Sustenna, the last 2 doses of Invega Sustenna prior to switching must be the same; **AND** ▪ Patient is NOT being switched from Invega Sustenna 39 mg, 78 mg, or 117 mg once per month doses OR Invega Trinza 273 mg or 410 mg every 3 months doses; **AND** ▪ Patient does NOT have a known hypersensitivity to paliperidone, risperidone, or any excipient contained within the product; **AND** ▪ Patients will be monitored for the following potential adverse effects, as appropriate: neuroleptic malignant syndrome, QT prolongation, tardive dyskinesia, metabolic changes (e.g., hyperglycemia, diabetes mellitus, dyslipidemia, weight gain), orthostatic hypotension/syncope, leukopenia/neutropenia/ agranulocytosis, hyperprolactinemia, cognitive and motor impairment, and seizures; **AND** ▪ Patient does NOT have renal impairment (e.g., patient's creatinine clearance [CrCl] is ≥ 90 mL/min); **AND** ▪ Patient will avoid concomitant use with strong inducers of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, or St. John's wort) since this may decrease paliperidone exposure. **Renewal Criteria** ▪ Patient has experienced clinical improvement or stabilization of schizophrenia symptoms; **AND** ▪ There is an absence of unacceptable toxicity from the drug (e.g., hypersensitivity reaction; neuroleptic malignant syndrome; QT prolongation; tardive dyskinesia; severe metabolic changes; orthostatic hypotension/syncope; severe neutropenia, leukopenia, or agranulocytosis; hyperprolactinemia; cognitive or motor impairment; seizures); **AND** ▪ Patient has received continuous treatment with Invega Hafyera.
Quantity Limit	2 doses per year
Duration of Approval	Initial: 29 weeks Renewal: 1 year
Drug to Disease Hard Edit	Dementia-related psychosis in elderly patients

REFERENCES

1 Invega Hafyera [package insert]. Titusville, NJ; Janssen; August 2021.
2 Invega Hafyera [package insert]. Titusville, NJ; Janssen; August 2021.
3 Invega Hafyera [package insert]. Titusville, NJ; Janssen; August 2021.
4 Invega Hafyera [package insert]. Titusville, NJ; Janssen; August 2021.
5 A study of paliperidone palmitate 6-month formulation. NCT03345342. Available at: https://clinicaltrials.gov/ct2/show/study/NCT03345342. Accessed October 4, 2021.
6 American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. 3rd ed. Arlington, VA: American Psychiatric Association; 2020. Available at: https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. Accessed October 4, 2021.
7 Abilify Maintena [package insert]. Rockville, MD; Otsuka; January 2020.
8 Aristada [package insert]. Waltham, MA; Alkermes; February 2020.
9 Zyprexa Relprevv [package insert]. Indianapolis, IN; Eli Lilly; October 2019.
10 Invega Sustenna [package insert]. Titusville, NJ; Janssen; August 2021.
11 Invega Trinza [package insert]. Titusville, NJ; Janssen; August 2021.