

3-Month paliperidone palmitate for preventing relapse in schizophrenia

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A 3-month paliperidone palmitate (PPM-3) extended-release injectable suspension was approved by the FDA in May 2015 for preventing relapse among patients with schizophrenia, under the brand name Invega Trinza (*Table 1*). Administered 4 times a year, PPM-3 provides the longest interval of any approved long-acting injectable antipsychotic (LAIA). PPM-3 can be administered to patients with schizophrenia who have been taking 1-month paliperidone palmitate (PPM-1) extended-release injectable suspension (brand name, Invega Sustenna), once a month, for at least 4 months.

How it works

PPM-3 is a LAIA injection. Because of its low solubility in water, paliperidone palmitate dissolves slowly once injected before being hydrolyzed as paliperidone and absorbed into the bloodstream. From time of release on Day 1, PPM-3 remains active for as long 18 months.

PPM-3 reaches a maximum plasma concentration between Day 30 and Day 33. In clinical trials, PPM-3 had a median half-life of 84 to 95 days when injected into the deltoid muscle and a median half-life of 118 to 139 days when injected into the gluteal muscle.

Paliperidone is not extensively metabolized in the liver. Although results of a study suggest that cytochrome P450 (CYP) 2D6 and CYP3A4 might play a role in metabolizing paliperidone, there is no evidence that it has a significant role.

Table 1

Fast facts about 3-month paliperidone palmitate

Brand name: Invega Trinza
Class: Atypical antipsychotic
Indication: Patients with schizophrenia who have been receiving 1-month paliperidone palmitate injections for at least 4 months
FDA approval date: May 19, 2015
Manufacturer: Janssen Pharmaceuticals, Inc.
Dosage forms: 273 mg, 410 mg, 546 mg, and 819 mg intramuscular injections
Recommended dosing: Dosages are based on the patient's previous 1-month paliperidone palmitate dosage. Injections are administered once every 3 months

PPM-3 is administered 4 times a year and provides the longest interval of any approved LAIA

Dosing and administration

PPM-3 is administered intramuscularly by a licensed health care professional, once every 3 months. The recommended dosage is based on the patient's previous dosage of PPM-1 (*Table 2, page 32*).

See the prescribing information for administration instructions.

Efficacy

The efficacy of PPM-3 was assessed in a long-term double-blind, placebo-controlled, randomized-withdrawal trial in adult patients with acute symptoms (previously treated with an oral antipsychotic) or adequately treated with a LAIA, either PPM-1 or another agent; patients receiving PPM-1, 39 mg, injections were ineligible. All patients entering the study

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Table 2

Recommended dosing of PPM-3^a

Last dose of PPM-1	Initiate PPM-3 dose
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

^aConversion from PPM-1, 39 mg, to PPM-3 dosage was not studied

PPM-1: paliperidone palmitate 1-month injection;
PPM-3: paliperidone palmitate 3-month injection

Source: Adapted from Invega Trinza [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2015

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From time of release into the bloodstream on Day 1, PPM-3 remains active for as long as 18 months

received PPM-1 in place of the next scheduled injection.

The study comprised 3 treatment periods:

- **17-Week flexible-dose open-label period with PPM-1** (ie, first part of a 29-week open-label stabilization phase): Patients (N = 506) received PPM-1 with a flexible dose based on symptom response, tolerability, and medication history. Patients had to achieve a Positive and Negative Syndrome Scale (PANSS) total score of <70 at Week 17 to enter the second phase.

- **12-Week open-label with PPM-3** (ie, second part of the 29-week open-label stabilization phase): Patients (N = 379) received a single injection of PPM-3 that was 3.5 times the last dose of PPM-1. Patients had to achieve a PANSS total score of <70 and ≤4 for 7 specific PANSS items.

- **A variable length double-blind treatment period:** Patients (N = 305) were randomized 1:1 to continue treatment with PPM-3 (273 mg, 410 mg, 546 mg, or 819 mg) or placebo (administered once every 12 weeks) until relapse, early withdrawal, or end of the study. The primary efficacy measure was time to first relapse, defined as psychiatric hospitalization, ≥25% increase or a 10-point increase in total PANSS score on 2 consecutive assessments, deliberate self-injury, violent behavior, suicidal or homicidal ideation, or a score of ≥5 (if the maximum baseline score was ≤3) or ≥6 (if the maximum baseline score was 4)

on 2 consecutive assessments of the specific PANSS items.

Among the patients in the third treatment period, 23% of those who received placebo and 7.4% of those who received PPM-3 experienced a relapse event. The time to relapse was significantly longer for patients who received PPM-3 than for those who received placebo.

See *Table 3* for adverse reactions reported in patients who received PPM-3 and those taking placebo in the study.

Contraindications

Allergic reactions. Patients who have a hypersensitivity to paliperidone, risperidone, or their components should not receive PPM-3. Anaphylactic reactions have been reported in patients who previously tolerated risperidone or oral paliperidone, which could be significant because the drug is slowly released over 3 months. Other adverse reactions, including angioedema, ileus, swollen tongue, thrombotic thrombocytopenic purpura, urinary incontinence, and urinary retention, were reported post-approval of paliperidone; however, these adverse effects were reported voluntarily from an unknown population size and, therefore, it is unknown whether there is a causal relationship to the drug or its frequency.

Drug-drug interactions. Although paliperidone is not expected to cause drug-drug interactions with medications that are metabolized by CYP isoenzymes, it is recommended to avoid using a strong inducer of CYP3A4 and/or P-glycoprotein.

Overdose. When assessing treatment options and recovery, consider the half-life of PPM-3 and its long-lasting effects.

Because PPM-3 is administered by a licensed health care provider, the potential for overdose is low. However, if overdose occurs, general treatment and management measures should be employed as with overdose of any drug and the pos-



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Table 3

Reported adverse reactions in >2% patients during clinical study (PPM-1 open label vs double-blind PPM-3 and double-blind placebo)

Adverse reactions	PPM-1	Placebo	PPM-3
Injection site reaction	12%	0%	3%
Weight increase	10%	3%	9%
Headache	7%	4%	9%
Akathisia	5%	2%	5%
Parkinsonism	5%	0%	4%
Upper respiratory tract infection	5%	4%	10%
Urinary tract infection	<1%	1%	3%

PPM-1: paliperidone palmitate 1-month injection; PPM-3: paliperidone palmitate 3-month injection

Source: Adapted from Invega Trinza [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2015

sibility of multiple drug overdose should be considered. There is no specific antidote to paliperidone. Contact a certified poison control center for guidance on managing paliperidone and PPM-3 overdose. Generally, management consists of supportive care.

Black-box warning in dementia. As with all atypical antipsychotics, the black-box warning for PPM-3 states that it is not approved for, and should not be used in, patients with dementia-related psychosis. An analysis of placebo-controlled studies revealed that patients taking an antipsychotic had (1) 1.6 to 1.7 times the risk of death than those who received placebo and (2) a higher incidence of cerebrovascular adverse reactions.

Adverse reactions

The safety profile of PPM-3 is similar to that of PPM-1. The most common adverse reactions are:

Related Resources

- Sedky K, Nazir R, Lindenmayer JP, et al. Paliperidone palmitate: once monthly treatment option for schizophrenia. *Current Psychiatry*. 2010;9(3):48-49.
- Berwaerts J, Liu Y, Gopal S, et al. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: a randomized clinical trial [published online March 29, 2015]. *JAMA Psychiatry*. doi: 10.1001/jamapsychiatry.2015.0241.

Drug Brand Names

Paliperidone palmitate • Invega Sustenna, Invega Trinza
Risperidone • Risperdal

- reaction at the injection site
- weight gain
- headache
- upper respiratory tract infection
- akathisia
- parkinsonism.

See the full prescribing information for a complete list of adverse effects.

Source: Invega Trinza [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2015.

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Time to relapse was significantly longer for patients who received PPM-3 than for those who received placebo