Paliperidone palmitate (Invega Sustenna and Trinza)

National Drug Monograph

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

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Paliperidone palmitate is a long-acting intramuscular injection formulation of paliperidone; an active metabolite of risperidone
- FDA label indications - acute and maintenance treatment of schizophrenia in adults.
- The VANF currently contains the long-acting IM injection formulations of haloperidol, fluphenazine and risperidone.
- To reduce the risk of hypersensitivity and that of first dose adverse effects such as orthostasis and extrapyramidal symptoms, patients who have never taken the oral or injectable forms of paliperidone or risperidone should be exposed to oral risperidone or paliperidone prior to initiation of paliperidone palmitate.
- Patients should not receive supplemental oral doses of antipsyhcotics after the first dose of IM paliperidone palmitate.
- The dose of paliperidone palmitate should be adjusted for patients with a creatinine clearance (CrCl) $\geq$50 to <80 mL/min. Paliperidone palmitate should not be used in patients with a CrCl <50 mL/min.
- Paliperidone palmitate's efficacy in schizophrenia separated from placebo as early as Day 8 in patients with moderate to severe symptoms as measured by a change in PANSS scores. Paliperidone palmitate demonstrated superiority to placebo in preventing relapse.
- Paliperidone palmitate's adverse effect profile is similar to that of risperidone and oral paliperidone. Pain and local reactions at the injection site appear to be minimal.

Introduction

Paliperidone palmitate is a long-acting intramuscular injection formulation of paliperidone approved by the FDA on July 31, 2009. Paliperidone is an active metabolite of risperidone (9-hydroxyrisperidone), an atypical antipsychotic. Paliperidone is available as an extended-release oral product and is not currently on the VA National Formulary.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating paliperidone palmitate for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1-3]

Paliperidone palmitate is a nearly insoluble ester. The formulation, an aqueous nanosuspension, is created by wet grinding paliperidone palmitate to increases its surface area. Following administration, the isotonic buffer penetrates muscle tissue where undissolved particles localize as an agglomerate. These nanoparticles dissolve in interstial fluids and are then hydrolyzed by esterases to palmitic acid and paliperidone. Dissolution of the agglomerate results in a bi-phasic appearance of paliperidone in the systemic circulation. There is an initial zero-order release of ~17% of the dose and the remainder is released via a first-order process which governs its long half-life. This slow dissolution process allows for once a month dosing.

Paliperione's exact mechanism of action, like that of all antipsychotics, is unknown. It is believed to have its therapeutic effects by antagonizing central dompamine (D_2) and serotonin Type 2 ($5\text{-}HT_{2A}$) receptors.

Pharmacokinetics

Parameter	Paliperidone palmitate
Metabolism	Initial hydrolysis by esters to palmitic acid and paliperidone (active). Paliperidone: hydroxylation, dehydrogenation and benzisoxazole scission. Minimal CYP2D6 and 3A4 involvement
Elimination	Renal
Half-life	Median: 25-49 days
Protein Binding	74%
Bioavailability	94%

FDA Approved Indication(s) and Off-label Uses[1]

FDA label indications: Acute and maintenance treatment of schizophrenia in adults.

Potential off-label uses: Treatment of schizoaffective disorder, bipolar disorders, and other conditions for which an atypical antipsychotic might be appropriate.

Current VA National Formulary Alternatives

The VANF currently contains the long-acting IM injection formulations of haloperidol, fluphenazine and risperidone.

Dosage and Administration[1, 2]

Dose Equivalents	
IM Paliperidone palmitate, mg	Paliperidone, mg
39	25
78	50
117	75
156	100
234	150

Initiation in paliperidone or risperidone naïve patients

Although they are uncommon, allergic and hypersensitivity reactions to paliperidone and risperidone have been reported. To reduce this risk and that of first dose adverse effects such as orthostasis and extrapyramidal symptoms, patients who have never taken the oral or injectable forms of paliperidone or risperidone should be exposed to oral risperidone or paliperidone prior to initiation of paliperidone palmitate. It is recommended that naive patients receive two oral daily doses of either paliperidone 3 mg or risperidone 1 mg. Table 1 provides recommendations for initiating paliperidone palmitate in patients who are not taking an antipsychotic in any form or who are currently taking an oral antipsychotic.

Table 1. Initiation and administration of paliperidone palmitate (with previous exposure)

Day	Dose (CrCl ≥80 mL/min)	*Injection site & needle size
1	234 mg	Deltoid muscle Patient ≥90 kg: 1.5 inch 22 gauge needle Patient <90 kg: 1.0 inch 23 gauge needle
8 (±2 days)	156 mg	Deltoid muscle (See Day 1)
36 (±7 days) then q28 days (±7 days)	117 mg Adjust dose based on need and tolerability	Deltoid (See Day 1) or Gluteal muscle: 1.5 inch 22 gauge needle (all weights)

*Injection site should be rotated monthly

As noted in Table 1, there is a flexible window around how soon the next dose needs to be administered during treatment initiation and maintenance. Management of missed doses outside these windows are recommended by the manufacturer is as follows (Doses need to be adjusted for renal function if necessary):

Missed second dose (Day 8):

- If less than 4-weeks have elapsed since the first injection (Day 1), then the patient should receive the second dose (156 mg) in the deltoid as soon as possible and their third dose (117 mg), in either the deltoid or gluteal muscle, should be administered 5 weeks after the first injection regardless of the time of the second injection.
- If 4 to 7 weeks have elapsed since the first injection, resume dosing by giving a 156 mg dose administered in the deltoid as soon as possible and a second 156 mg in the other deltoid one week later.
- If >7 weeks have elapsed since the first injection, re-initiate dosing following the recommended regimen in Table 1 starting at Day 1.

Missed maintenance dose:

- 1 to 1.5 months since last injection: Administer previous maintenance dose in the deltoid muscle as soon as possible, followed by monthly injections
- >1.5 to 6 months since last injection: Administer two previous maintenance doses in the deltoid muscle 1-week apart. If previous maintenance dose was 234 mg, then give doses of 234 mg and 156 mg in the detoid 1-week apart. Resume monthly injections.

- ≥6 months since last injection: Same as starting treatment, i.e., 234 mg and 156 mg injections in the deltoid muscle 1-week apart, then resume monthly maintenance dose.

Switching to paliperidone palmitate in patients currently receiving oral antipsychotics
Patients who have never taken paliperidone or risperidone (in any form) should receive oral doses of one or the other prior to starting IM paliperidone palmitate (See above: **Initiation in paliperidone or risperidone naïve patient)**. Dose initiation is outlined in Table 1. Once a patient has received a dose of IM paliperidone, all oral antipsychotics are to be discontinued. Table 2 provides recommended maintenance doses for patients being switched from oral paliperidone to paliperidone palmitate.

Table 2. Recommended maintenance dose conversions from oral ER to IM paliperidone (based on pharmacokinetic model simulations)

Paliperidone oral ER, mg/day	Paliperidone palmitate IM, mg every month
12	234
6	117
3	39 or 78

Switching to paliperidone palmitate in patients currently receiving a long-acting IM antipsychotic
When switching patients from long-acting IM injections of haloperidol, fluphenazine, or risperidone, paliperidone palmitate can be started at the time of the patients next scheduled injection in lieu of their current antipsychotic, i.e., no washout period is required. Patients should be started on their anticipated paliperidone maintenance dose. Estimated equivalent doses based on pharmacokinetic model simulations for risperidone long-acting IM and paliperidone palmitate are provided in Table 3. It is recommended that the first dose be given in the deltoid muscle to achieve higher serum concentrations. Patients who have never taken paliperidone or risperidone should receive should receive oral doses of one or the other prior to starting IM paliperidone palmitate. (See above: **Initiation in paliperidone or risperidone naïve patient)**. Once a patient has received a dose of IM paliperidone, all oral antipsychotics are to be discontinued.

Table 3. Recommended maintenance dose conversions from IM risperidone long-acting to IM paliperidone

Risperidone IM, mg every 2-weeks	Paliperidone IM, mg every month
12.5	39
25	78
37.5	117
50	156
Unknown	234

Why do other antipsychotics need to be discontinued when paliperidone palmitate is started?
Unlike other long-acting IM antipsychotics, paliperidone palmitate's biphasic release allows initiation plasma concentrations within the range observed with 6 to 12 mg oral paliperidone. Pharmacokinetic model simulations have estimated that when paliperidone palmitate (234 mg Day, 156 mg Day 8, and then 117 mg every month) is added to oral paliperidone 6 mg per day the median Cmax was 55 ng/mL compared to a median Cmax of 19 ng/mL for oral paliperidone 6 mg/day. A second simulation using a 234 mg dose of paliperidone palmitate for initiation and maintenance in addition to 12 mg/day of oral paliperidone estimated a median Cmax of 80 ng/mL compared to 38 ng/mL for oral paliperidone 12 mg/day.
All clinical trials with paliperidone palmitate required the discontinuation of all antipsychotics following the initiation of paliperidone including trials for the acute treatment of schizophrenia. In those trials patients were hospitalized per protocol at least until receiving their Day 8 injection.

Prolonged use of oral antipsychotics with long-acting IM antipsychotics increases the risk for adverse events which may affect the patient's acceptance of the long-acting drug. In the case of paliperidone palmitate, the supplementation of oral antipsychotics will make it difficult to determine which drug is the cause of the patient's adverse events and whether he/she is on the correct maintenance dose of paliperidone palmitate.

Dosing and Use in Special Populations

Dose adjustment in patients with impaired kidney function
Paliperidone's major route of elimination is as unchanged drug via the kidney. Hence, a dose reduction is recommended for patients with a creatinine clearance (CrCl) ≥50 to <80 mL/min (mild kidney impairment). The recommended dose is 156 mg paliperidone palmitate on Day 1 and 117 mg on Day 8 given in the deltoid muscle. A monthly maintenance dose of 78 mg is recommended and can be administered in the deltoid or gluteal muscle. Paliperidone palmitate is not recommended for patients with moderate or severe kidney impairment (CrCl <50 mL/min).
Dose adjustment in hepatic impairment
Paliperidone palmitate has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, the manufacturer states that no dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh Class B). Paliperidone has not been studied in patients with severe hepatic impairment.
Dose adjustment in the elderly
Paliperidone has not been studied sufficiently in the elderly. It is recommended that the dose be adjusted based on kidney function and that renal function be monitored for changes that could affect dosing. Patients should also be assessed for sufficient muscle mass at the injection sites to allow safe and tolerable administration.
*Dose adjustments are **not** necessary based on patient*
Race
Gender
Smoking status

Injection preparation, administration, and disposal
The paliperidone palmitate kit includes a single use, prefilled syringe and 2 safety needles (1.5 inch 22 gauge and 1 inch 23 gauge). Refer to Table 1 for when to use the different sized safety needles. The kit should be stored at room temperature. No reconstitution is necessary. The syringe should be shaken for at least 10 seconds prior to attaching the needle. The entire contents are to be injected into the selected injection site (deltoid or gluteal muscle). The needle protection system should be activated after the injection is complete and prior to discarding the syringe and needle.

Table 4. Injection volumes

Paliperidone, mg	Volume, mL
39	0.25
78	0.5
117	0.75
156	1.0
234	1.5

Risperidone long-acting injection volume is 2 mL for all strengths.

Paliperidone palmitate is not to be given intravenously or subcutaneously.

Efficacy[1, 4-7]

Efficacy Measures

Positive and Negative Symptom Scale for Schizophrenia (PANSS) – Often used as an entrant criteria as well as a primary efficacy measure. The PANSS is a 30-item rating scale that adapts earlier scales such as the Brief Psychiatric Rating Scale to assess the positive and negative symptoms of schizophrenia. Each item is rated by physician observation and scored from 1 to 7 (the greater the value, the greater the severity). This scale has been validated.

Clinical Global Impressions – Severity (CGI-S) – The CGI-S is a subscale of the CGI scale that measures severity of illness; the other two CGI subscales assess global improvement and therapeutic response. Severity of illness is rated on a 7-point spectrum with 1 signifying "normal" and 7 "among the most severely ill." The CGI-S measures illness severity over time.

Summary of efficacy findings

Paliperidone palmitate's efficacy in the acute treatment of schizophrenia was established in one 9-week and three 13-week double-blind, randomized, placebo-controlled, fixed-dose studies of patients who have acutely relapsed. Only the 9-week trial and one 13-week trial have been published, while the others are described in the product's package insert. The results of an unpublished, non-inferiority, comparison trial with risperidone long-acting injection are available, while the findings of two others are not yet available.

Published 9-week Clinical Trial[4]

Men and women, ages 18-65 years, meeting criteria for DSM-IV diagnosis of schizophrenia for at least 1-year were enrolled in a Phase 2b study to evaluate the safety and efficacy of paliperidone palmitate compared to placebo. The PANSS and the CGI-S served as the primary and secondary efficacy measures, respectively. To be eligibe participants had to have a PANSS total score of 70-120 (moderate to severe symptoms) at screening and 60 – 120 on Day 1 prior to receipt of study drug. The study had three phases: Phase 1 – up to 5 days for screening and washout of disallowed medications, Phase 2 – a 7 day run in phase during which participants were hospitalized and received open-label oral paliperidone, and Phase 3 – a 64 day double-blind treatment period with subjects randomly assigned (1:1:1) to paliperidone palmitate 78 mg or 156 mg, or placebo. Doses were administered on Days 1, 8 and 36 in alternate gluteal muscles. Patients were hospitalized a minimum of 14 days. The study had a 90% power to detect a difference of at least 10 points on the change from baseline to endpoint in total PANSS score between placebo and either active treatment arm, with a significance level of 0.1 (two-sided) and at least 70 patients per treatment arm.

A total of 266 patients met initial eligibility requirements and were sequentially assigned to 4 different doses of oral paliperidone. Ninety-three percent (247) completed this phase (Phase 2) and entered the double-blind treatment phase (Phase 3). One hundred twenty-five patients completed the study (receipt of all 3 doses of IM paliperidone or placebo): 35/84 (42%) assigned to placebo and 107/163 (66%) assigned to paliperidone.

At the study's endpoint, the mean changes in total PANSS differed significantly from placebo for both palidperidone treatment arms (Table 5); these changes were statistically significant by Day 8 in both active treatment arms. Both doses of paliperidone resulted in significant decreases in the 5 PANSS factor scores compared to placebo with the exception of uncontrolled hostility/excitement in the 78 mg group. Response, a 30% or greater improvement in baseline PANSS score, was more common in the two paliperidone treatment arms: 14% placebo, 33% paliperidone 78 mg and 37% paliperidone 156 mg. Both paliperidone treatment groups had greater symptom improvement in CGI-S scores at the study's end compared to placebo ($p \leq 0.004$).

Table 5. Change in PANSS and CGI-S Scales by Treatment Arm

Outcome	Placebo n= 66	Paliperidone 78 mg n=63	Paliperidone 156 mg n=68
PANSS total			
Baseline (SD)	87.8 (13.90)	88.0 (12.39)	85.2 (11.09)
Change from baseline	6.2 (18.25)	-5.2 (21.52), p=0.001	-7.8 (19.40), p<0.001
CGI-S Scale			
Marked-extremely severe			
Baseline	51%	53%	44%
Endpoint	50%	36%	32%

Published 13-week, double-blind, placebo-controlled, multi-center, Phase III trial[5]
Randomizing 652 patients with schizophrenia (1:1:1:1) investigators compared placebo to three fixed doses of paliperidone (39 mg, 156 mg and 234 mg) started 1-week (Day 8) after a 234 mg (or placebo) initial dose given in the deltoid. Patients then received their fixed dose every 4-weeks. All IM injections after Day 1 were given in the deltoid or gluteal muscle based on patient preference. Inclusion and exclusion criteria and outcome measures were similar to those described above for the 9-week trial. Ninety-eight percent of both groups were included in the intention-to-treat analysis and 100% of participants were included in the safety analysis.

Fifty-four percent in the paliperidone palmitate treatment arm completed the study compared to 43% in the placebo arm. All 3 paliperidone treatment groups achieved a significant and dose-related change in total PANSS score compared to placebo. The differences from placebo in least squares means change at study endpoint were -5.1, -8.7, and -9.8 for the paliperidone 39 mg, 156 mg, and 234 mg groups, respectively. Patients receiving placebo appeared to experience a 4 point decline (approximately) in total PANSS score between baseline and study endpoint. Compared with placebo, the estimated effect sizes based on standard differences in least squares mean values between groups were 0.28 for the 39 mg dose, 0.49 for the 156 mg dose, and 0.55 for the 234 mg dose. Patients assigned to the 156 mg and 234 mg doses of paliperidone were found to improve significantly on all secondary outcome measures including the Personal and Social Performance Scale, CGI-S, and all PANSS subscales. The lower paliperidone group did not differ from placebo in either the Personal and Social Performance Scale or CGI-S, and had mixed results on the PANSS subscales. All three paliperidone groups had significantly more patients respond to treatment (a $\geq$ 30% reduction in PANSS score) compared to placebo (20%), 39 mg group 33.5%, 156 mg 41%, and 234 mg 40%. Sleep quality was reported to be improved by patients assigned to the 156 and 234 mg paliperidone groups.

Unpublished Clinical Trials in Schizophrenia[1]
Paliperidone's superiority to placebo, based on change in PANSS scores, was also demonstrated in two other 13-week clinical trials.
One trial of 349 patients using the same design as above (substituting a 78 mg dose for the 39 mg) found only the 156 mg to be superior to placebo.
A second trial of 513 patients compared fix doses of 39 mg, 78 mg and 156 mg given on Days 1 and 8, then every 4-weeks. All three doses of paliperiodone were superior to placebo.

Published 25-week Injection Site Cross-over Trial[6]
Efficacy was a secondary outcome measure in a 25-week, open-label, safety and tolerability study that enrolled patients with schizophrenia and a PANSS total score $\leq$70 at screening. The change in median PANSS scores from baseline was minimal (0 to -2) in patients treated with 78 mg, 117 mg and 156 mg doses of paliperidone palmitate. At the study's conclusion CGI-S scores (compared to baseline) worsened or stayed the same in 21% of patients and improved in 79% of patients.
Unpublished Clinical Trials as Maintenance Therapy

To establish paliperidone's efficacy in maintaining symptomatic control in schizophrenia the manufacturer sponsored a double-blind, randomized extension trial following a fixed dose stabilization period of at least 12-weeks. A total of 410 stabilized patients were randomized to either the dose of paliperidone they received during the stabilization phase (39 mg, 78 mg, or 156 mg) or placebo administered every 4-weeks. Patients were followed until they experienced a relapse of schizophrenia symptoms. Relapse was predefined as the time to first emergence of one or more of the following: psychiatric hospitalization, >25% increase (if the baseline score was $\geq$40) or a 10-point increase (if the baseline score was $\leq$ 40) in total PANSS score on two consecutive assessments, deliberate self-harm, violent behavior, suicidal/homicidal ideation, or a score of $\geq$ 5 or $\geq$ 6 on individual PANSS items depending on the maximum baseline score on two consecutive assessments. Time to relapse was the primary efficacy outcome measure. The study was stopped prematurely when a pre-planned analysis demonstrated a significantly longer time to relapse in patients treated with paliperidone compared to placebo.

Unpublished Comparison Trial to Risperidone LAIM (RLAIM)[7]

The findings of a 53-week randomized, double-blind, parallel-group comparison, non-inferiority trial are posted on clinicaltrials.gov. All subjects had a diagnosis of schizophrenia per DSM-IV for at least l-year and a PANSS score of 60 to 120. Subjects received flexible dose paliperidone palmitate (39, 78, 117, or 156 mg) or RLAIM (25, 37.5, or 50 mg). After a 4-day tolerability test with 3 mg/day oral paliperidone (if necessary), subjects were randomized to one of the above doses of paliperidone or RLAIM. Subjects in the paliperidone group received their assigned dose on Days 1 and 8, and then every 4-weeks, while those assigned to RLAIM were dosed every 2-weeks. Both groups received their IM injections in the gluteus throughtout the trial. The RLAIM group was permitted 1 to 6 mg/day of oral risperidone during the first 4-weeks of the study and 1 to 4 mg/day for 3-weeks after a dose adjustment. The paliperidone group was permitted oral placebo during the same time frames. The study's primary objective was to demonstrate that paliperidone is not clinically less effective than RLAIM for the treatment of schizophrenia. The conclusion of non-inferiority would be met if the lower limit of the 2-sided 95% CI for the least-squares means change in total PANSS score point estimate exceeded -5.

A total of 749 subjects were randomized: 370 to paliperidone and 370 to RLAIM. An intention-to-treat analysis included 674 subjects who received study drug, had base-line and post-baseline efficacy measures, and were not excluded from 2 study sites. The Per-Protocol Analysis Set consisted of 570 subjects who received at least 4 injections with no two being given more than 35 days apart; had baseline assessments; and no major protocol violations. A total of 747 subjects received study drug and were included in the safety analysis. So that pharmacokinetic analyses could be performed participants had blood samples drawn at baseline and weeks 9, 29, 37-43 and at study end/early withdrawal.

The primary efficacy variable of interest was the change from baseline to endpoint in total PANSS score. The mean change (SD) values from the Per-Protocol Analysis Set were -11.6 (21.22) for the paliperidone group and -14.4 (19.76) for the RLAIM group. The difference in least-squares means for change in total PANSS scores between paliperidone and RLAIM was 2.6 points (95% CI [-5.84, 0.61]). Similar results were reported for the intention-to-treat analysis set. Thus, paliperidone "was not demonstrated to be non-inferior to RLAIM."

Insomnia, psychotic disorders, schizophrenia, and anxiety were the most commonly reported treatment emergent adverse events: 25% paliperidone, 20% RLAIM. Psychotic disorders adverse events leading to discontinuation were observed in both groups: 3% paliperidone, 2% RLAIM. Severe psychotic disorders (psychosis andschizophrenia) were reported in 18% of paliperidone and 14% of RLAIM subjects.

Paliperidone's failure to demonstrate non-inferiority may be the result of several factors. First, initiation of paliperidone differed from that recommended in the product labeling while dose initiation of RLAIM was at least equivalent to what is in its label. No data are provided on dose distrubiton or mean/median doses in either treatment arm. In addition, both drugs were initiated in the gluteus as opposed to the deltoid as recommended

for paliperidone. This, along with other factors (e.g., oral supplementation) may explain why plasma concentrations were reported to be lower on Day 64 in paliperidone group compared to the dose equivalent RLAIM group. Second, the point estimates (95% CI) for the PANSS met the non-inferiority criteria for subjects with a BMI <25 kg/m^2, -0.3 (-4.63, 4.05) but not for subjects with a BMI ≥25 to < 30 kg/m^2, -0.7 (-5.29, 3.96) or ≥30 kg/m^2, -7.5 (-12.1, -2.82). Third, the change in mean PANSS scores for both drugs was consistent with those reported in placebo-controlled trials.

The authors concluded that the lower initial plasma concentration may have led to a higher incidence of psychiatric adverse events and higher rate of withdrawal due to lack of efficacy in the paliperidone group. The authors suggested that the dose regimen would need to be adjusted to optimize plasma concentrations.
Note: The results from 2 other comparative trials using the dosing regimen in paliperidone's labeling are not available although both studies have been completed.

Adverse Events (Safety Data) [1,4-7]

Deaths and Other Serious Adverse Events (Sentinel Events)

No cases of overdose were reported in clinical trials of paliperidone palmitate due to the drug being administered by a health professional. A similarly low probabilty of overdose is unlikely in clinical practice for the same reason.

Paliperidone palmitate's package insert reports that 8 patients out of the 1232 (0.6%) who received paliperidone pamitate in clinical trials reported suicidal ideation compared to 2/510 (0.4%) who received placebo. One of these trials reported 5 patients (2% of study patients) had suicide-related events such as suicidal ideation or attempts, and events suggestive of self-injury; including one case of completed suicide.

One death in a patient assigned to 234 mg of paliperidone was reported in the 13-week trial. Death was due to a cerebrovascular accident and it was determined that it was "doubtfully related to study treatment."

No data on sentinel events was identified.

Common Adverse Events

The profile of common adverse effects reported with paliperidone are not different from those reported with other atyipcal antipsychotics. See Table 6.

Table 6. Incidence of Treatment Emergent Adverse Events in ≥ 2% of Paliperidone palmitate-Treated Subjects with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials

System Organ Class Adverse Event	Placebo[a] (N=510)	39 mg (N=130)	78 mg (N=302)	156 mg (N=312)	234/39 mg (N=160)	234/156 mg[b] (N=165)	234/234 mg[b] (N=163)
Total percentage of subjects with adverse events	70	75	68	69	63	60	63
Gastrointestinal disorders							
Abdominal discomfort/pain	1	0	3	3	1	2	3
Constipation	5	3	5	5	2	4	1
Diarrhea	2	0	3	2	1	2	2
Dry mouth	1	3	1	0	1	1	1
Nausea	3	4	4	3	2	2	2
Toothache	1	1	1	3	1	2	3
Vomiting	4	5	4	2	3	2	2
General disorders and administration site conditions							
Asthenia	0	2	1	<1	0	1	1
Fatigue	1	1	2	2	1	2	1
Injection site reactions	2	0	4	6	9	7	10
Infections and infestations							
Nasopharyngitis	2	0	2	2	4	2	2
Upper respiratory tract infection	2	2	2	2	1	2	4
Urinary tract infection	1	0	1	<1	1	1	2
Injury, poisoning and procedural complications							
Skin laceration	<1	2	<1	0	1	0	0
Investigations							
Alanine aminotransferase increased	2	0	2	1	1	1	1
Weight increased	1	4	4	1	1	1	2
Musculoskeletal and connective tissue disorders							
Back pain	2	2	1	3	1	1	1
Musculoskeletal stiffness	1	1	<1	<1	1	1	2
Myalgia	1	2	1	<1	1	0	2
Pain in extremity	1	0	2	2	2	3	0
Nervous system disorders							
Akathisia	3	2	2	3	1	5	6
Dizziness	1	6	2	4	1	4	2
Extrapyramidal disorder	1	5	2	3	1	0	0
Headache	12	11	11	15	11	7	6
Somnolence/sedation	3	5	7	4	1	5	5
Psychiatric disorders							
Agitation	7	10	5	9	8	5	4
Anxiety	7	8	5	3	5	6	6
Insomnia	15	15	15	13	12	10	13
Nightmare	<1	2	0	0	0	0	0
Suicidal ideation	2	0	1	2	2	2	1
Respiratory, thoracic and mediastinal disorders							
Cough	1	2	3	1	0	1	1
Vascular disorders							
Hypertension	1	2	1	1	1	1	0

Table taken from paliperidone palmitate's package insert.

a Placebo group is pooled from all studies and included either deltoid or gluteal injection depending on study design.

b Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection.

Other Adverse Events

Extrapyramidal Symptoms (EPS)

Treatment-emergent EPS exhibited a dose-related pattern in the 13-week trial that most closely mirrors dosing in the label: 234 mg on Day 1 followed by 39 mg, 156 mg or 234 mg on Day 8 and then every 4-weeks. EPS was reported in 8% of patients randomized to placebo and 6%, 10% and 11% in the 39 mg, 156 mg and 234 mg groups, respectively. Hyperkinesia was reported by 1.3%, 4.8% and 5.5% in the 39 mg, 156 mg and 234 mg groups, respectively, and by 4.9% who received placebo. Akathesia was the most frequently reported EPS-related adverse event (<6%) across all treatment groups in the 13-week trial. The use of anti-EPS medication declined during the course of the study and was deemed similar between the four treatment groups, 8% to 12%, at the end of the study.

In the 9-week published trial, the incidence of Parkinsonism and akathesia were higher in paliperidone 78 mg (9% and 5%) and 156 mg (18% and 11%) treatment groups than placebo (7% and 4%).

Orthostatic hypotension and syncope

Orthstatic hypotension was reported by <1% of trial patients who received paliperidone palmitate compared to 0% with placebo.

Syncope was reported by <1% of trial patients who received paliperidone palmitate compared to 0% with placebo.

QT prolongation

No subject in 9- or 13-week studies experienced a change in QTcLD exceeding 60 msec or had a QTcLD value >500 msec.

In the maintenance study, the QTcLD change did not exceed 60 msec in any subject. One subject, with a heart rate of 45 beats per minute, had a QTcLD of 507 msec (corrected QTcB = 483 msec).

Hyperprolactenemia

The 9-week trial reported a dose-related increase in prolactin has been reported resulting in 3 cases of galactorrhea and 1 case of ammenorrhea in women, and 1 case of erectile dysfunction (Table 7).

Table 7. Median prolactin concentrations (ng/mL) by gender, study time point and treatment arm

Gender/Time point	Placebo	Paliperidone 78 mg	Paliperidone 156 mg
Males			
Pre-dose, oral run-in	7.0	6.5	7.0
Baseline, dbl-blind	29.0	27.0	33.0
Endpt, dbl-blind	6.0	18.0	30.0
Females			
Pre-dose, oral run-in	15.0	12.0	20.0
Baseline, dbl-blind	92.0	94.5	124.0
Endpt, dbl-blind	8.0	33.5	66.5

Metabolic Effects
Hyperglycemia was reported in the clinical trials with paliperidone palmitate.
Weight gain – paliperidone palmitate resulted in a dose-related weight gain.

Table 8. Percent of subjects experiencing a ≥7% weight gain

Study	Placebo	Paliperidone 39 mg	Paliperidone 78 mg	Palieridone 156 mg	Paliperidone 234 mg
9-week	4	-	8	6	-
13-week	5	6	-	8	13
13-week pooled data	2	6	9	10	-

In a 33-week open-label maintenance trial, paliperidone palmitate subjects gained a mean of 0.7 kg and 12% of subjects experienced ≥7% weight gain.

Median cholesterol and triglyceride concentrations did not differ from treatment with placebo in any of the clinical trials.

Tolerability
The percentages of patients who discontinued paliperidone palmitate or placebo due to adverse effects in the four-fixed dose, double-blind, placebo-controlled trials were 5% and 7.8%, respectively.

Injection site pain and discomfort
Pain at the injection site was measured by a visual analog scale (0 = no pain, 100 = unbearably painful) in the clinical trials. Pooled data from two 13-week, placebo-controlled, fixed dose trials reported subject's pain at their injection sites decreased in all treatment groups (placebo and paliperidone palmitate 39 mg, 78 mg and 156 mg) over time. At first dose pain scale scores ranges from 10 to 11.1 and at the last dose ranged from 7.7 to 9.8.

Following an initial dose of 234 mg paliperidone palmitate or placebo, inspection of the injection site by blinded personnel noted infrequent induration, redness, or swelling with both groups had a similar incidence. Site reactions decreased with time. Investigators reported that pain or local reaction was absent in 69% to 100% after the first dose and absent in 95% to 100% subjects at Day 92.

At U.S. trial sites 77% of patients stated they preferred injection in the deltoid muscle.

Precautions/Contraindications[1]

Like all antipsychotics, paliperidone palmitate's labeling includes a box warning of increased mortality in elderly patients with dementia-related psychosis.

Precautions

Like all antipsychotics, paliperidone palmitate's labeling includes a warning about a higher incidence of cerebrovascular adverse events in placebo-controlled trials with risperidone, aripiprazole and olanzapine in elderly patients with dementia.

Neuroleptic malignant syndrome
QT prolongation
Tardive dyskinesia
Hyperglycemia and diabetes melitus
Weight gain
Hyperprolactinemia
Orthostatic hypotension and syncope
Leukopenia, neutropenia, and agranulcytosis
Potential for cognitive and motor impairment
Seizures

Dysphagia
Suicide
Priapism
Thrombic thrombocytopenia purpura
Disruption of body temperature regulation

Use in Pregnancy and Lactation
Pregnancy Category C
Paliperidone is excreted in milk. Women are advised not to breast feed infants while taking paliperidone palmitate.

Contraindications
Previous hypersensitivity reactions to any form of paliperidone or risperidone.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:
LA/SA for generic name ***Paliperidone***: risperidone, paroxetine, haloperidol
LA/SA for trade name ***Invega Sustenna***: Inderal, Inspra, Invagesic

Drug Interactions

Drug-Drug Interactions
In vitro paliperidone did not inhibit Cytochrome P450 isozymes known to be responsible for drug metabolism or P-glycoprotein. It is not expected that paliperidone will inhibit the clearance of medications reliant on these pathways for their clearance.
The renal clearance of oral paliperidone was increased by 35% when taken with carbamazepine. The dose of paliperidone palmitate should be re-evaluated with the initiation or discontinuation of carbamazepine.
The Cmax and AUC of a single oral dose of paliperidone were increased by ~50% when taken by patients at steady-state on divalproex. The dose of paliperidone palmitate should be re-evaluated with the initiation or discontinuation of divalproex.
Paliperidone may enhance the properties of alcohol and other drugs that affect the central nervous system.
Paliperidone may antagonize levodopa and dopamine agonists.
Paliperidone's minimal dependence on the CYP2D6 and 3A4 make it unlikely that inhibitors or competitive substrates for these enzymes will affect paliperidone's clearance.

Drug-Lab Interactions
No drug-lab interactions are known.

Pharmacoeconomic Analysis

No pharmacoeconomic data are available.

Conclusions

Paliperidone palmitate offers another long-acting injectable option for the treatment of schizophrenia. These formulations are typically reserved for patients who are nonadherent with oral medications. Paliperidone palmitate's chief advantages over the long-acting IM formulations of haloperidol, fluphenazine and risperidone are its once a month dosing interval and that supplementary oral doses of antipsychotics are not needed after the

first dose. Other advantages vary by comparison agent and include administration in the deltoid or gluteal muscle after treatment initiation, an aqueous formulation with no need for refrigeration, and no need for reconstitution. It should be pointed out that there is evidence supporting a dosing frequency as long as every 6 weeks with fluphenazine decanoate.[8]

Possible disadvantages include the requirement that patient's return for a second injection ~1 week after the first, convincing providers that supplementary oral doses are not recommended during initiation particularly if the patient is markedly ill. Unlike riserpidone long-acting injection, paliperidone palmitate does not have a label indication for bipolar I disorder and no trials have been published to support such off-label use. The product cost of paliperidone long-acting IM is markedly greater than haloperidol or fluphenazine decanoate. The actual cost difference between the long-acting IM forms of paliperidone and risperidone is uncertain.

Given that the active end product, paliperidone, is the active metabolite of risperidone, the efficacy and safety of paliperidone palmitate is expected to be comparable to that of risperidone long-acting injection. One unpublished head-to-head trial for which preliminary results are available found that paliperidone palmitate failed to meet the non-inferiority criteria compared to risperidone long-acting IM. However, there are several issues with study design that may explain this result. Until the findings from this study and two others that do not share the methodological concerns are published final conclusions on comparative efficacy between the two drugs remain premature.

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Addendum: INVEGA TRINZA

Paliperidone palmitate's availability as a 3-month formulation is indicated for the treatment of patients with schizophrenia for whom the drug has been shown to be effective and tolerated after at least 4 monthly injections of the 1-month formulation. The 3 month dosing interval is possible due to the drug's prolonged period of release from the injection site of up to 180 days and long half-life of 84 to 95 days and 118 to 139 days following deltoid and gluteus injection, respectively.

The efficacy and safety of the 3-month formulation was demonstrated in a single double-blind, placebo-controlled, multi-national relapse trial. Persons with schizophrenia per *DSM-IV TR* criteria of at least one year's duration with a PANSS score of <120 (out of a maximum of 210) were eligible to participate barring any of the usual exclusion criteria such as another active *DSM-IV* diagnosis, a 6 month history of substance dependence, history of neuroleptic malignant syndrome or tardive dyskinesia, and malignant neoplasm with 5 years. Following a 3-week screen process (n=620), enrolled patients entered into two open-label phases. The first was a 17-week translational phase (n=506) during which the 1-month paliperidone injection formulation was introduced and a maintenance dose was selected using a flexible dose regimen with the doses on Days 64 and 92 to be identical. The second was a 12-week maintenance phase (n=379) during which subjects received the 3-month formulation in a dose of paliperidone equivalent to 3.5 times the dose received on Day 92. Next, was the double-blind phase when stable patients were randomized to either 3-month injection of placebo (n=145) or the same dose of paliperidone as Day 120 (n=160). The primary outcome measure was time to first relapse event in the double-blind phase. A relapse event was defined the same as in trials of the extended-release oral and 1-month injection formulations and could be the occurrence of any of the following after randomization: 1) hospitalization for schizophrenia; 2) a 25% increase in total PANSS score for 2 consecutive assessments for patients with a PANSS score of >40 at randomization or a 10-point increase for those with a PANSS $\leq$40 at randomization; 3) increases in distinct PANSS item scores for 2 consecutive assessments, e.g., conceptual organization, persecution, and hallucinatory behavior; 4) clinically significant deliberate self-injury or violence; or suicidal or homicidal behavior and aggressive behavior.

The study was stopped after a predetermined interim analysis (42 cumulative relapses) of 283 patients (n=148 paliperidone and n=135 placebo) with the conclusion that every 3-month injections of paliperidone was superior to placebo. A relapse event was experienced by 7% in the paliperidone group (n=11) and 23% assigned to placebo (n=31); hazard ratio = 3.45 (95% CI 1.73-6.88). The median time to relapse was 274 days for placebo and not estimable for paliperidone. Analysis of the final data set of 305 randomized patients (n=160 paliperidone) revealed findings similar to the interim analysis: 29% of placebo patients relapsed compared to 9% assigned to paliperidone; hazard ratio 3.81, 95% CI 2.08-6.99; and median time to relapse was 395 days for placebo and not estimable for paliperidone. Patients assigned to paliperidone maintained or improved on secondary outcome measures such as mean PANSS score, Clinical Global Impression-Severity, and Personal and Social Performance scores. The 350 mg and 525 mg were the most common doses of the paliperidone 3-month formulation at the end of the maintenance phase (n=185 (49%) and n=149 (39%), respectively) and at the start of the double-blind phase (n=78 (49%) and n=61 (38%), respectively. A greater proportion of patients receiving 525 mg every 3 months completed the double-blind phase than the other strengths (n=14/61, 23%). Overall, 25/160 patients (15.6%) completed the double-blind phase.

The table below displays common treatment emergent adverse events reported in the double-blind phase of the trial.

Treatment Emergent Adverse Event (TEAE) in the Double-Blind Phase (q3 month injections)

TEAE	Placebo, % (n=145)	Paliperidone, % (n=160)
$\geq$1 TEAE	58	62
• Serious	10	3
• Drug withdrawal	1	0
Common TEAE ($\geq$2%)		

• Anxiety • Insomnia • Headache • Schizophrenia-related • Agitation • Suicidal ideation • Upper respiratory infection • Urinary tract infection	11 12 4 10 2 2 2 1	8 7 9 1 1 0 4 3
Metabolic TEAE • Weight loss • Weight gain • Increased blood glucose • Hyperglycemia	 8 3 2 3	 1 9 2 0
EPS TEAE ≥1% • Akathisia	3 1	8 4
Injection site reactions	0	4

Dose and Administration (Please refer to the package insert for detailed information)

- Patients should be transitioned to paliperidone 3-month injection after being adequately treated with the paliperidone 1-month injection for at least 4 months.
- Injection can be given in the deltoid or gluteus muscle.
- Initiate paliperidone 3-month injection at the time the next monthly injection is due with the dose based on the previous 1-month injection using the following table:

If the Last Dose paliperidone 1-month is:	Initiate paliperidone 3-month injection at the following dose:
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

- Pharmacokinetic studies with the 3-month formulation have not been conducted in special populations including persons with kidney or hepatic impairment. Dosage recommendations are based on modeling of oral paliperidone and the 3-month injection.
    - Not recommended for patients whose CrCl is <50 mL/min
- Missed doses
    - Doses may be administered within 2-weeks before or after each scheduled 3-month time point.
    - If more than 2-weeks but less than 4 months have elapsed since the last 3-month injection, the previously administered 3-month dose should be administered, then continue with an every 3-month schedule.
    - If 4 months up to and including 9 months have elapsed since the last 3-month injection, then a 3-month injection should not be given as re-initiation is necessary with two 1-month injections given 7-days a part (Days 1 and 8) based on the previous dose of 3-month paliperidone injection, followed by a 3-month injection 30 days after the second 1-month injection. See the package insert for more detailed instructions.

In summary, paliperidone 3-month injection is a viable option for patients with schizophrenia in whom paliperidone's effectiveness and tolerability have been established with at least 4 months of the 1-month paliperidone injection and less frequent injections is a convenience. Whether the reduced frequency of injections translates to fewer contacts between patient and mental health care providers is best determined on an individual basis.

References

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