

Formulary Monograph
Paliperidone Palmitate
Extended-Release Injectable Suspension
(Invega[®] Sustenna[™])

Classification: Atypical antipsychotics (AHFS 28:16.08.04)

Medicinal Chemistry and Pharmaceutics

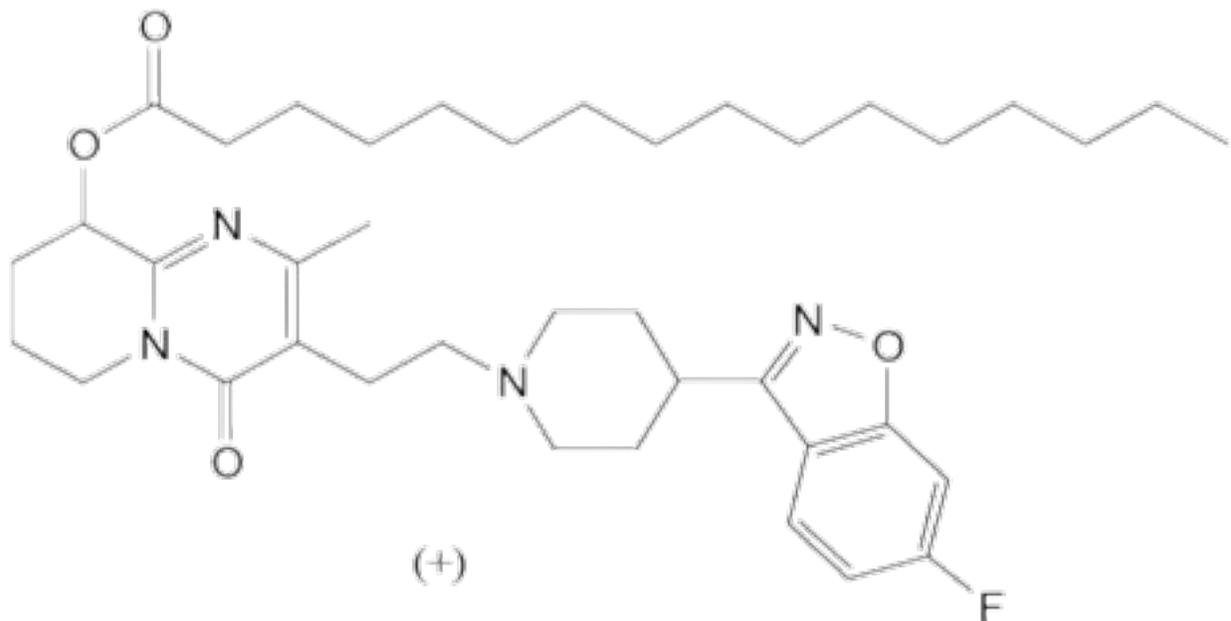


Illustration 1: Structure of paliperidone palmitate

Paliperidone palmitate's chemical name is (9RS)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl hexadecanoate. The structure shows the (+) enantiomer. It is very slightly soluble in ethanol and methanol, practically insoluble in polyethylene glycol 400 and propylene glycol, and slightly soluble in ethyl acetate. The commercial product is a racemic mixture of paliperidone palmitate enantiomers wet-milled into nano particles that have an increased surface area resulting in an increased rate of drug absorption and bioavailability. The nano particles sustained release profile provides a therapeutic effect throughout the four-week intramuscular dosing interval.

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Clinical Pharmacology

Mechanism Of Action

Paliperidone is the major active metabolite of risperidone, also described as 9-OH-risperidone. The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown, but it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central D₂ and 5-HT_{2A} receptor antagonism.

Pharmacodynamics

Paliperidone is an antagonist at the dopamine D₂ receptor, serotonin 5-HT_{2A} receptor, α₁ and α₂ adrenergic receptors, and H₁ histaminergic receptor. Paliperidone has virtually no affinity for cholinergic muscarinic M₁.

Comprehensive listings of ligand binding kinetics can be found in the [Collaborative Drug Discovery Public Access Database](#) and the [PDSP Ki Database](#). Since these data do not include the pharmacologic activity (inert, agonist, antagonist, inverse agonist, or inverse antagonist) that results from the binding of paliperidone to any specific receptor, it is not possible to make valid *a priori* conclusions regarding the effects of paliperidone.

The binding coefficients for the most highly bound receptors for either paliperidone or risperidone are shown in the table.

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| Receptor | Paliperidone | Pali SEM | Risperidone | Risp SEM |
|--------------------|---------------------|-----------------|--------------------|-----------------|
| 5-HT1B | 47.90 | 30.57 | 27.80 | 13.24 |
| 5-HT1D | 68.00 | 51.01 | 57.71 | 41.79 |
| 5-HT2A | 1.14 | 0.30 | 0.96 | 0.51 |
| 5-HT2B | 61.86 | 0.00 | 61.93 | 26.78 |
| 5-HT2C | 48.00 | 0.00 | 32.56 | 5.55 |
| 5-HT7 | 2.70 | 0.00 | 5.63 | 0.58 |
| Adrenergic Alpha1 | 10.10 | 0.00 | 2.70 | 0.00 |
| Adrenergic Alpha1A | 2.50 | 0.00 | 5.00 | 0.00 |
| Adrenergic Alpha1B | 0.70 | 0.00 | 9.00 | 0.00 |
| Adrenergic Alpha2 | 80.00 | 0.00 | 8.00 | 0.00 |
| Adrenergic Alpha2A | 17.35 | 12.65 | 83.70 | 38.89 |
| Adrenergic Alpha2B | 33.20 | 23.80 | 74.70 | 33.10 |
| Adrenergic Alpha2C | 7.35 | 3.65 | 3.73 | 1.85 |
| Dopamine D1 | 41.04 | 0.00 | 243.53 | 141.94 |
| Dopamine D2 | 3.40 | 2.06 | 3.85 | 1.42 |
| Dopamine D2 Long | 4.80 | 0.00 | 5.98 | 2.69 |
| Dopamine D2 Short | 4.10 | 0.00 | 4.73 | 0.84 |
| Dopamine D2A | | | 1.70 | 0.00 |
| Dopamine D3 | 2.63 | 2.15 | 7.56 | 1.54 |
| Dopamine D4 | 54.30 | 0.00 | 7.12 | 2.08 |
| Dopamine D4.2 | 30.00 | 0.00 | 16.70 | 2.03 |
| Dopamine D4.4 | | | 26.25 | 18.75 |
| Dopamine D5 | 29.00 | 0.00 | 289.50 | 273.50 |
| Histamine H1 | 13.67 | 9.19 | 17.08 | 5.65 |

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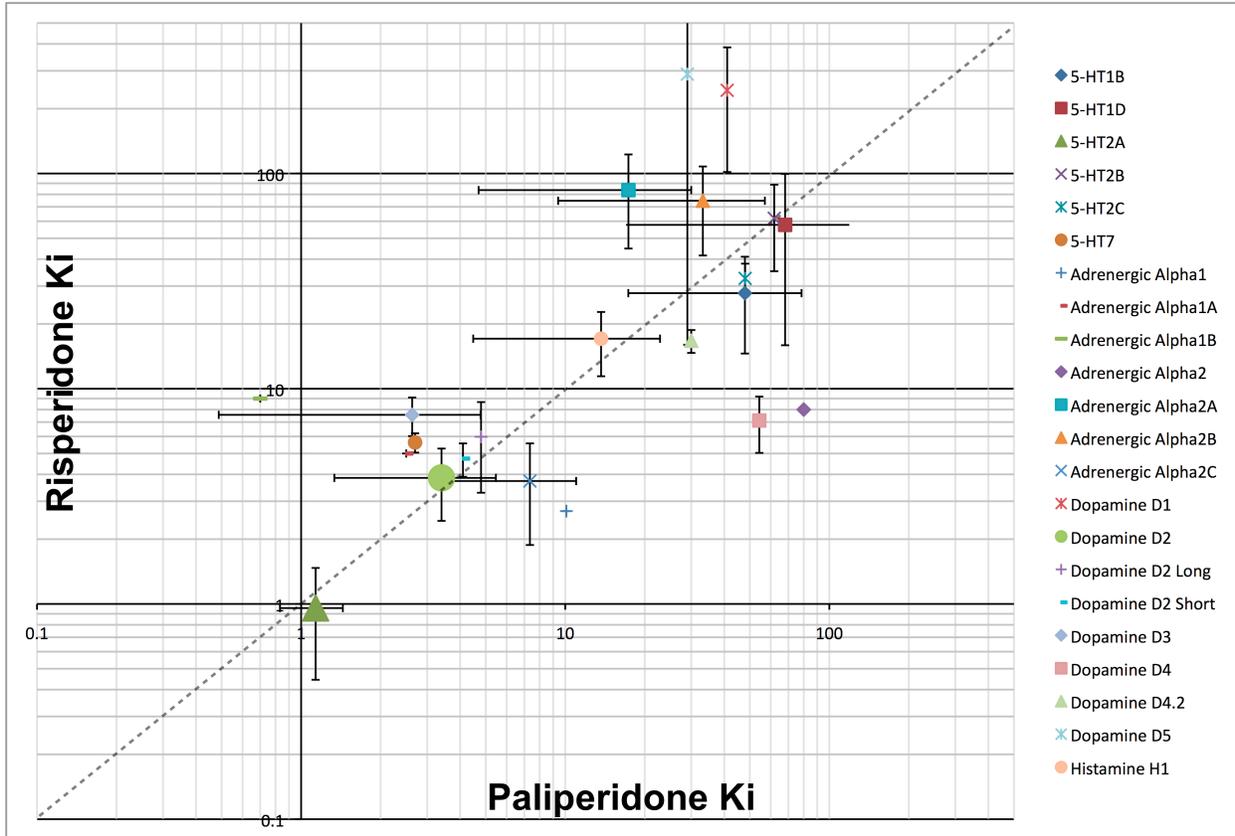


Illustration 2: Logarithmic graph comparing paliperidone to risperidone binding inhibition at mostly highly bound receptors

The logarithmic graph shows the most highly bound receptors for paliperidone on the X-axis and risperidone on the Y-axis. The line of identity, where the receptors have exactly equal binding, is shown with the dashed line. Where there are more than one measurement of that receptor system, the Standard Error of the Mean (SEM) is shown as the error bars. This demonstrates that while paliperidone is a metabolite of risperidone, it does not have the same pharmacology for all receptors. In the case of the receptors that are believed to be the most important for psychotropic activity, 5-HT_{2A} and D₂ (shown in with larger markers), they are quite similar.

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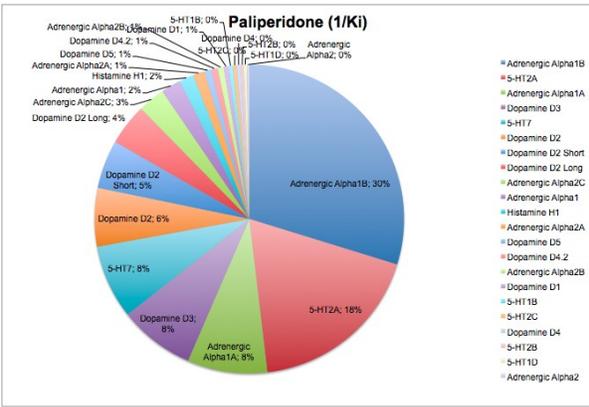


Illustration 3: Pie chart of relative receptor binding of paliperidone

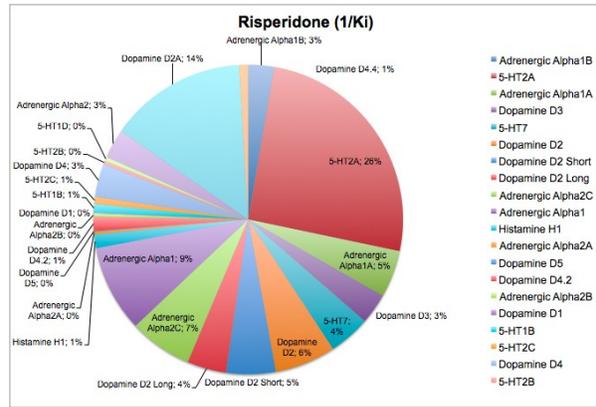


Illustration 4: Pie chart of relative receptor binding of risperidone

Some clinicians prefer to use pie charts to visualize receptor binding data. These are provided using the same Ki data set and subject to the same caveats regarding interpretation as previously stated.

The apparent clinical significance of the various receptors is summarized in the following table:

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| Summary of Receptors and Associated Side Effects | | | | | | |
|--|-------------|---------------------|----------|--------------------------|---------------------|---------------------------|
| Receptor Activity | Side Effect | | | | | |
| | Weight Gain | Glucose Intolerance | Sedation | Extra-pyramidal Symptoms | Prolactin Elevation | Anti-cholinergic Symptoms |
| Serotonin 5-HT _{2C} Antagonism | ✓ | ✓ | | | | |
| Serotonin 5-HT _{1A} | ✓ | | | | | |
| Histamine H ₁ Antagonism | ✓ | ✓ | ✓ | | | |
| Dopamine D ₂ Antagonism | ✓ | | | ✓ | ✓ | |
| Muscarinic M ₁ Antagonism | | | | | | ✓ |
| Muscarinic M ₃ Antagonism | | ✓ | | | | |

Based upon: Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. *Molecular Psychiatry* 2008;13:27–35. [[Full Text](#)]

Pharmacokinetics

All current published poster presentations and most of the clinical trials used doses reported as milligram equivalents (mg eq.) to paliperidone. However, the commercially available product dosage strengths are labeled in milligrams of paliperidone. Therefore the following conversion table is useful:

| Prescribing Information Dosage Strength (milligrams of paliperidone palmitate) | Clinical Trial Dosage Strength (milligram equivalents of paliperidone) |
|---|---|
| 39 mg | 25 mg eq. |
| 78 mg | 50 mg eq. |
| 117 mg | 75 mg eq. |
| 156 mg | 100 mg eq. |
| 234 mg | 150 mg eq. |

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Absorption

Paliperidone palmitate nano particle suspension dissolves slowly after IM injection due to its lipophilic character, then is hydrolyzed rapidly to paliperidone and absorbed into the systemic circulation. Following a single IM dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations (C_{max}) at a median time to maximum concentration (T_{max}) of 13 days. The release of the drug from the depot injection site begins the first day and lasts for as long as 126 days (Paliperidone Palmitate PI).

Following IM injection of single doses (39–234 mg) in the deltoid muscle, on average, a 28% higher C_{max} was observed compared with injection in the gluteal muscle (Paliperidone Palmitate PI). In a multi-dose study, deltoid administration of 156 mg paliperidone palmitate yielded higher C_{max} than did gluteal administration after the second injection; the difference was less after the fourth injection. The T_{max} and the cumulative exposure after four injections (area under the curve [AUC] from time zero to infinity [AUC_∞]) did not differ between the two injection sites (Cleton A, Rossenu S, Hough D, et al. Evaluation of the pharmacokinetic profile of deltoid versus gluteal intramuscular injections of paliperidone palmitate in patients with schizophrenia [Poster PI-75; [Abstract](#)]. Presented at American Society for Clinical Pharmacology and Therapeutics Annual Meeting; Orlando, FL; April 2-5, 2008.). The two initial deltoid IM injections of 234 mg on Day 1 and 156 mg on Day 8 help attain therapeutic concentrations rapidly. The release profile and dosing regimen of Paliperidone Palmitate result in sustained therapeutic concentrations. The AUC of paliperidone following Paliperidone Palmitate administration was dose-proportional over a 39–234 mg dose range, and less than dose-proportional for C_{max} for doses exceeding 78 mg. The mean steady-state peak:trough ratio for a Paliperidone Palmitate dose of 156 mg was 1.8 following gluteal administration and 2.2 following deltoid administration (Paliperidone Palmitate PI).

Distribution

Based on a population analysis, the apparent volume of distribution of paliperidone is 391 L. The plasma protein binding of racemic paliperidone is 74% (Paliperidone Palmitate PI).

Metabolism

No mass balance or other studies to delineate the metabolic pathways of paliperidone palmitate were conducted. These studies were conducted with the oral paliperidone and are believed to be representative of what would be expected for paliperidone palmitate.

One week following administration of a single *oral* dose of 1 mg immediate-release ¹⁴C-paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolized in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces.

Four metabolic pathways (dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission) have been identified *in vivo*; none of these accounted for more than 10% of the oral dose administered. While *in vitro* studies have demonstrated metabolism of paliperidone by CYP2D6 and CYP3A4, *in vivo* there is no evidence that

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these metabolic pathways have a clinically significant role in the elimination of paliperidone. Population pharmacokinetic analyses indicated no discernible difference in the apparent clearance of paliperidone after administration of oral paliperidone between CYP2D6 extensive and poor metabolizers. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of substrates of CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

While *in vitro* studies have shown that paliperidone is a P-glycoprotein (P-gp) substrate and a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available and the clinical relevance is unknown. It is believed that P-gp may be an important transporter across the blood brain barrier (BBB) and alter brain concentrations of some medications. Since risperidone is a prodrug for paliperidone and is a stronger inhibitor of P-gp than paliperidone, it may increase paliperidone brain concentrations through inhibiting P-gp-mediated efflux of paliperidone across endothelial cells of the BBB. This effect would not be present when paliperidone oral or paliperidone palmitate IM was given instead of risperidone oral or risperidone long-acting injection. (Zhu HJ, Wang JS, Markowitz JS, Donovan JL, Gibson BB, and DeVane CL. Risperidone and Paliperidone Inhibit P-Glycoprotein Activity *In Vitro*. *Neuropsychopharmacology* 2007;32:757–764.)

Elimination

The median apparent half-life of paliperidone following Paliperidone Palmitate single-dose administration over the dose range of 39 mg–234 mg ranged from 25 days to 49 days. See table.

| Injection site | Median Dose-Normalized Half-life after Single Injection (days) | | | |
|----------------|--|-------|--------|--------|
| | 39 mg | 78 mg | 156 mg | 234 mg |
| Deltoid | 24.9 | 29.1 | 43.7 | 40.6 |
| Gluteal | 25.1 | 31.2 | 40.0 | 49.1 |

Cleton A, Rossenu S, Crauwels H, *et al.* Assessment of the dose proportionality of paliperidone palmitate 25, 50, 100 and 150 mg eq, a new long-acting injectable antipsychotic, following administration in the deltoid or gluteal muscle [Poster PI-74; [Abstract](#)]. Presented at American Society for Clinical Pharmacology and Therapeutics Annual Meeting; Orlando, FL; April 2–5, 2008.

The paliperidone AUC_∞ increased proportionally with increasing paliperidone palmitate doses (39–234 mg eq.), regardless of gluteal or deltoid injection routes. C_{max} was less than proportional for doses >50 mg eq. The T_{max} was earlier and C_{max} higher (except for 156 mg eq.) for deltoid vs gluteal injection. (Cleton A, Rossenu S, Crauwels H, *et al.* Assessment of the dose proportionality of paliperidone palmitate 25, 50, 100 and 150 mg eq, a new long-acting injectable antipsychotic, following administration in the deltoid or gluteal muscle [Poster PI-74; [Abstract](#)]. Presented at American Society for Clinical Pharmacology and Therapeutics Annual Meeting; Orlando, FL; April 2–5, 2008.)

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Indications

Paliperidone palmitate extended-release injectable suspension is indicated for

- acute treatment of schizophrenia in adults
- maintenance treatment of schizophrenia in adults.

Contraindications

Known hypersensitivity to paliperidone, risperidone, or to any of the components in the formulation, is a contraindication to use.

Dosage Considerations

Initiation Dosing

Paliperidone palmitate is recommended to be initiated with IM doses in the deltoid muscle of 234 mg on Treatment Day 1 and 156 mg one week later. Following single IM injections with doses of 39 mg to 234 mg in the deltoid muscle a mean 28% higher C_{max} was observed compared with injection in the gluteal muscle (Paliperidone Palmitate PI). The two initiation deltoid IM injections of 234 mg on Day 1 and 156 mg on Day 8 represent a loading dose strategy that achieves and maintains therapeutic concentrations more rapidly.

Pharmacokinetic Rationale For Initiation Dosing

Paliperidone palmitate extended-release injectable suspension is designed to deliver paliperidone over a monthly period, while extended-release oral paliperidone is administered on a daily basis (Paliperidone Palmitate PI). The figure below presents the median pharmacokinetic profiles for paliperidone for five weeks following paliperidone

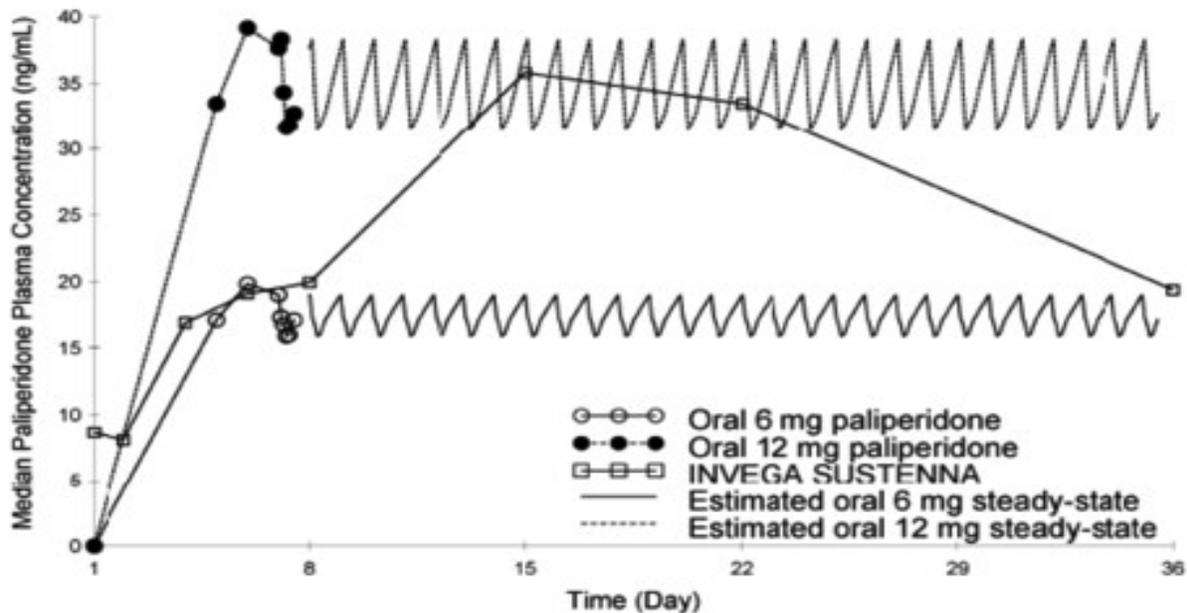


Illustration 5: Median Pharmacokinetic Profile of Paliperidone Palmitate for the First Five Weeks After the Recommended Initiation Regimen

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palmitate administration with the recommended initiation regimen and for daily administration of an oral paliperidone extended-release tablet (6 mg or 12 mg) (figure from data on file with Ortho-McNeil Janssen).

Clinical trial data consisting of 18,530 Cp samples from 1975 patients showed the

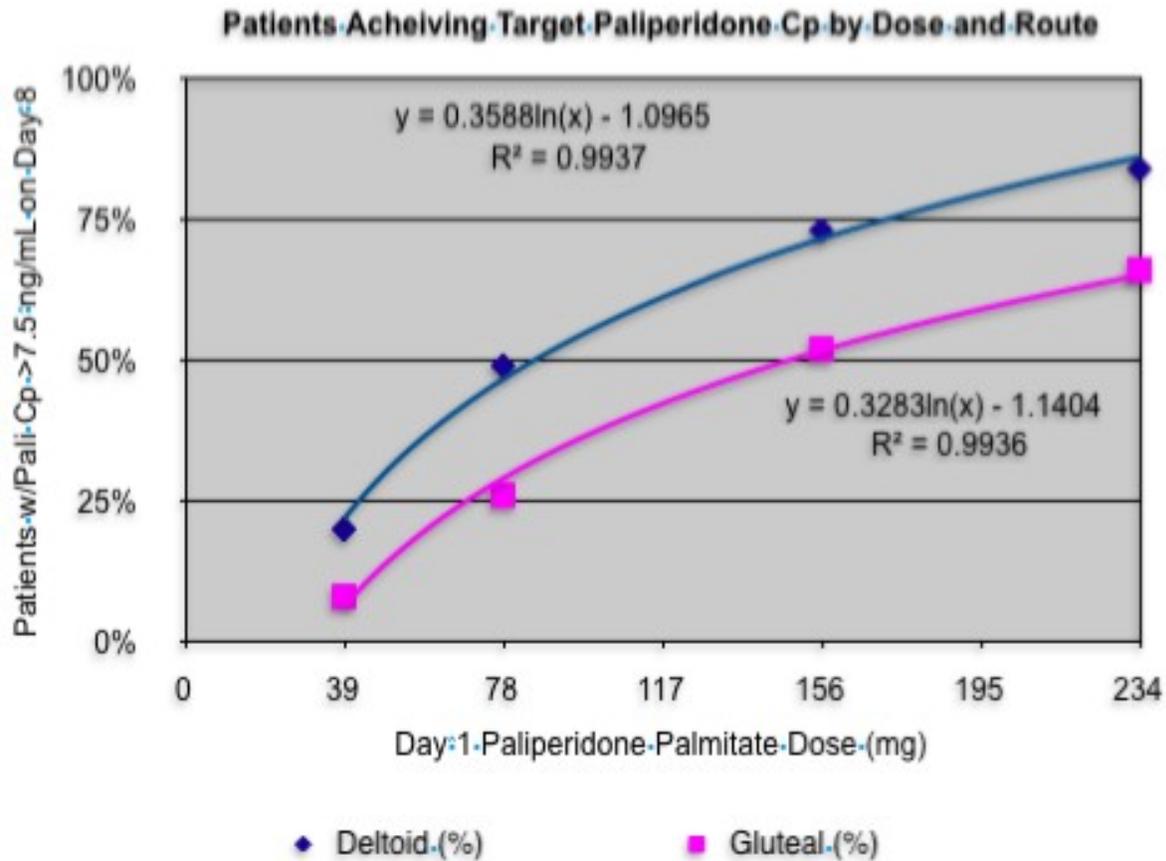


Illustration 6: Fraction of Patients Achieving Target Paliperidone Concentration of 7.5 ng/mL by Dose and Route

fraction of patients achieving the target paliperidone Cp of >7.5 ng/mL at the end of Day 8. these are shown in the graph. The regression equations and correlation coefficients are shown for each route. (Samtani MH, Sliwa JK, Haskins JT, Alphs L, Stuyckens K, Herben V, Vermeulen A. Initiation dosing of deltoid intramuscular paliperidone palmitate in schizophrenia: pharmacokinetic rationale based on modeling and simulation [Poster 2929; [Abstract](#)]. Presented at Annual Meeting of College of Psychiatric and Neurologic Pharmacists (CPNP); Jacksonville, FL; April 19–22, 2009.)

The pharmacokinetic model developed that best described the pharmacokinetics of of paliperidone palmitate extended-release injectable suspension was a 1-compartment disposition model with zero/1st order absorption. The following were identified as important predictors in the pharmacokinetic model:

- injection site/volume
- needle length

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- renal function
- Body Mass Index [BMI = Height (m)² / Weight (kg)]

Different loading dose or initiation regimens were tested *in silico* and compared to 117 mg deltoid IM dosing to steady state. Semi-logarithmic graphs showing the median

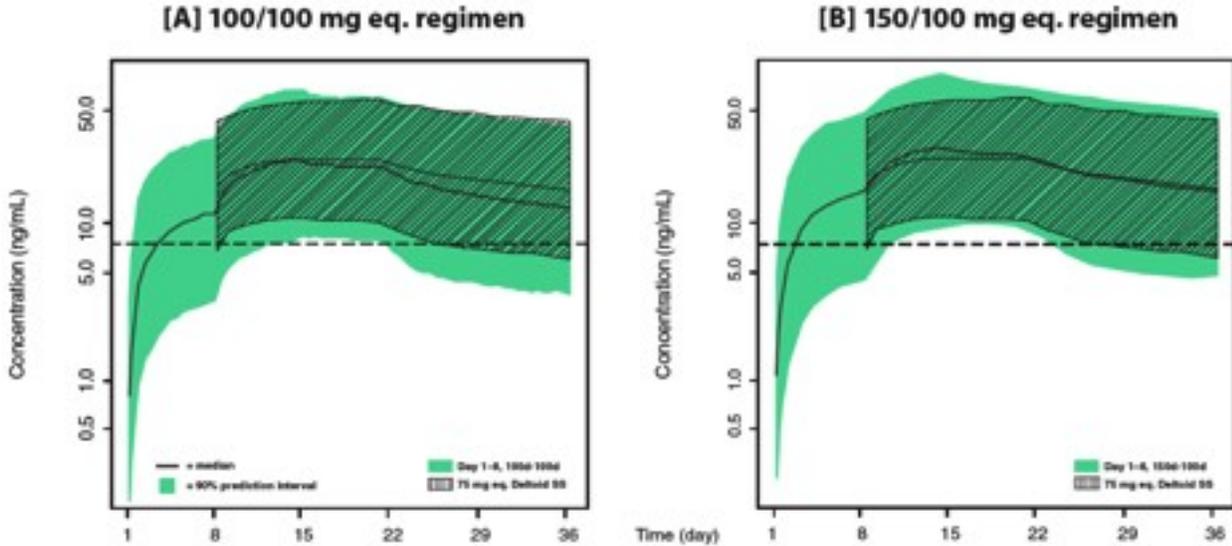


Illustration 7: Pharmacokinetic model of two initiation regimens
concentration ± 90% prediction interval of these simulations are shown below for

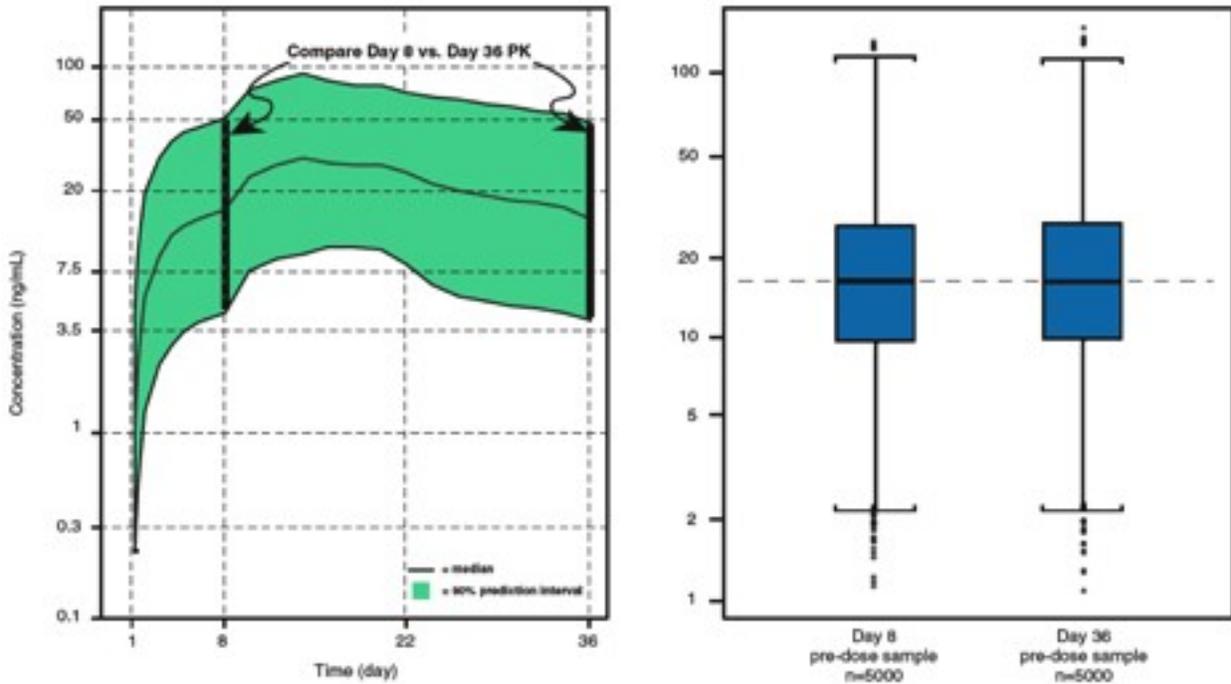


Illustration 8: Pharmacokinetic simulation of final recommended initiation regimen
156 mg on Day 1 and Day 8 [A] as well as the final recommendation of 234 mg on Day 1 and 156 mg on Day 8 [B]. In addition, these recommendations were compared for Day 8 and Day 36 as shown in the graphics.

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These simulations predict that on Day 8, 73% of patients on the paliperidone palmitate 156 mg / 156 mg initiation dose will achieve target paliperidone plasma concentration >7.5 ng/mL, while 84% will achieve this with the paliperidone palmitate 234 mg / 156 mg loading dose. Initial exposure during the 1st month following paliperidone palmitate 234 mg / 156 mg regimen overlapped with that observed with paliperidone palmitate 117 mg steady-state exposure at 1 year. The higher initial dose resulted in faster attainment of steady state and eliminates any need for oral overlap dosing.

Comparison of pre-dose exposure on Days 8 and Day 36 showed that the paliperidone palmitate 234 mg / 156 mg regimen resulted in patients remaining within an efficacious concentration window (3.5–50 ng/mL) at trough, prior to the third injection on Day 36.

The initiation regimen for paliperidone palmitate of 234 mg on Day 1 & 156 mg Day 8 in the deltoid muscle was designed to rapidly attain steady-state paliperidone C_p during initiation of therapy without requiring any oral supplementation. The recommended initiation regimen (paliperidone palmitate 234 mg / 156 mg) was studied in a Phase III trial (n=76) and was efficacious and well tolerated with total treatment-emergent adverse events occurring at similar rates for paliperidone palmitate (60.0–63.2%) and placebo (65.2%).

Adjustment for Body Mass Index

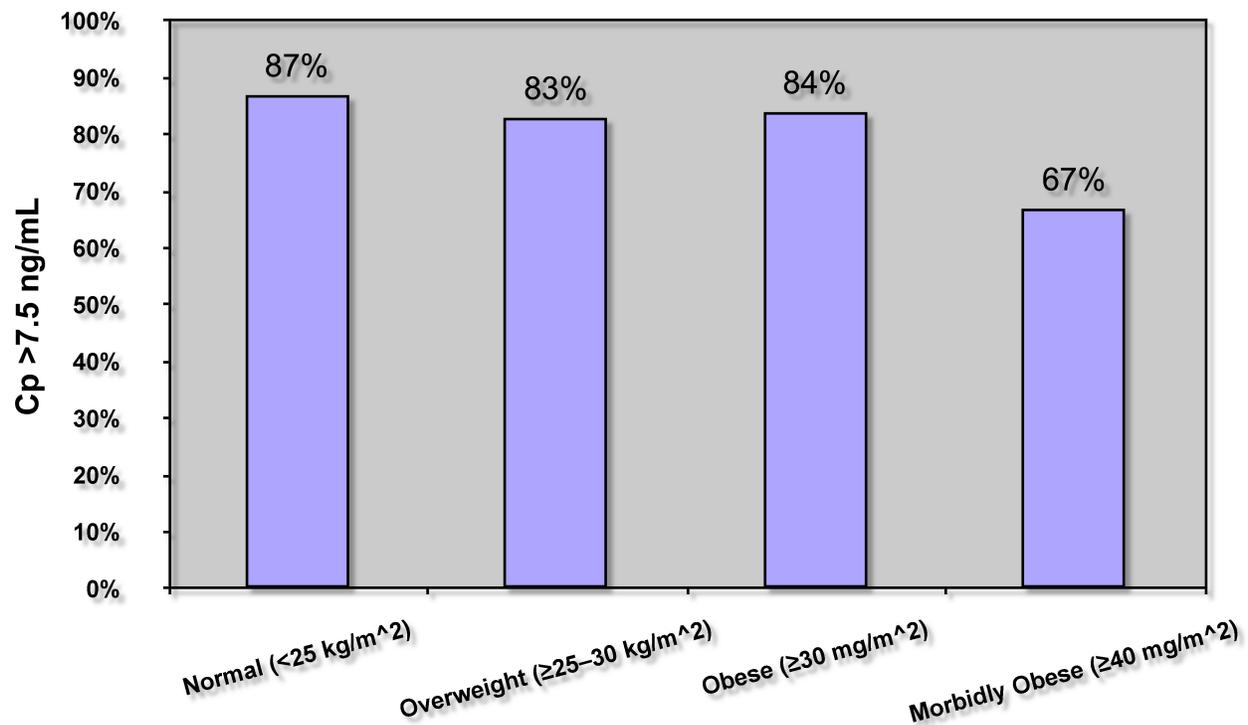


Illustration 9: Effect of Body Mass Index (BMI) on Paliperidone Plasma Concentrations
Median paliperidone C_p were lower during the initiation of treatment in overweight patients (≥25 kg/m²) compared to patients with a normal BMI (<25 kg/m²) prior to the third injection on Day 36. There was no obvious relationship observed between C_p and BMI after Day 36.

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The difference in paliperidone plasma C_{max} was greater when a 1.5 inch (38 mm) versus a 1 inch (25 mm) needle was used to administer the intramuscular injection in the deltoid versus gluteal muscle. Population-pharmacokinetic modeling identified both BMI and needle length as important variables for paliperidone palmitate absorption kinetics following intramuscular administration. Use of a longer needle (1.5 inch) in the deltoid muscle for the heavier (≥ 90 kg) individuals might be associated with an initial faster release of paliperidone into the systemic circulation, which could help overcome the slower absorption in heavier individuals.

The recommended initiation regimen appears to substantially reduce the influence of BMI on the initial rising plasma concentrations for three out of the four BMI categories. Therefore, for dosing recommendation purposes weight is a useful and practical surrogate for BMI, since in the schizophrenic population the obesity threshold (30 kg/m^2) corresponds well with the 90 kg cut-off. (Samtani MH, Sliwa JK, Haskins JT, Alphs L, Stuyckens K, Herben V, Vermeulen A. Initiation dosing of deltoid intramuscular paliperidone palmitate in schizophrenia: pharmacokinetic rationale based on modeling and simulation [Poster 2929; [Abstract](#)]. Presented at Annual Meeting of College of Psychiatric and Neurologic Pharmacists (CPNP); Jacksonville, FL; April 19–22, 2009.)

Comparison of Oral to IM Paliperidone Dosing at Steady State

The series of pharmacokinetic simulations were able to demonstrate that at steady state the following relationship between oral paliperidone extended-release capsules compared to paliperidone palmitate extended-release injectable suspension. Note that the simulations were carried out for the 39 mg, 117 mg, and 236 mg paliperidone palmitate doses only. The oral paliperidone equivalents, were estimated from the simulations presented

in the poster presentation. Since only 3 mg, 9 mg, and 12 mg oral paliperidone extended release capsules are available, the 2 mg and 4 mg daily doses are shown for illustration only: there are no marketed oral equivalent doses of oral paliperidone extended release capsules that have been simulated for the 39 mg and 78 mg paliperidone palmitate extended-release injectable suspension. (Samtani MN, Haskins JT, Alphs L, Sliwa JK, Stuyckens K, Herben V, Vermeulen A. Maintenance dosing of once-monthly (4-weekly) paliperidone palmitate in schizophrenia: pharmacokinetic rationale based on population simulations [Poster 2933; [Abstract](#)]. Presented at Annual Meeting of College of Psychiatric and Neurologic Pharmacists (CPNP); Jacksonville, FL; April 19–22, 2009)

| Equivalent Paliperidone Dosages | |
|---------------------------------|-----------------|
| Oral (mg/day) | IM (mg/4 weeks) |
| 2 | 39 |
| 4 | 78 |
| 6 | 117 |
| 9 | 156 |
| 12 | 234 |

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Maintenance Dosing

The usual recommended monthly maintenance dose is 117 mg. Some patients may benefit from lower or higher maintenance doses within the recommended range of 39–234 mg based on individual patient tolerability and/or efficacy. Following the second dose, monthly doses can be administered in either the deltoid or gluteal muscle (see the summary figure from the product label that follows: *Initiation and Maintenance Dosage Regimens for INVEGA SUSTENNA*). The recommended initiation and maintenance dosage regimens, as well as the injection site recommendations, are supported by population pharmacokinetic simulation models derived from clinical trials of patients with schizophrenia (Samtani MH, Sliwa JK, Haskins JT, Alphs L, Stuyckens K, Herben V, Vermeulen A. Initiation dosing of deltoid intramuscular paliperidone palmitate in schizophrenia: pharmacokinetic rationale based on modeling and simulation [Poster 2929; [Abstract](#)]. Presented at Annual Meeting of College of Psychiatric and Neurologic



Illustration 10: Recommended initiation dosage regimen

Pharmacists (CPNP); Jacksonville, FL; April 19–22, 2009; Samtani MN, Haskins JT, Alphs L, Sliwa JK, Stuyckens K, Herben V, Vermeulen A. Maintenance dosing of once-monthly (4-weekly) paliperidone palmitate in schizophrenia: pharmacokinetic rationale based on population simulations [Poster 2933; [Abstract](#)]. Presented at Annual Meeting of College of Psychiatric and Neurologic Pharmacists (CPNP); Jacksonville, FL; April 19–22, 2009).

Adjustment of the maintenance dose may be made with each monthly dose. However, when such dose adjustments are made, the prolonged-release characteristics of paliperidone palmitate extended-release injectable suspension should be considered, since the pharmacokinetic time to the new steady state and subsequent clinical effects of the dose adjustment may not be evident for several months. Based upon the half-lives reported previously, the time to 90% of steady state should be in the range of 82–162 days.

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Dose Administration Window

It is recommended that the second initiation dose of paliperidone palmitate be given one week after the first dose. To avoid a missed dose, patients may be given the second dose 2 days before or after the one-week time point. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly time point as shown in the table.

| Dosing Window Flexibility | | |
|----------------------------------|---------------------------|---|
| Dose | Dosing Flexibility | Dose and Injection Site |
| Day 8 Initiation Dose | ±2 days | 156 mg in the deltoid muscle |
| Monthly (from Day 36) | ±7 days | Stabilized maintenance dose (39–234 mg) in either gluteal or deltoid muscle |

Samtani MN, Gopal S, Kern Sliwa J, et al. Management of missed paliperidone palmitate doses based on pharmacokinetic modeling and simulation [Poster 62]. Presented at New Clinical Drug Evaluation Unit; Hollywood, FL; June 29–July 2, 2009.

Possible Tactics to Change Steady State Maintenance Dose

It should be emphasized that the table doesn't have recommendations that were included in the product label, and were not developed by OMJ. They are extrapolation from Samtani's PK Model by the monograph author and have not been tested. They are only a possible suggestion of how to move from one maintenance dose to another. The **bold** values in the table are single dose increments or decrements and less of an extrapolation than the non-bold and gray values. Until more experience has been gained, it would be prudent to avoid ≥1 dose increment or decrement per month.

| | | Original Maintenance Dose | | | | |
|---------------------------------|---------------|----------------------------------|---------------------|---------------------|---------------------|---------------------|
| | | 39 mg | 78 mg | 117 mg | 156 mg | 234 mg |
| New Dose (Day 1 / 8) | 39 mg | — | Hold 25 days | Hold 40 days | Hold 50 days | Hold 65 days |
| | 78 mg | 117 / 78 | — | Hold 15 days | Hold 25 days | Hold 40 days |
| | 117 mg | 234 / 117 | 117 / 117 | — | Hold 11 days | Hold 25 days |
| | 156 mg | 234 / 234 | 234 / 156 | 156 / 117 | — | Hold 15 days |
| | 234 mg | 234 / 234 | 234 / 234 | 234 / 234 | 234 / 234 | — |

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Management of Missed Paliperidone Palmitate Doses

The complexity of dealing with substantial intervals following the last dose of paliperidone palmitate were simulated using same pharmacokinetic model previously described. Based upon the simulation, the following recommendations are in the product label for a variety of missed dose scenarios.

| Management of Missed Management of Missed Paliperidone Palmitate Doses | | |
|--|---|---|
| Missed Dose | Re-initiation regimen | Dose and injection site |
| From 1 month to 6 weeks since last injection | Resume injection as soon as possible | Previously stabilized maintenance dose in the deltoid muscle |
| >6 weeks to 6 months since last injection | Two injections, 1 week apart | Previously stabilized maintenance dose (unless the patient was stabilized on a dose of 234 mg, then the first two injections should each be 156 mg) in the deltoid muscle |
| >6 months since last injection | Re-initiate with recommended initiation regimen | 234 mg on Day 1 and 156 mg on Day 8, both in the deltoid muscle |
| Samtani MN, Gopal S, Kern Sliwa J, et al. Management of missed paliperidone palmitate doses based on pharmacokinetic modeling and simulation [Poster 62]. Presented at New Clinical Drug Evaluation Unit; Hollywood, FL; June 29–July 2, 2009. | | |

Special Populations

Renal impairment

Paliperidone palmitate has not been systematically studied in patients with renal impairment. In the absence of data, the product label recommends:

- For mild renal impairment (CrCl ≥50 mL/min to <80 mL/min)
 - ▶ Day 1: 156 mg in the deltoid muscle
 - ▶ Day 8: 117 mg in the deltoid muscle
 - ▶ Day 36 and thereafter: 78 mg in either the deltoid or gluteal muscle.
- Not recommended for use in patients with moderate to severe renal impairment (CrCl <50 mL/min)

Elderly

- Same as for younger adults
- Adjust dose as needed for renal function
- There is a class warning that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

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Nursing Mothers

- The product label states that patients that are treated with paliperidone palmitate should not breastfeed
- Based upon the single dose half-life, six months may be required for the medication to decay to <10% of therapeutic steady state concentrations

Pediatric Use

- Patients <18 years of age have not yet had safety and effectiveness established

Use for Unlabeled Indications

While use in patients for indications that are not approved by the US FDA is explicitly not prohibited, additional documentation is essential. (Edersheim JG. Off-Label Prescribing. *Psychiatric Times*. 2009;26(4).)

The following documentation elements are suggested:

- Identify the specific problems that require an intervention in this patient.
- Describe of all therapeutic interventions that could be considered for this problem and why they are not appropriate in this specific patient.
- State the scientific rationale for use of paliperidone palmitate in this patient, with explicit discussion of any possible warnings, precautions, drug interactions, adverse effects, and other considerations that pertain to this patient. Include any consultations or discussions with colleagues regarding this unlabeled indication.
- Describe when and how the patient (and caregiver) have been prospectively informed of this unlabeled use. If there are known or suspected risks associated with a particular unlabeled use, the patient (and caregiver) should be warned of this risk and instruct the patient (and caregiver) on how to recognize the symptoms and what to do if they are noticed. This should include instructions about whom to contact in the event the patient (and caregiver) believes that they might have an ADR or has any concerns about the medication. Responsible caregivers should be included if this patient is a minor, has a guardian, or requires assistance.
- State that patient (and caregiver) has had any questions answered, understands the risks and what to do if they have any concerns, and have agreed to the use of paliperidone palmitate. Responsible caregivers should be included if this patient is a minor, has a guardian, or requires assistance.

Administration Instructions

Tolerability Testing

Prior to initiation of treatment with paliperidone palmitate extended release injectable suspension, any patient that does not have documented tolerability to either oral paliperidone, risperidone, or risperidone long-acting injection should have their tolerability established with either oral paliperidone or risperidone. During the clinical studies of paliperidone palmitate, patients with no previous exposure to paliperidone or risperidone received oral risperidone 1 mg or 6 mg or paliperidone 3 mg or 6 mg for

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three to six days (depending on the clinical study) to establish tolerability (Nasrallah HA, Gopal S, Gassmann-Mayer C, et al. Efficacy and safety of three doses of paliperidone palmitate, an investigational long acting injectable antipsychotic, in schizophrenia [Poster NR4-036]. Presented at American Psychiatric Association 161st Annual Meeting; Washington, DC; May 3-8, 2008.).

Instructions for Use

Paliperidone palmitate extended-release injectable suspension is intended for IM use only. Inject slowly, deep into the muscle. Care should be taken to avoid inadvertent injection into a blood vessel. Each injection should be administered by a health care professional. Administration should be in a single injection. Do not administer the dose in divided injections. Do not administer intravascularly or subcutaneously.

Deltoid injections should be alternated between the two deltoid muscles.

Gluteal injections should be alternated between the two gluteal muscles. Administration should be made into the upper-outer quadrant of the gluteal area.

The kit contains a prefilled syringe and two safety needles (a 1½-inch 22-gauge needle and a 1-inch 23-gauge needle) for IM injection. Each kit is for single use only.

1. Shake the syringe vigorously for a minimum of 10 seconds to ensure a homogeneous suspension.
2. Select the appropriate needle
 - For **DELTOID** injection, if the patient weights <200 lb (<90 kg), use the 1-inch 23-gauge needle (needle with the blue colored hub); if the patient weighs ≥200 lb (≥90 kg), use the 1½-inch 22-gauge needle (needle with gray colored hub).
 - For **GLUTEAL** injection, use the 1½-inch 22-gauge needle (needle with gray colored hub).
3. While holding the syringe upright, remove the rubber tip cap with an easy clockwise twisting motion.
4. Peel the safety needle pouch half way open. Grasp the needle sheath using the plastic peel pouch. Attach the safety

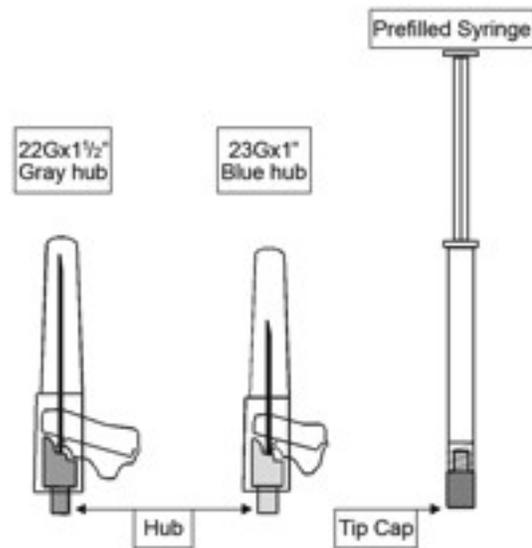


Illustration 11: Contents of Invega Sustenna prefilled syringe kit



Illustration 12: Photograph of the two needles contained in Invega Sustenna kit

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needle to the Luer-lock connection ([ISO 594](#)) of the syringe with an easy clockwise twisting motion.

5. Pull the needle sheath away from the needle with a straight pull. Do not twist the sheath as the needle may be loosened from the syringe.
6. Bring the syringe with the attached needle in upright position to de-aerate. De-aerate the syringe by moving the plunger rod carefully forward.
7. Using appropriate technique, inject the entire contents intramuscularly into the selected deltoid or gluteal muscle of the patient. Do not administer intravascularly or subcutaneously. (see Malkin B. Are techniques used for intramuscular injection based on research evidence? [Nursing Times. 2008;104:50/51,48–51.](#))
8. After the injection is complete, use either thumb or finger of one hand or a flat surface to activate the needle protection system. The needle protection system is fully activated when a 'click' is heard. Discard the syringe with needle appropriately.

Location for injections:

Illustration 13: Deltoid Injection Site

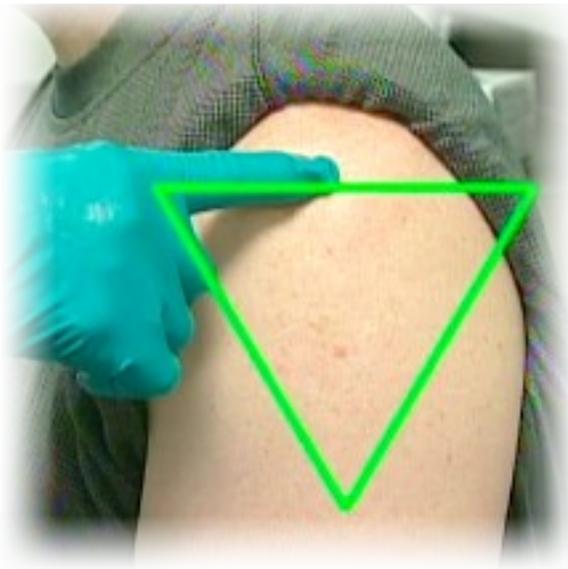
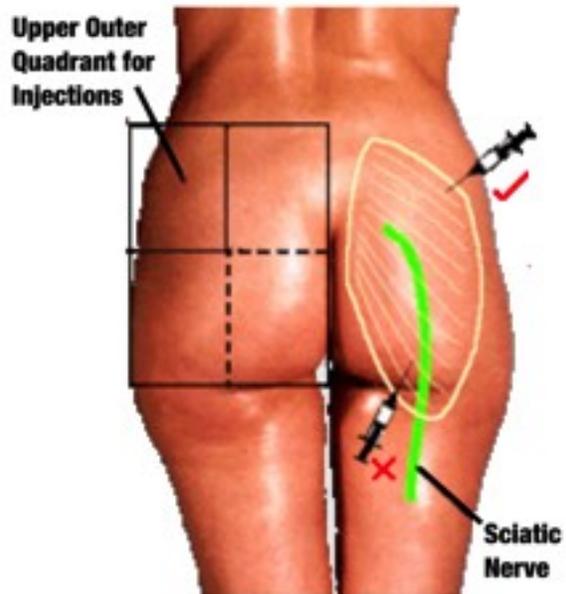


Illustration 14: Gluteal Injection Site



Clinical Trials

Acute Studies

Paliperidone palmitate's efficacy in the acute treatment of schizophrenia was evaluated in one 9-week and three 13-week double-blind, randomized, placebo-controlled, fixed-dose studies of acutely relapsed adult inpatients who met DSM-IV criteria for schizophrenia.

The fixed doses of paliperidone palmitate in these studies were given on at the intervals currently recommended: at a weekly interval for the initial two doses and then every 4 weeks for maintenance. However, the doses administered were fixed and didn't

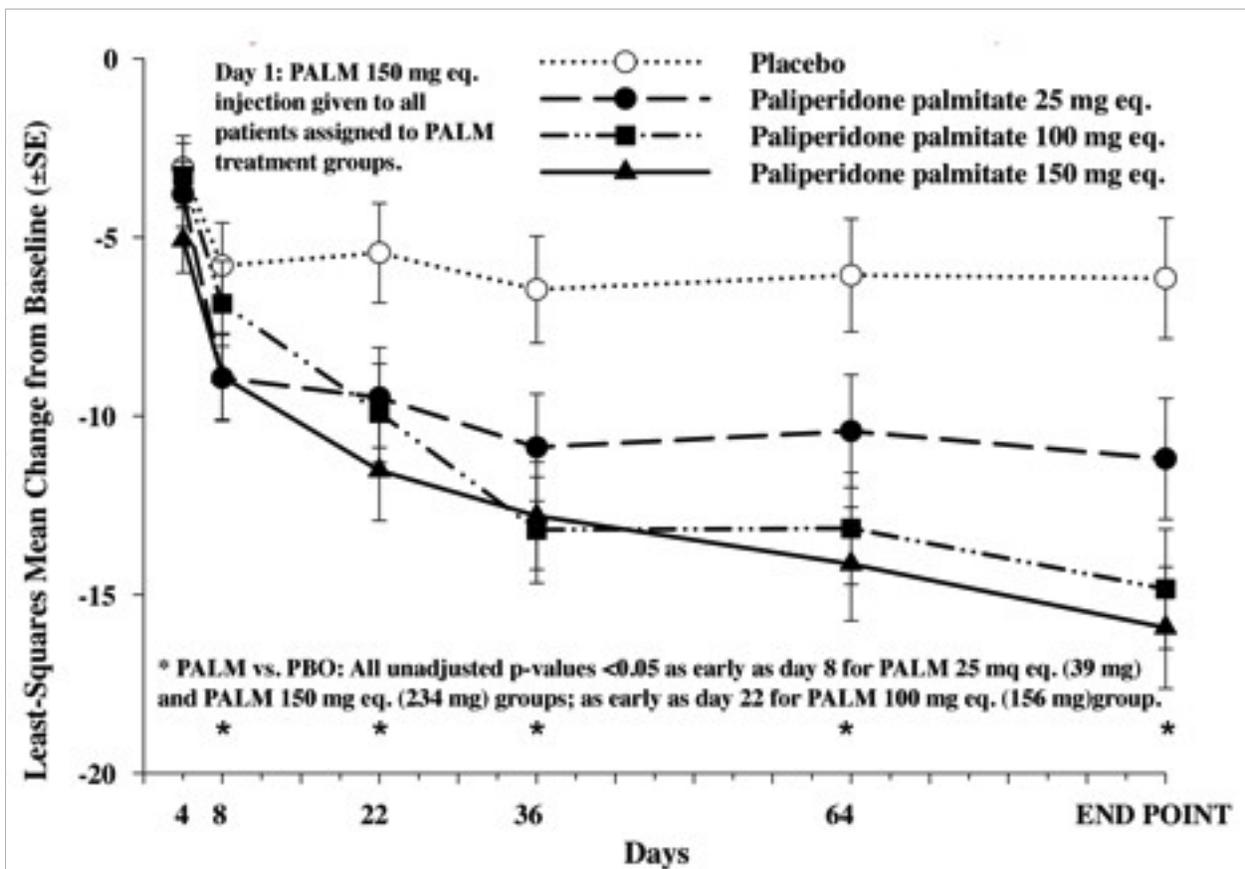


Illustration 15: Change from Baseline PANSS Total Score by Time and Dose

include the initiation regimen that was developed to achieve therapeutic and sustained concentrations more rapidly without the need for any oral overlap. Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS).

In the 9-week study (SCH 201; n=197) comparing two fixed doses of paliperidone palmitate (78 mg/4 weeks and 156 mg/4 weeks) to placebo, both doses of paliperidone palmitate were superior to placebo in improving PANSS total score. (Kramer M, Litman R, Lane R, et al. Efficacy and tolerability of two fixed dosages of paliperidone palmitate in the treatment of schizophrenia: results of a 9-week placebo-controlled trial [poster]. Presented at US Psychiatric and Mental Health Congress; Orlando, FL; October 11-14, 2007.)

A 13-week study (PSY 3004; n=513) comparing three fixed doses of paliperidone palmitate (39 mg/4 weeks, 78 mg/4 weeks, and 156 mg/4 weeks) to placebo, found that all three doses of paliperidone palmitate were superior to placebo in improving the PANSS total score. (Nasrallah HA, Gopal S, Gassmann-Mayer C, et al. Efficacy and safety of three doses of paliperidone palmitate, an investigational long acting injectable antipsychotic, in schizophrenia [poster]. Presented at American Psychiatric Association 161st Annual Meeting; Washington, DC; May 3-8, 2008.)

Another 13-week study (PSY 3007; n=636) comparing three fixed doses of paliperidone palmitate (initial deltoid injection of 234 mg followed by 3 gluteal or deltoid doses of either 39 mg/4 weeks, 156 mg/4 weeks or 234 mg/4 weeks) to placebo, similarly found that all three doses of paliperidone palmitate were superior to placebo in improving the PANSS total score. The graph of this, the largest and most recently reported, study is

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shown as an example of the change in total PANSS score versus time. The other acute schizophrenia studies are similar. (Pandina GJ, Lindenmayer J-P, Lull J, *et al.* A randomized, placebo-controlled study to assess the efficacy and safety of three doses of paliperidone palmitate in adults with an acute exacerbation of schizophrenia [poster]. Presented at International Congress on Schizophrenia Research; San Diego, CA; March 28–April 1, 2009.)

Finally, an additional 13-week study (n=349) attempted to compare three fixed doses of paliperidone palmitate (78 mg/4 weeks, 156 mg/4 weeks, and 234 mg/4 weeks) to placebo. In the end, this study was only able to demonstrate that the 156 mg/4 weeks paliperidone palmitate group was superior to placebo in improving the PANSS total score since a medication mismatch error occurred during the study, and 88 patients in the placebo and paliperidone palmitate 234 mg groups either were assigned to receive medication that did not match their original randomization group (mismatch error) or they were erroneously switched to a different medication at some time during the study (medication kit allocation error). This resulted in fewer patients treated with paliperidone palmitate 234 mg, and more patients treated with placebo than planned. In addition, 31 of these patients were switched from active treatment to placebo or from placebo to active treatment for one or more doses, and were excluded from the primary efficacy analysis set. The results of this study showed that the mean change from baseline to endpoint (LOCF) in PANSS total score was an improvement of 4.1 for those receiving placebo (n=135), 7.9 for patients receiving paliperidone palmitate 78 mg (n=94; NS), 11.0 for those receiving 156 mg (n=97; p=0.019), and 5.5 for those receiving 234 mg (n=30). The statistical analysis plan was to test the 234 mg group against placebo only if both the paliperidone palmitate 78 mg and 156 mg doses were significantly different from placebo. Since the 78 mg group did not reach statistical significance, no statistical comparison was performed for the 234 mg group. This study was not included in the summary table of acute studies. (Brown, 2009; Protocol [NCT00210548](#), [Results](#))

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| Summary of Clinical Trial Results in Schizophrenia Acute Studies | | | | | | | |
|--|-------------|---------|-------|-------|--------|--------|--------|
| Trial | Result | Placebo | 39 mg | 78 mg | 117 mg | 156 mg | 234 mg |
| Kramer SCH-201 9 Weeks [2007] | Effect Size | -0.11 | | 0.10 | | 0.14 | |
| | ADR Dropout | 10% | | 3% | | 2% | |
| | N | 84 | | 79 | | 84 | |
| Nasrallah PSY 3004 (NCT 00101634) 13 Weeks [2008] | Effect Size | 0.28 | 0.41 | 0.40 | | 0.46 | |
| | ADR Dropout | 6% | 6% | 2% | | 5% | |
| | N | 127 | 131 | 129 | | 131 | |
| Pandina PSY 3007 (NCT 00590577) 13 Weeks [2009] | Effect Size | 0.13 | 0.38 | | | 0.54 | 0.62 |
| | ADR Dropout | 7% | 6% | | | 6% | 8% |
| | N | 164 | 160 | | | 165 | 163 |
| Effect Size (<i>Cohen's d</i>) = (Baseline - Endpoint) / SD _{pooled} ; Larger shows improvement | | | | | | | |

Maintenance Study

Prevention of relapse in schizophrenia was established by a single longer-term double-blind, placebo-controlled, flexible-dose study involving adult subjects who met DSM-IV criteria for schizophrenia (PSY 3001; n=410). This study included a minimum 12-week fixed-dose stabilization phase, and a randomized, placebo-controlled phase to observe for relapse. During the double-blind phase, patients were randomized to either the same dose of paliperidone palmitate they received during the stabilization phase, i.e., 39 mg, 78 mg, or 156 mg administered every 4 weeks, or to placebo.

Relapse was pre-defined as *time to first emergence* of one or more of the following:

- psychiatric hospitalization
- increase (worsening) in total PANSS score on two consecutive assessments
 - ▶ if the baseline score was >40, then a ≥25% increase; or
 - ▶ if the baseline score was ≤40, then 10-point increase

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- deliberate self-injury
- violent behavior
- suicidal / homicidal ideation, or
- score on any one of the specific pre-planned individual PANSS items on two consecutive assessments.
 - ▶ if the maximum baseline score was ≤ 3 , then a score of ≥ 5 ; or
 - ▶ if the maximum baseline score was 4, then ≥ 6

Specific PANSS Items for Relapse

| | |
|----|------------------------------|
| P1 | Delusions |
| P2 | Conceptual disorganization |
| P3 | Hallucinatory behavior |
| P6 | Suspiciousness / Persecution |
| P7 | Hostility |
| G8 | Uncooperativeness |

The primary efficacy variable was time to relapse.

A preplanned interim analysis conducted by an Independent Data Monitoring Committee was performed after 68 recurrence events (50% of the total planned for study termination). There were 312 patients included in the interim analysis:

- 68 (22%) completed the double-blind recurrence prevention phase
- 204 (65%) were ongoing at the time of the interim analysis, and
- 40 (13%) had discontinued the double-blind recurrence prevention phase

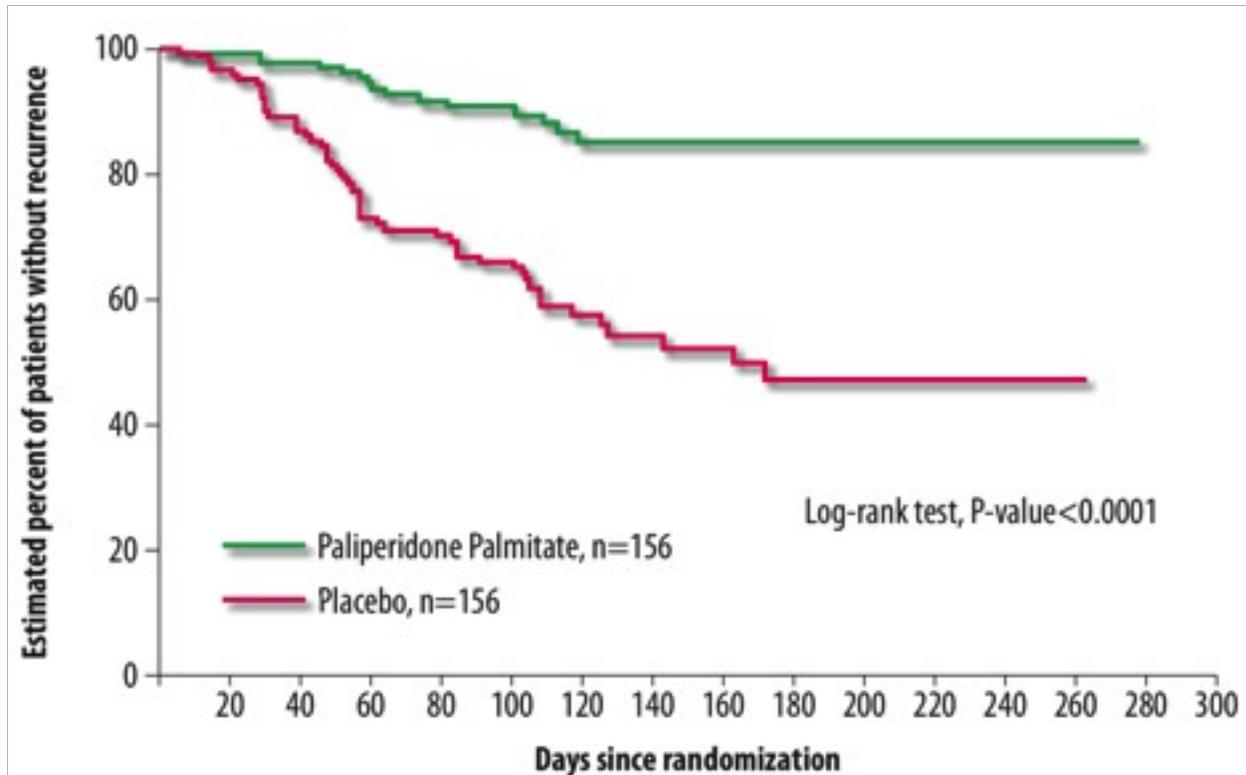


Illustration 16: Kaplan-Meier survival curve for maintenance study

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The intent-to-treat analysis set at the end of the double blind phase included 408 patients, of whom 351 (86%) completed the double-blind phase of the study. Two randomized patients, one in each treatment group, did not receive study medication and not included in intent-to-treat cohort.

The results are shown in the Kaplan-Meier survival curve (Illustration 16).

| Recurrence Type and Reasons | | | | |
|--|-----------------|---|--------------------------------|---|
| Type of Recurrence | Placebo (n=156) | | Paliperidone Palmitate (n=156) | |
| | n | % | n | % |
| Psychiatric hospitalization | 7 | | 3 | |
| PANSS Total Score | 47 | | 12 | |
| ↑ 25% | 39 | | 10 | |
| ↑ 10-point | 8 | | 2 | |
| Deliberate self-injury, violent behavior | 4 | | 0 | |
| Suicidal or homicidal ideation | 3 | | 1 | |
| PANSS items | 17 | | 6 | |
| ≥5 | 16 | | 5 | |
| ≥6 | 1 | | 1 | |

The number of recurrence events in the placebo group was 53 versus 15 for paliperidone palmitate. Patients may have had more than 1 reason for recurrence.

An examination of population subgroups did not reveal any clinically significant differences in responsiveness on the basis of gender, age, or race. (Hough, D, Gopal S, Vijapurkar U, *et al.* Paliperidone palmitate, an atypical injectable antipsychotic, in prevention of symptom recurrence in patients with schizophrenia: a randomized, double-blind, placebo-controlled study [poster]. Presented at American Psychiatric Association 161st Annual Meeting; Washington, DC; May 3-8, 2008.)

Warnings and Precautions

- Increased mortality in elderly patients with dementia-related psychosis
- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis
- Neuroleptic malignant syndrome

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- QT prolongation
- Tardive dyskinesia
- Hyperglycemia and diabetes mellitus
- Weight Gain
- Hyperprolactinemia
- Orthostatic hypotension and syncope
- Leukopenia, neutropenia, and agranulocytosis
- Potential for cognitive and motor impairment
- Seizures
- Dysphagia
- Suicide
- Priapism
- Thrombotic thrombocytopenic purpura (TTP)
- Disruption of body temperature regulation
- Avoidance of inadvertent injection into a blood vessel
- Antiemetic effect
- Use in patients with concomitant illness
 - Increased sensitivity in patients with Parkinson's disease or dementia with Lewy bodies
 - Use in patients with diseases or conditions that could affect metabolism or hemodynamic responses (e.g., recent history of myocardial infarction, unstable heart disease or other known cardiovascular disease)

Adverse Reactions

The most common and likely drug-related adverse events (rates $\geq 5\%$ in any paliperidone palmitate group & $>2 \times$ placebo rate) from the double-blind, placebo-controlled trials were (NNH = Number Needed to Harm for highest incidence paliperidone group compared to placebo group):

- injection site reactions (NNH ≥ 12.5)
- dizziness (NNH ≥ 20)
- extrapyramidal disorder (NNH ≥ 25)
- akathisia (NNH ≥ 33)
- somnolence / sedation (NNH ≥ 50)

The rates of subjects who discontinued because of adverse events in the four fixed-dose, double-blind, placebo-controlled trials were 5.0% for paliperidone palmitate and

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7.8% in placebo-treated subjects. Therefore, for discontinuation from adverse effects, the absolute risk was 2.8% and the NNH was 36; for every 36 subjects treated with paliperidone palmitate and 36 subjects treated with placebo, there was one more drop out on paliperidone palmitate.

There appear to be two dose-related adverse effects: akathisia and prolactin elevation.

| Incidence of Treatment Emergent Adverse Events in ≥2% of Paliperidone Palmitate-Treated Subjects with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials | | | | | | | |
|---|---------------------------------|------------------|------------------|-------------------|--|---|---|
| Adverse Event | Placebo ^a (N=510) | 39 mg (N=130) | 78 mg (N=302) | 156 mg (N=312) | 234 / 39 mg ^b (N=160) | 234 / 156 mg ^b (N=165) | 234 / 234 mg ^b (N=163) |
| | System Organ Class | | | | | | |
| Total percentage of subjects with adverse event | 70 | 75 | 68 | 69 | 63 | 60 | 63 |
| | Gastrointestinal disorders | | | | | | |

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| Incidence of Treatment Emergent Adverse Events in ≥2% of Paliperidone Palmitate-Treated Subjects with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials | | | | | | | |
|---|--|------------------|------------------|-------------------|--|---|---|
| Adverse Event | Placebo ^a (N=510) | 39 mg (N=130) | 78 mg (N=302) | 156 mg (N=312) | 234 / 39 mg ^b (N=160) | 234 / 156 mg ^b (N=165) | 234 / 234 mg ^b (N=163) |
| | System Organ Class | | | | | | |
| Abdominal discomfort / Abdominal pain upper | 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 | | | | | | |

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| Incidence of Treatment Emergent Adverse Events in ≥2% of Paliperidone Palmitate-Treated Subjects with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials | | | | | | | |
|---|---|------------------|------------------|-------------------|--|---|---|
| Adverse Event | Placebo ^a (N=510) | 39 mg (N=130) | 78 mg (N=302) | 156 mg (N=312) | 234 / 39 mg ^b (N=160) | 234 / 156 mg ^b (N=165) | 234 / 234 mg ^b (N=163) |
| | System Organ Class | | | | | | |
| 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 |

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| Incidence of Treatment Emergent Adverse Events in ≥2% of Paliperidone Palmitate-Treated Subjects with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials | | | | | | | |
|---|---|------------------|------------------|-------------------|--|---|---|
| Adverse Event | Placebo ^a (N=510) | 39 mg (N=130) | 78 mg (N=302) | 156 mg (N=312) | 234 / 39 mg ^b (N=160) | 234 / 156 mg ^b (N=165) | 234 / 234 mg ^b (N=163) |
| | System Organ Class | | | | | | |
| | Respiratory, thoracic and mediastinal disorders | | | | | | |
| Cough | 1 | 2 | 3 | 1 | 0 | 1 | 1 |
| | Vascular disorders | | | | | | |
| Hypertension | 1 | 2 | 1 | 1 | 1 | 1 | 0 |
| Percentages are rounded to whole numbers. All incidence ≥10% are shown in bold type. Table includes adverse events that were reported in ≥2% of subjects in any paliperidone palmitate dose group and incidence > placebo group. | | | | | | | |
| 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. | | | | | | | |

Monitoring: Laboratory Test

According to the FDA-approved prescribing information, no specific laboratory tests are recommended.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (*e.g.*, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. The national consensus recommendations for routine monitoring of body weight and body mass index (BMI), waist circumference, blood pressure, glucose levels, and lipid levels for all patients receiving second-generation antipsychotics should be followed. See table reproduced below. (American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care*. 2004;27(2):2004 [[Full Text](#)]).

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| Monitoring Protocol for Patients on SGAs* | | | | | | | |
|---|----------|---------|---------|----------|-----------|----------|---------------|
| | Baseline | 4 weeks | 8 weeks | 12 weeks | Quarterly | Annually | Every 5 years |
| Personal/family history | X | | | | | X | |
| Weight (BMI) | X | X | X | X | X | | |
| Waist circumference | X | | | X | | | |
| Blood pressure | X | | | X | | X | |
| Fasting plasma glucose | X | | | X | | X | |
| Fasting lipid profile | X | | | X | | | X |

* More frequent assessments may be warranted based on clinical status

Drug Interactions

- Due to central nervous system effects, use caution in combination with centrally acting drugs and alcohol.
- Paliperidone may antagonize the effect of levodopa and other dopamine agonists.
- An additive effect may be observed when drugs that may cause orthostatic hypotension are co-administered with paliperidone palmitate.
- Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes.
- Paliperidone is a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.
- Co-administration of oral paliperidone extended release once daily with carbamazepine 200 mg twice daily decreased mean steady-state C_{max} and AUC of paliperidone by approximately 37%. Adjust dose of paliperidone palmitate if necessary.
- Co-administration of a single 3 mg dose of oral paliperidone extended release with paroxetine 20 mg/day increased paliperidone exposure on average by 16% in CYP2D6 extensive metabolizers. The clinical relevance is unknown.
- Co-administration of a single dose of an oral paliperidone extended-release 12 mg tablet with divalproex sodium extended-release tablets (two 500 mg tablets once daily at steady-state) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone. Although this interaction has not been studied with paliperidone palmitate, a clinically significant interaction would not be expected between divalproex sodium and paliperidone palmitate intramuscular injection.

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Relative Cost of Drug Therapy

The relative cost of one month of drug therapy with each of the long-lasting depot antipsychotic medications available are shown in the table. The table is based upon assumption that the average doses of paliperidone palmitate are 117 mg/28 days, risperidone LAI 25 mg/14 days, haloperidol decanoate 100 mg/28 days, and fluphenazine decanoate 25 mg/14 days. The table intentionally obscures the actual confidential contract price paid by the State of Texas, but the rank order relationships between products are evident. A lower numeric relative rank cost shows that the product has a lower acquisition cost.

| Description | Relative Cost Ranking Per Month |
|---------------------------------|---------------------------------|
| Invega Sustenna 39 mg Inj Kit | 1 |
| Invega Sustenna 78 mg Inj Kit | 2 |
| Invega Sustenna 117 mg Inj Kit | 2 |
| Invega Sustenna 156 mg Inj Kit | 3 |
| Invega Sustenna 234 mg Inj Kit | 4 |
| Risperdal Consta 12.5 mg VI/Kit | 1 |
| Risperdal Consta 25 mg VI/Kit | 2 |
| Risperdal Consta 37.5 mg VI/Kit | 2 |
| Risperdal Consta 50 mg VI/Kit | 3 |
| Haloperidol Dec 100 mg/mL | 1 |
| Haloperidol Dec 50 mg/mL | 1 |
| Fluphenazine Dec 25 mg/mL | 1 |

Product Identification:

INVEGA® SUSTENNA™ is available as a white to off-white sterile aqueous extended release suspension for intramuscular injection in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate.

Each kit contains a prefilled syringe and two safety needles (a 1½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle).

- 39 mg paliperidone palmitate kit (NDC 50458-560-01)

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- 78 mg paliperidone palmitate kit (NDC 50458-561-01)
- 117 mg paliperidone palmitate kit (NDC 50458-562-01)
- 156 mg paliperidone palmitate kit (NDC 50458-563-01)
- 234 mg paliperidone palmitate kit (NDC 50458-564-01)

Storage and Handling

- The product label states that the product should be, “stored at room temperature (25°C, 77°F); excursions between 15°C and 30°C (between 59°F and 86°F) are permitted.” This is not the same as the standard description found in USP for room temperature storage.
- Keep out of reach of children.
- Requires prescription.

Recommendation

Addition to the formulary is recommended.

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Last revision 10 October 2009 (Added ADA Section 508 accessibility features)