



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Paliperidone palmitate

Proprietary Product Name: Invega Sustenna

Sponsor: Janssen-Cilag Australia Pty Ltd

**September 2010**

**TGA** Health Safety  
Regulation

## About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

## About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

### Copyright

© Commonwealth of Australia 2010

This work is copyright. Apart from any use as permitted under the Copyright Act 1968, no part may be reproduced by any process without prior written permission from the Commonwealth. Requests and inquiries concerning reproduction and rights should be addressed to the Commonwealth Copyright Administration, Attorney General's Department, National Circuit, Barton ACT 2600 or posted at <http://www.ag.gov.au/cca>

---

## Contents

<b>I.</b>	<b>Introduction to Product Submission.....</b>	<b>4</b>
	<b>Submission Details.....</b>	4
	<b>Product Background .....</b>	4
	<b>Regulatory Status .....</b>	5
	<b>Product Information.....</b>	5
<b>II.</b>	<b>Quality Findings .....</b>	<b>5</b>
	<b>Drug Substance (active ingredient).....</b>	5
	<b>Drug Product .....</b>	6
	<b>Biopharmaceutics .....</b>	6
	<b>Consideration by PSC .....</b>	7
	<b>Quality Summary and Conclusions .....</b>	7
<b>III.</b>	<b>Nonclinical Findings.....</b>	<b>8</b>
	<b>Introduction .....</b>	8
	<b>Pharmacology .....</b>	8
	<b>Pharmacokinetics and Relative Drug Exposures .....</b>	8
	<b>Toxicology .....</b>	10
	<b>Nonclinical Summary and Conclusions .....</b>	14
<b>IV.</b>	<b>Clinical Findings.....</b>	<b>15</b>
	<b>Introduction .....</b>	15
	<b>Pharmacodynamics .....</b>	15
	<b>Pharmacokinetics .....</b>	15
	<b>Efficacy .....</b>	18
	<b>Safety.....</b>	31
	<b>Clinical Summary and Conclusions .....</b>	49
<b>V.</b>	<b>Pharmacovigilance Findings .....</b>	<b>50</b>
<b>VI.</b>	<b>Overall Conclusion and Risk/Benefit Assessment.....</b>	<b>50</b>
	<b>Quality .....</b>	50
	<b>Nonclinical .....</b>	50
	<b>Clinical.....</b>	50
	<b>Risk-Benefit Analysis .....</b>	55
	<b>Outcome.....</b>	55
<b>Attachment 1. Product Information.....</b>		<b>56</b>

## I. Introduction to Product Submission

### Submission Details

<i>Type of Submission</i>	New Salt of a Previously Approved Active Ingredient
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	20 July 2010
<i>Active ingredient(s):</i>	Paliperidone palmitate
<i>Product Name(s):</i>	Invega Sustenna
<i>Sponsor's Name and Address</i>	Janssen-Cilag Australia Pty Ltd Locked Bag 2070 North Ryde NSW 1670
<i>Dose form(s):</i>	Injectable solution
<i>Strength(s):</i>	25 mg, 50 mg, 75 mg, 100 mg and 150 mg
<i>Container(s):</i>	Pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper and tip cap (bromobutyl rubber). The kit contains 2 safety needles (1.5-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle).
<i>Pack size(s):</i>	One per pack
<i>Approved Therapeutic use:</i>	Acute and maintenance treatment of schizophrenia in adults
<i>Route(s) of administration:</i>	Intramuscular injection
<i>Dosage:</i>	Recommended initiation of Invega Sustenna is with a dose of 150 mg on treatment day 1 and 100 mg one week later (day 8), both administered in the deltoid muscle. The recommended subsequent monthly dose is 75 mg; this can be increased or decreased in the range of 25 to 150 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.
<i>ARTG Number (s):</i>	160856, 160857, 160858, 160859, 160860

### Product Background

Invega (paliperidone) modified release tablets were first registered in September 2007 for the treatment of schizophrenia, including acute treatment and recurrence prevention. In November 2009 its indications were extended to include treatment of schizoaffective disorder and its full indications are as follows:

*Schizophrenia, including acute treatment and recurrence prevention*

*Acute exacerbations of schizoaffective disorder as a monotherapy and in combination and/or mood stabilisers (lithium and valproate).*

Paliperidone is the 9-hydroxy metabolite of risperidone. Paliperidone is a centrally active dopamine D<sub>2</sub> antagonist with predominant serotonergic 5HT<sub>2A</sub> antagonistic activity. Paliperidone is also active as an antagonist at alpha<sub>1</sub> and alpha<sub>2</sub>-adrenergic receptors and H<sub>1</sub> histaminergic receptors. Paliperidone has no affinity for cholinergic muscarinic or beta<sub>1</sub> and

beta<sub>2</sub>-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar.

The current application by Janssen Cilag Australia Pty Ltd is to register a new salt (paliperidone palmitate [Invega Sustenna]) 25 mg, 50 mg, 75 mg, 100 mg and 150 mg modified release aqueous solution for intramuscular injection. The sponsor stated that paliperidone has been formulated as a long acting intramuscular injectable ester suitable for a dosing interval of 4 weeks. The proposed indication is for:

*Acute and maintenance treatment of schizophrenia in adults*

### Regulatory Status

A similar application has been approved in the US on 31 July 2009 and New Zealand on 11 March 2010. In the US, the indication is for:

*Treatment of schizophrenia and the prevention of recurrence of symptoms of schizophrenia*

In New Zealand, the approved indication is the same as that applied for in Australia.

Applications are under consideration in Canada and Switzerland.

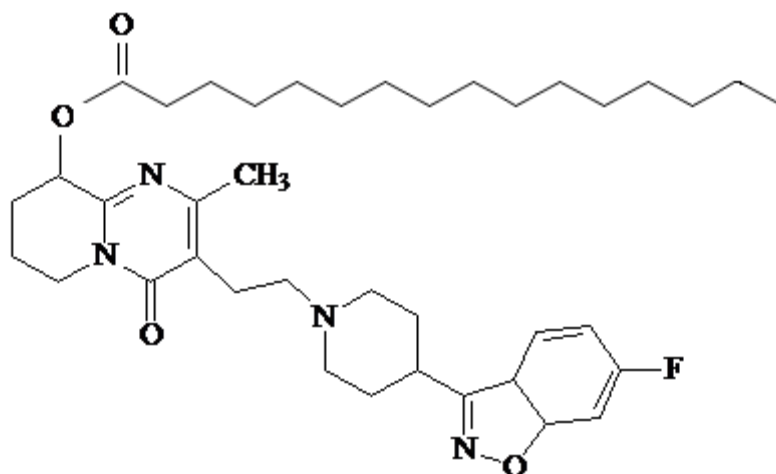
### Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

## II. Quality Findings

### Drug Substance (active ingredient)

The structure of paliperidone palmitate is shown below. There is one chiral centre, and the drug substance is produced as the racemate. The registered drug, paliperidone, is also the racemate.



The drug substance is manufactured by esterification of paliperidone with palmitic acid. The drug substance is a white to almost white, crystalline powder that does not exhibit polymorphism. It is practically insoluble (less than 0.001%) in water over the pH range 1.1-12.9.

There are six impurities with a proposed limit greater than the relevant International Council on Harmonization (ICH) qualification threshold of 0.15%. The Medicines Toxicology Evaluation Section of the TGA has advised that the proposed limits are acceptable.

The proposed retest period of 36 months has been satisfactorily justified.

## Drug Product

The finished product is a sterile, isotonic, aqueous suspension for intramuscular injection. It contains macrogol 4000 as suspending agent, polysorbate 20 as wetting agent and citric acid as chelating agent (to inhibit the oxidation of the macrogol). It is buffered to pH 7.0 with phosphate buffering agents. It contains no antimicrobial preservative. The product is manufactured from sterile drug substance using aseptic manufacturing processes.

The drug product commercial presentation consists of an assembled, plastic, pre-filled syringe (with plunger rod attached) and two syringe needles: a 22-g, 1.5-inch safety needle and a 23-g, 1-inch safety needle, for gluteal and deltoid administration, respectively.

An *in vitro* dissolution test was applied to the injection.

Adequate data have been provided to support the proposed shelf life of 2 years below 25°C.

## Biopharmaceutics

Due to its extremely low aqueous solubility, paliperidone palmitate dissolves slowly after intramuscular injection. It is then hydrolysed to paliperidone, which is absorbed into the systemic circulation. The median time to maximal plasma concentration ( $T_{max}$ ) of the intramuscular injection is 13 days. The absolute bioavailability is claimed to be 94% based on population pharmacokinetic analysis of results obtained at doses of 25-150 mg.

Paliperidone is predominantly excreted unchanged in the urine, although there are several minor metabolic pathways.

The active entity is paliperidone, and the (+) and (-) enantiomers have similar pharmacological activity *in vitro*. After oral administration of paliperidone or intramuscular administration of paliperidone palmitate, the (+) and (-) enantiomers of paliperidone interconvert, reaching an equilibrium +/- ratio of about 1.7.

The principal bioavailability study submitted with the application (Study PSY-1002) was a parallel group study in 143 schizophrenic patients at 15 study sites. Each patient received an intramuscular dose of paliperidone solution in Period 1, followed by one of five paliperidone palmitate intramuscular injections: four were of the formulation proposed for registration (F013) but subjected to different milling times during manufacture, leading to different particle sizes and different *in vitro* dissolution rates; the fifth paliperidone palmitate injection was a formulation (F011) used in some of the earlier Phase 3 clinical trials. Plasma levels of paliperidone were monitored for 18 weeks following administration (36 weeks for the batch that had an extra slow *in vitro* dissolution profile). No dose dumping was evident. This study demonstrated the following:

- Based on the area under the plasma concentration time curve from time zero to the last quantifiable concentration ( $AUC_t$ ), the bioavailability of the formulation proposed for registration (with target dissolution profile) relative to the intramuscular injection of paliperidone was 99.6% (90% confidence intervals [CI] 82.4-120.3%).
- The formulation proposed for registration (with target dissolution profile) appears to be bioequivalent to the earlier clinical trial formulation, although the study was slightly underpowered. Confidence intervals are shown in the following table.

	Ratio (F013/F011)	90% CI
$AUC_t$	93.7%	76.6 – 114.6%
$AUC_{\infty}$	105.2%	85.4 – 129.5%

$C_{\max}$	102.8%	77.4 – 136.5%
------------	--------	---------------

$AUC_{\infty}$ : area under the plasma concentration time curve from time zero to infinite time

$C_{\max}$ : maximal plasma concentration

- There is a linear correlation between the *in vitro* dissolution rate of the intramuscular injection and the *in vivo* absorption rate of paliperidone.

Study PSY-2004 showed that AUC is dose-proportional across the dose range 25-150 mg, while  $C_{\max}$  increases less than proportionally. This study also indicated that the rate of absorption of the drug is slightly greater following deltoid administration compared to gluteal administration.

Study BEL-4 was a multiple dose study that showed that steady state is reached after four or five monthly injections, with AUC and  $C_{\max}$  increasing by a factor of 2-3 from the first dose to the last. The median peak/trough ratio at steady state is 1.7-2.1.

### Consideration by PSC

The application was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its March 2010 meeting.

The PSC reviewed additional data and comments provided by the sponsor and the TGA.

- The PSC agreed that the issues of concern in relation to the submitted data on population pharmacokinetics have been adequately resolved.
- However, the PSC noted that body mass index (BMI) instead of lean body weight or fat free mass was used as a significant covariate in the studies. The Committee had concerns about the switch from a BMI-based to a weight-based needle selection approach recommended in the “Administration Instructions” section of the Product Information (PI).
- The Committee agreed that data showing the range of effects at the extremes of BMI for a 90 kg weight would have been very useful.
- The PSC concluded that there should be no objection on quality and pharmaceutical grounds to approval of this application provided all outstanding issues are addressed to the satisfaction of the TGA.

### Quality Summary and Conclusions

There were no objections in respect of chemistry, manufacturing and controls to the registration of this product.

The following matters were brought to the attention of the Delegate:

- No absolute bioavailability study was submitted in the clinical section of the application. The clinical evaluator should assess the claimed absolute bioavailability of 94% based on a population pharmacokinetic analysis.
- Dose dumping of the product is unlikely based on a consideration of formulation factors. The clinical evaluator should assess the risk of partial intravenous administration of the drug during intramuscular administration, which could lead to dose dumping.
- The statement in the PI that, on average, deltoid injection gives a 28% higher  $C_{\max}$  than gluteal injection is based on the results of Study PSY-1004. However, the sponsor has simply averaged the mean deltoid/gluteal  $C_{\max}$  ratios at each of the four dose levels examined, even though the mean ratios at the 25, 50 and 100 mg doses were only 1.20, 1.20 and 1.09, respectively, and were not significantly different from unity. It is only the

high mean ratio observed at the 150 mg dose (1.65) that increases the average ratio to 1.28. The PI statement is simplistic, and possibly misleading.

- None of the studies submitted in the clinical section of the application involved a comparison of Invega Sustenna with Invega modified release tablets. Therefore, the basis for Figure 1 in the proposed PI was not clear.

### **III. Nonclinical Findings**

#### **Introduction**

Paliperidone is a currently registered oral anti-psychotic agent (Invega), and is itself the main active metabolite of risperidone, also currently registered (Risperdal). The sponsor has now submitted an application for paliperidone palmitate, a slow release form intended for monthly intramuscular (IM) administration. The proposed loading doses for naïve patients are 150 mg initially followed by 100 mg one week later, and a maintenance dose in the range 25-150 mg.

Additional pharmacological studies (primary, secondary, safety) were not submitted. Previously evaluated studies have indicated that paliperidone binds to 5-HT<sub>2A</sub> and dopamine D<sub>2</sub> receptors, with the (+) and (-) enantiomers showing similar affinities.

#### **Pharmacology**

##### **Primary pharmacodynamics**

The paliperidone moiety of the palmitate ester is the main active (9-hydroxy) metabolite of the currently registered Janssen-Cilag antipsychotic agent risperidone (Risperdal). The pharmacology of paliperidone is considered to have been well established in earlier studies into the mechanism of action of risperidone and additional studies were not conducted and are not required for the current submission. Previously evaluated *in vitro* receptor binding studies have shown paliperidone and its (+) and (-) enantiomers to have similar affinities for 5-HT<sub>2A</sub> and dopamine D<sub>2</sub> receptors as risperidone.

Potential activity of the palmitate ester is unlikely to be of significance, with apparently only low sporadic plasma levels being seen in the clinical trials with IM dosing and an expected relatively rapid ester hydrolysis after inadvertent intravenous (IV) administration (*Pharmacokinetics and relative drug exposures*). There were, however, no pharmacological or toxicity studies conducted with IV administration of paliperidone palmitate.

##### **Safety and secondary pharmacology**

An extensive range of *in vitro* and *in vivo* cardiovascular safety pharmacological studies have been evaluated for the original Invega submission, and in dogs, paliperidone generally increased heart rates and reduced blood pressures. Consistent with this, blood pressures were slightly reduced in high dose (HD) dogs in the 12 month (but not the 6 month) IM paliperidone palmitate toxicity study, at a dose (40 mg/kg/month) resulting in a paliperidone exposure well in excess of the expected human value, although this may be related to anaphylactoid reactions seen in dogs (*General toxicity*). Additional safety pharmacological studies were not conducted for the current submission and are not required given that both risperidone and paliperidone are registered drugs.

##### **Pharmacokinetics and Relative Drug Exposures**

The pharmacokinetics of paliperidone after IM administration were characterised by variable and often prolonged plasma T<sub>max</sub> values (up to 396 hours in the dog) and little presence in plasma of the palmitate ester when it was measured (rat carcinogenicity study, dog single dose toxicity study). The latter is consistent with only sporadic low concentrations being measurable in the clinical trials (clinical summary). Two peak paliperidone concentrations were noted in the



rat, typically at 1-5 hours and 7 days, with the former being (plausibly) ascribed in one (3 month) study to inadvertent IV administration of a fraction of the dose. Presumably this was not seen in the other species investigated because of the greater ease of giving IM injections in larger animals.

Experiments in minipigs showed that bioavailability after intra-fat injection was only slightly lower than the IM value (61% versus 77%), with similar prolonged  $T_{max}$  values (192 versus 240 hours). This suggests that inadvertent injection into fat would not result in additional systemic effects, but this may not be the case if a substantial fraction of the dose entered the circulation. IV injection resulted in relatively low plasma concentrations of the ester, which was not measurable beyond 3 hours, and overall exposure ( $AUC_{0-last}$  value) that was only about 6% of the value for paliperidone base, indicative of relatively rapid hydrolysis and consistent with *in vitro* data. Resulting peak paliperidone concentrations were, however, considerably higher than after IM or intra-fat injections (12-15 x assuming dose-proportionality from 1.25 to 5 mg), occurring at about 5 hours. IV administration was apparently not conducted in the clinical trials.

Paliperidone plasma data obtained during the toxicity studies are tabulated below, with separate values given only when there was an apparent sex difference. Comparison of drug exposures relative to that expected in humans was difficult in terms of AUC because of the apparent lack of multiple dosing data with the maximum recommended dose (MRD) of 150 mg/day. Additionally, values in the dog studies were not for the whole of the 28 day dosing interval. Drug exposures relative to that expected in humans have been calculated both using comparisons with human single dose  $AUC_{0-\infty}$  (as was used in the sponsor's *Nonclinical Overview*) and repeat dose midpoint concentration values. The latter would approximate average concentrations, which were calculated (by the evaluator) from the animal data as  $AUC_{0-last}/time_{last}$ .

It is noted that the clinical exposure values to paliperidone at the MRD (150 mg) of Invega Sustenna ( $AUC_{0-\infty}$  36.9  $\mu\text{g}\cdot\text{h}/\text{mL}$ , concentration at steady state ( $C_{ss}$ ) 30.6 ng/mL) are similar to the corresponding values at the MRD (12 mg/day) of the oral formulation Invega ( $AUC_{0-24h}$  0.936  $\mu\text{g}\cdot\text{h}/\text{mL}$ , 48.8 ng/mL).

The proposed dosing of Invega Sustenna is 150 mg initially, followed by 100 mg one week later, then monthly maintenance dosing of 75 mg (range 25-150 mg). The initial dose of 250 mg (2 divided doses a week apart) is to rapidly achieve steady-state plasma concentrations. Although such a regimen would suggest greater exposure in the first month than in subsequent months, this is not confirmed by the clinical kinetic data.

Paliperidone exposures were in excess of the expected human value with the MRD, except in the minipig, and although margins were not high they were adequate. Additional comparisons show that high-dose AUC values obtained with monthly IM dosing were also higher than those obtained in humans treated with the oral (PO) formulation at the MRD of 12 mg/day. For example, the  $AUC_{0-24 h}$  values for the rat carcinogenicity study of 2.9-4.1  $\mu\text{g}\cdot\text{h}/\text{mL}$  ( $AUC_{0-28 \text{ days}}/28$ ) were 3-4 times the reported human value of 936 ng.h/mL.

Table 1: Relative Drug Exposures

Species	Duration (months)	Dose (mg eq./kg/month)	AUC ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	$C_{\text{max}}$ (ng/mL) <sup>#</sup>	Relative exposure ratios <sup>&amp;</sup>	
					AUC	$C_{\text{av}}$
<i>General toxicity</i>						
Rat	3	20, 80, 160 male	18.0, 84.9, 125	74, 461, 369	0.5, 2.3, 3.4	0.9, 4.1, 6.1
		female	24.3, 131, 179 (0-28 days)	413, 631, 955	0.6, 3.6, 4.9	1.2, 6.4, 8.7
Rat	6	20, 80, 160	30.1, 109.9, 230 (0-30 days)	56.5, 189, 422	0.8, 3.0, 6.2	1.4, 5.0, 10.4
Rat	6	20, 80, 160	24.1, 64.8, 180.8 (0-28 days)	78, 162, 448	0.7, 1.8, 4.9	1.2, 3.1, 8.8
Rat	24*	10, 30, 60 male	15.9, 42.8, 82.5	50.3, 474, 539	0.4, 1.1, 2.2	0.8, 2.1, 4.0
		female	16.6, 59.9, 114 (0-28 days)	73.8, 189, 391	0.4, 1.6, 3.1	0.8, 2.9, 5.5
Dog	6	5, 10/20, 40/80 <sup>i</sup>	18.6, 72.8, 274 (0-21 days)	52.5, 181, 638	0.5, 2.0, 7.4	1.2, 4.7, 17.8
Dog	12	5, 20/10, 80/40 <sup>d</sup>	57, 88, 321 (0-21 days)	378, 366, 1327	1.5, 2.4, 8.7	3.7, 5.7, 20.8
Minipig	3	5, 20	9.9, 61.2 (0-84 days) <sup>§</sup>	10.8, 64.1	0.1, 0.6	0.2, 1.0
<i>Reproductive toxicity</i>						
Rat	GD 3**	20, 80, 160	25.1, 91.4, 153 (0-18 days)	118, 381, 665	0.7, 2.5, 4.1	1.9, 6.9, 11.6

<sup>#</sup> rats showed two peaks (generally at 1-5 h and at 7 days), and the highest values are included in the above table

\* carcinogenicity study

<sup>&</sup> animal AUC values relative to a human single dose value of 36.9  $\mu\text{g}\cdot\text{h}/\text{mL}$ , and animal  $C_{\text{av}}$  values relative to a human repeat dose value of 30.6 ng/mL (Section 5.2.5)

<sup>i, d</sup>  $\uparrow$  or  $\downarrow$  mid dose (MD) and high dose (HD) after the first administration, \*\* single dose

<sup>§</sup> AUC for the whole dosing period (i.e. includes 3 injections)

## Toxicology

The toxicity studies submitted were adequate, given the previously evaluated studies with paliperidone and risperidone, with the latter often being included as a comparator in the paliperidone studies, and overall there were no unexpected findings. As may be predicted, prominent findings in the repeat dose studies with monthly IM dosing included those attributable to elevated prolactin, which was shown to occur in the rat 6 month and dog 12 month studies. These included mammary gland stimulation in both sexes (rats), prostate granulocytic infiltration/fibrosis (rats) or reduced glandular development (dogs), and ovarian, vaginal and uterine changes indicative of a resting state (rats, dogs). Prolactin was increased in both sexes during the clinical trials, which is an expected effect of dopamine D<sub>2</sub> antagonists (clinical overview).

IM injections were into the biceps femoris (semimembranosus, semitendinosus in the 6 month dog study), but although there were often prominent injection site (IS) reactions, these had little effect on draining iliac lymph nodes. These sometimes showed pigmented macrophages or

reduced medullary cord plasmacytosis, while sporadic splenic changes were related to increased relative weight and severity of red pulp erythrocyte hyperplasia. The latter were, however, also noted in a 6 month rat paliperidone/risperidone study. Haematological findings of slightly reduced erythroid values in rats and dogs contrast with consistent increases seen in rats (and mice) treated with PO paliperidone or risperidone, although slight reductions were generally seen in dogs. Other findings of slightly reduced serum glucose (rats) and potassium (dogs) have been previously noted with PO paliperidone. Serum glucose elevations were seen infrequently in the clinical trials (sponsor's *Clinical Overview*).

Injection site changes included chronic inflammation, fibro-granulomatous reactions and focal muscle necrosis or degeneration, with clinical swelling/hardness and white powdery deposits generally being seen at gross examination. However, these were not associated with consistent elevations of neutrophils and monocytes, with only slight (rat 6 month) or moderate (minipig) increases sometimes being seen, and counts tended to be lower in high dose (HD) dogs. The intended formulation (F013) was used only in 3 toxicity studies (3 month minipig, rat embryofetal development (single dose), rat carcinogenicity), with local lesions being graded as slight to moderate in minipigs and slight to severe in repeat-dosed rats. The latter included abscess formation. These IS reactions may not be predictive of those in humans but pain, redness, induration and swelling were observed clinically (sponsor's *Clinical Overview*).

Anaphylactoid reactions (cyanosis, hyperpnoea, red skin spots, swollen eyelids/head/paws) were noted in the vehicle and HD groups of the 12 month dog study, and were probably related to the polysorbate 20 component of the formulation (F004, 12 mg/mL). This was also apparent in 2 single dose dog toxicity studies, but was not seen in rats (multiple dosing) or minipigs and pigs (single dose), and polysorbates are known to elicit histamine release *in vivo*, particularly in dogs<sup>1</sup>. The injection volume in the 12 month study was 8 mL/m<sup>2</sup> (0.4 mL/kg x 20) giving a polysorbate 20 dose of 96 mg/m<sup>2</sup>. This compares with a corresponding value of 11.9 mg/m<sup>2</sup> with the MRD of 150 mg (1.5 mL/50 kg = 0.03 mL/kg x 33 = 0.99 mL/m<sup>2</sup> x 12 mg/mL). Anaphylactoid reactions were apparently not observed in the clinical trials (sponsor's *Clinical Overview*).

The 3 month study in minipigs was primarily to compare formulations F015 (single dose) and F013 (monthly dosing, intended commercial formulation) in terms of local tolerance and toxicokinetics. Systemic paliperidone exposures achieved were low (*Pharmacokinetics and relative drug exposures*), and the study did not add any additional information. It is noteworthy, however, that the HD resulted in reduced erythroid values, potassium and glucose, and increased neutrophils and monocytes.

### **Genotoxicity and carcinogenicity**

Paliperidone was shown not to be genotoxic in adequate previously evaluated studies of bacterial reverse mutation and forward mutation in mouse L51784 lymphoma cells, and in a rat micronucleus test. Although the ester would not be expected to differ from the base, 2 additional studies using paliperidone palmitate were submitted, with negative results. These were adequate, although concentrations used (up to 500 µg/plate in a bacterial reverse mutation test and 15 µg/mL (-S9 x 24 hours) or 70 µg/mL (±S9 x 3 hours) in the L51784 lymphoma assay) were limited by solubility.

Long-term carcinogenicity studies have not been previously carried out with paliperidone, but mouse and rat dietary studies using risperidone were submitted previously and reports were included in the Invega evaluation report. Significant neoplastic findings were of mammary

<sup>1</sup> Haruyama, E. et al. Investigation of histamine release after single intravenous administration of polysorbate 80 to beagles, cynomolgus monkeys and rats. *J Toxicol Sci* 2005; 30: S86.

gland adenocarcinomas and pituitary adenomas in female mice, and mammary gland adenocarcinomas (both sexes) and endocrine pancreas adenomas (males) in rats, considered by the original risperidone nonclinical evaluator to be related to elevated prolactin.

Respective high-dose plasma *paliperidone* concentrations in males and females were 46 or 37 ng/mL in mice, and 102 or 124 ng/mL in rats, which were comparable (mice) or 3-4 times higher (rats) than the expected human concentration of about 30 ng/mL with IM administration of the palmitate ester (*Pharmacokinetics and relative drug exposures*). The neoplastic potential of paliperidone after IM administration can thus be considered to be covered in rats, and to a lesser extent in mice, as was considered to be the case with PO paliperidone.

A 24 month rat carcinogenicity study with monthly IM administration of paliperidone palmitate was submitted for the current application, with less pronounced findings also considered to be related to elevated prolactin. Males showed significantly increased mammary gland tumours, but only with the mid-dose (MD), and a trend for higher pancreatic islet cell tumours (mainly adenomas), but this was not clear cut. Females showed only increased incidences of malignant mammary gland tumours with all doses, but these were common tumours and increases were not dose-related or significant compared with a saline control. Serum prolactin was dose-dependently increased in males, as assessed by AUC<sub>0-24 h</sub> values, but increases were more difficult to demonstrate in females for whom control levels were higher and several rats showed sporadic very high levels. A proper dose-response may have been apparent with a larger measurement group size, although (in contrast to males), a significant increase was seen only with the HD of 160 mg/kg/month in a 6 month toxicity study with measurements being carried out in all rats at necropsy (20/sex/group).

### Reproductive toxicity

A full package of paliperidone reproductive toxicity studies was evaluated for the Invega submission, with average drug concentrations or expected concentrations (AUC<sub>0-24 h</sub>/24) that were about 6 times (rat fertility and pre-/postnatal studies)<sup>2</sup> or >35 times (rat and rabbit embryofetal toxicity)<sup>3</sup> a human value of 30.6 ng/mL. The summary section from the nonclinical Invega evaluation report detailing findings from these studies is as follows:

*In male and female rats, fertility was unaffected at doses (up to 2.5 mg/kg/day PO) producing some toxicity and prolactogenic effects at up to twice clinical exposure. There was no evidence of teratogenicity when pregnant rats and rabbits received paliperidone during organogenesis at up to 10 and 5 mg/kg/day (28- and >17-fold, respectively, the clinical exposure), despite maternal toxicity and increased fetal deaths in rabbits at 5 mg/kg/day. In pre/post-natal rat studies, pup viability, body weight and righting reflex were reduced at dam doses of ≥1.25 mg/kg/day but not ≤0.63 mg/kg/day (ca 2-fold and less than clinical exposure, respectively). Neonatal rats that received paliperidone (via milk or directly) developed clinical signs consistent with the pharmacological action of paliperidone.*

These studies are considered to cover the potential effects of the IM administered palmitate ester, although an additional rat embryofetal toxicity study with single IM administration of paliperidone palmitate was submitted for the current application. Fetal findings were restricted to increased incidences of minor fetal skeletal variations (for example, absent sternum bones, impaired ossification, wavy ribs), but without dose-responses and associated with maternal weight loss at the highest dose (160 mg eq/kg). The study report considered these to be transient developmental delays or unrelated to treatment, because of the lack of dose-responses, but it is noteworthy that similar changes seen in the previously evaluated rat and rabbit studies using

<sup>2</sup> Based on the HD tested, 2.5 mg/kg/day.

<sup>3</sup> Based on the HDs tested, 10 mg/kg/day (rat) and 5 mg/kg/day (rabbit).

daily PO paliperidone administration were most apparent with the low dose (LD) and MD. Rats showed increased incidences of rudimentary sternum bones and reduced metatarsal ossification, while absent sternum bones were seen in rabbits. The relative exposure ratios achieved in the IM palmitate study were 4 (based on AUC) and 11 (based on  $C_{av}$ ).

### Local tolerance

The two local tolerance studies submitted used formulation F011, which differs slightly from the F013 formulation proposed for registration, and which was compared with either 10% or 20% Intralipid (commercial fat emulsion). When given IM to dogs at the clinical MRD (1.5 mL of 100 mg eq/mL), paliperidone palmitate elicited marked/severe reactions including diffuse necrotising inflammation. This formulation was also used in the rat 3 month study, albeit with a lower injection volume (0.8 mL/kg/IS), while F013 was used in the minipig single dose and 3 month studies, and the rat carcinogenicity and embryofetal toxicity studies. Although IS reactions were apparent (not examined in the latter), these may have little or no relevance to clinical reactions which have been well documented (*General toxicity*).

Although IV and intra-fat administration was used in a minipig study to investigate absorption and plasma kinetics after inadvertent misdosing, there were no data regarding possible local reactions with these routes.

### Impurities

Specified impurities with proposed limits above the ICH threshold are tabulated below. Paliperidone does not require qualification, as this is the active metabolite.

Table 2: Information on Impurities

Impurity*	Proposed limit (%)	Maximal monthly intake (mg/m <sup>2</sup> ) <sup>#</sup>	Batch content (%) <sup>§</sup>	Intake in the rat 6 month study (mg/m <sup>2</sup> /month) <sup>&amp;</sup>
R206474	0.3	0.463	0.15	2.25
R206475	0.3	0.463	0.06	0.90
R207919	0.3	0.463	0.10 (0.07)	1.50
R208224	0.3	0.463	0.27 (0.13)	4.04
R208225	0.3	0.463	0.26 (0.21)	3.89
(Paliperidone)	0.2	0.309	-	-

\* homologue esters structurally related to paliperidone palmitate

<sup>#</sup> 234 mg (150 mg eq. of paliperidone) for a 50 kg person = 4.68 mg/kg x 33 = 154.4 mg/m<sup>2</sup> x 0.003 = 0.463 mg/m<sup>2</sup>

<sup>&</sup> HD in the rat 6 month study = 249.6 mg/kg (160 mg eq./kg) x 6 = 1497.6 mg/m<sup>2</sup>

<sup>§</sup> batch ZR092670EXA002 (ZR092670EXA003, second batch used in the dog 12 month study)

Impurity data were available for paliperidone palmitate batches used in the 6 month rat and 12 month dog studies, with 2 batches being used in the dog study. As tabulated above, the rat study high-doses resulted in impurity intakes above those in humans treated with the MRD (1.9-8.7x), and any effects of these compounds will have been included in the toxicity profile of the batch

used. Similarly the dog study high-dose (62.4 mg/kg or 1248 mg/m<sup>2</sup>) resulted in impurity intakes that were 1.6-5.6 times higher than the maximum human value.

However, additional data in the toxicology written summary for the batches used in the 2 submitted genotoxicity studies indicated that the only impurities present at concentrations higher than the proposed limits were R206474 (0.5%), R206475 (1.14%) and R208225 (0.72%) in the batch used for the L5178Y lymphoma assay. The latter compound was also present at low concentration (0.13%) in the batch used for the bacterial reverse mutation assay. However, they are all esters closely related to paliperidone palmitate (C16), that is, C12, C14, C15, C17 and C18 homologues. As such, they would not be expected to show any genotoxicity (or general toxicity) not exhibited by paliperidone palmitate. Because of their close structural similarity, the proposed limits for these impurities are considered to be acceptable. The fatty acids liberated following probable hydrolysis are commonly naturally occurring.

### Nonclinical Summary and Conclusions

Following single IM injection, plasma paliperidone T<sub>max</sub> values were variable and often prolonged, and little palmitate ester was present in rat and dog plasma. In minipigs, injection into fat gave a slightly lower bioavailability than IM administration, while IV injection resulted in low exposure to the palmitate ester (6% of the value for paliperidone base in terms of AUC) and a paliperidone T<sub>max</sub> of 4.8 h, indicative of relatively rapid hydrolysis in blood. Peak tissue concentrations of <sup>14</sup>C radioactivity were seen at 168 hours after IM injection of [<sup>14</sup>C]paliperidone [<sup>3</sup>H]palmitate in rats, with high concentrations present in several tissues including adrenals, salivary glands, prostate, spleen and bone marrow. Brain <sup>14</sup>C was < limit of quantification.

*In vitro* studies showed ester hydrolysis by liver preparations (hepatocytes, 12000 g supernatants, microsomal preparations), blood and plasma from rats, dogs and humans, and by human liver, kidney and muscle 12000 g fractions. Hydrolysis by dog muscle homogenate was low. Experiments with inhibitors suggested serine esterases were involved in hydrolysis, at least in part, and there was no evidence for the involvement of oxidoreductases. Hydrolysis resulted in some stereoselectivity, with generally higher (+) enantiomer concentrations, especially in plasma.

Repeat-dose toxicity studies were carried out in rats (3-6 months) and dogs (6-12 months) using monthly IM injections with mid- and high-doses that achieved systemic drug exposures in excess of that expected in humans. There were no unexpected findings, and prominent changes (for example mammary gland development) were attributable to elevated prolactin which was shown to occur in both species. Injection site reactions included chronic inflammation, fibro-granulomatous reactions and focal muscle necrosis/degeneration, but with little change in the draining iliac lymph nodes. Anaphylactoid reactions were noted in dogs (including those treated with vehicle), which were most likely related to the polysorbate 20 content of the formulations (12 mg/mL).

Previously-evaluated studies have not shown any evidence for paliperidone genotoxicity, and this was also the case in two adequate additional new *in vitro* studies with paliperidone palmitate (bacterial reverse mutation and mouse L51784 lymphoma forward mutation assays).

Paliperidone has previously been investigated in long-term carcinogenicity studies only as the major active metabolite of oral risperidone. Neoplastic findings (mammary gland adenocarcinomas, pituitary adenomas, pancreatic adenomas) were ascribed to elevated prolactin, a known carcinogenic mechanism for D<sub>2</sub> antagonists in rodents. A new 24 month rat study with monthly IM paliperidone palmitate administration was submitted with the current application. Less pronounced findings in this study (increased mammary gland tumours and possibly

pancreatic islet cell tumours) were also considered to be related to prolactinaemia which was demonstrable in males and to a lesser extent females. The proposed formulation was used, and this elicited slight-severe injection site lesions including abscesses.

A full set of reproductive toxicity studies has been previously evaluated for the Invega submission, in which no teratogenicity or effects on fertility were observed. A new rat embryofetal toxicity study has been submitted in which paliperidone palmitate treatment was by single IM injection on gestation day 3. This resulted in minor fetal skeletal changes, generally without dose-responses and associated with maternal weight loss at the high-dose (160 mg/kg).

*Issues addressable from the nonclinical data.* In view of the previously evaluated studies for the Invega and Risperdal submissions, the nonclinical submission for paliperidone palmitate was adequate, and there were no findings that should preclude approval of registration. Although probably benign, it should be noted that local tolerance after IV or intra-fat injection was not investigated or documented.

*Issues likely to be addressable from the clinical data.* Often pronounced local injection site reactions were observed with the proposed formulation, indicative of a potential for local irritation in clinical use, although these may not be predictive of human responses. The acceptability of likely reactions in humans will have to be determined from the clinical results.

Anaphylactoid reactions were observed in dogs (but not in rats, minipigs or pigs), most likely related to the polysorbate 20 content of the formulation. Dogs have been reported to be particularly sensitive to histamine release elicited by polysorbate, and these findings are probably not predictive of similar responses in humans. It is suggested, however, that the potential for such reactions be determined from the clinical data.

## **IV. Clinical Findings**

### **Introduction**

The submission comprised 14 bioavailability and pharmacokinetic studies and 7 clinical efficacy and safety studies. The safety and efficacy studies included more than 2000 patients with schizophrenia who were treated with paliperidone palmitate. The application was detailed, clear and well presented.

### **Pharmacodynamics**

There were no new pharmacodynamic studies.

### **Pharmacokinetics**

Paliperidone palmitate is the palmitate ester pro-drug of paliperidone (9-hydroxy-risperidone). Because of its extremely low water solubility, paliperidone palmitate dissolves slowly after intramuscular (IM) injection before being hydrolysed to paliperidone which then enters the systemic circulation. Paliperidone is the racemic mixture of R078543 (+) and R078544 (-) enantiomers with similar pharmacological activity. The pharmacokinetic pathways have been established for oral paliperidone previously so this submission is only concerned with the bioavailability/pharmacokinetic parameters for the new formulation.

There were 6 bioavailability studies submitted. Three studies (**R092670-BEL-1**, **R092670-BEL-2** and **R092670-BEL-4**) involved various early formulations of the depot preparation of paliperidone palmitate. Three further studies (**R092670-INT-12 (INT-12)**, **R092670-PSY-1004 (PSY-1004)**, **R092670-PSY-1002 (PSY-1002)**) involved formulations F011 and F013. The latter was the final to-be-marketed formulation which was the same as F011 with the addition of citric acid to aid stability at room temperature. Both of these formulations were used in Phase 2/3 clinical studies. These studies addressed the following:

R092670-INT-12 (INT-12): Pharmacokinetics, tolerability and safety of 9-hydroxy-risperidone after a single intramuscular injection of the depot formulation of 9-hydroxy-risperidone in schizophrenic volunteers;

R092670-PSY-1004 (PSY-1004): Open-label, parallel, randomised, dose-proportionality pharmacokinetic study of paliperidone after intramuscular injection of paliperidone palmitate in the deltoid or gluteal muscle in subjects with schizophrenia;

R092670-PSY-1002 (PSY-1002): Open-label, parallel, randomised study to explore the in vitro/in vivo correlation of paliperidone palmitate long-acting formulations and the comparability of the F011 and F013 formulations in subjects with schizophrenia

There were 6 pharmacokinetic studies submitted. **R092670-BEL-7** involved an earlier formulation of the depot paliperidone palmitate. The studies involving the formulations used in the Phase 2/3 studies were **R092670-INT-11 (INT-11)**, **PALM-JPN-1**, **PALM-JPN-2**, **R092670-PSY-1001 (PSY-1001)** and **R092670-USA-3 (USA-3)**. These studies addressed the following:

R092670-INT-11 (INT-11): Double-blind, multiple dose study in schizophrenic volunteers exploring the comparative pharmacokinetics, tolerability and safety following IM injections of paliperidone palmitate (R092670) originating from 2 different production methods,

PALM-JPN-1: A single dose study of JNS010 in patients with schizophrenia,

PALM-JPN-2: A repeated dose study of JSN010 (paliperidone palmitate) in patients with schizophrenia,

R092670-PSY-1001 (PSY-1001): Open-label, parallel, randomised, multiple-dose pharmacokinetic study of paliperidone after intramuscular injection of paliperidone palmitate in the deltoid or gluteal muscle in subjects with schizophrenia,

R092670-USA-3 (USA-3): Pharmacokinetics, tolerability, and safety of paliperidone after repeated intramuscular injection of paliperidone palmitate in the arm or buttock of subjects with schizophrenia.

Following a single-dose of IM paliperidone palmitate, plasma paliperidone reaches a peak concentration within 14 days with an apparent half-life ranging from 25 to 49 days over the dose range of 25-150 mg. Both depot formulations used for Phase 2/3 studies have been shown to result in a controlled release rate of paliperidone suitable for once-monthly dosing with relative bioavailability close to 100% for the 2 formulations (F011/F013). Dose-proportionality was achieved for total exposure ( $AUC_{\infty}$ ) over the recommended dose range for both deltoid and gluteal IM administration. Steady-state was achieved more rapidly with 2 injections a week apart rather than using a higher loading dose. Deltoid administration resulted in higher peak concentrations than gluteal thus the recommended initiation regime is 2 injections a week apart into the deltoid muscle. To avoid possible administration of paliperidone palmitate into adipose tissue and delaying absorption, a longer needle is recommended for subjects over 90 kg.

Paliperidone palmitate is hydrolysed to paliperidone which enters the systemic circulation. Paliperidone palmitate itself was not detectable in the majority of blood samples (<2%) confirming its low systemic exposure. Partial intravenous administration did not seem to be of concern as abnormally high paliperidone or paliperidone palmitate values were rare<sup>4</sup>. The ratio of the enantiomers was consistent at all doses and there was no indication of an effect of

---

<sup>4</sup> In the Phase 2/3 studies unexpected increases in plasma paliperidone concentrations (> 63 ng/mL) occurred in only 8 subjects, the majority of whom also had measurable concentrations of paliperidone palmitate.



cytochrome P450 (CYP) 2D6 or CYP 3A4/5 metaboliser status on paliperidone kinetics. There were no new safety or tolerability concerns with the new formulation. There were in general more pain/reactions at the injection site for deltoid compared to gluteal administration but both sites were acceptable with few severe reactions at either site.

A population pharmacokinetic model was developed using data from 1795 subjects from 6 Phase 1 and 5 Phase 2/3 studies of the F011/F013 formulations. A total of 18,530 valid samples were available for the analysis. A one-compartment model with first order elimination was found to best describe the pharmacokinetics of paliperidone following IM administration of paliperidone palmitate. The effects of various covariates were evaluated and resulted in the following conclusions:

- repeated injections into the deltoid muscle (compared with gluteal) resulted in a faster increase in plasma concentrations and enhanced time to achieve steady-state but did not influence overall exposure;
- higher doses associated with larger injection volumes increased the apparent half-life which increased time to steady-state.

Other important variables were needle length and BMI: a slower rise in plasma concentrations was found for obese subjects which can be mitigated by use of a longer needle in heavier subjects. Renal function was also important indicating that renal impairment required a reduced dose. Concomitant medications used by >10% subjects (for example, lorazepam, paracetamol, diazepam, olanzapine) were found to have negligible effects as expected for parenteral administration. There were no clinically relevant effects for age (when poor renal function is controlled for), race or gender.

The model was also used to simulate expected plasma concentrations using the initiation regimen of deltoid doses of 100 mg IM on Days 1 and 8 which was found to attain potential therapeutic concentrations rapidly based on plasma concentrations obtained from previous oral paliperidone studies. It was also used to assess the impact of switching injection sites after Day 36 which was found to not have a major effect on maintenance of steady-state concentrations. The model was then revalidated with new data from **R092670-PSY-3007 (PSY-3007)**. Initiation with a higher dose of 150 mg into the deltoid muscle with appropriate needle length resulted in rapid achievement of target concentrations and estimated model pharmacokinetic parameters remained unchanged.

All studies were well designed with adequate sample sizes; appropriate sampling times and validated analytical methodology. Non-compartmental methods were used for the calculation of the pharmacokinetic parameters, and appropriate statistical analyses were performed. All studies were carried out in the target population for use of this medication with a mix of ages, genders and races. Tolerability and safety were thoroughly assessed. There was no absolute bioavailability study submitted comparing the new formulation with IV paliperidone. Comparison of the F011/F013 formulations with paliperidone-immediate release (IR) solution 1 mg IM found their relative bioavailability to be 114% and 126% respectively (sponsor's *Clinical Summary*). Oral paliperidone-IR has been previously found to be 100% bioavailable as it has negligible first pass elimination. Comparison of dose-normalised AUC for paliperidone IV with paliperidone palmitate IM at four doses and from both injection sites found a mean of 94% bioavailability.

In addition, the population pharmacokinetic model simulations for the recommended dosage regime for paliperidone palmitate IM showed good agreement with plasma concentration ranges for oral paliperidone-extended release (ER) where the recommended dose of 6 mg/d resulted in 90% of subjects achieving a plasma concentration of paliperidone of between 3.5 and 50 ng/mL which is probably of more relevance than establishing absolute bioavailability. Further

simulations detailed in the sponsor's *Clinical Overview* showed that the steady-state peaks and troughs for paliperidone palmitate 25, 75, 150 mg were contained within the paliperidone-ER (2, 6, 12 mg/d respectively) exposure window. It should be noted that none of the studies evaluated the pharmacokinetics of paliperidone using the final recommended dosing regime of paliperidone palmitate, that is, Day 1, IM 150 mg, Day 8, 100 mg, both deltoid followed by monthly IM 75 mg (25-150 mg) either deltoid or gluteal. Nonetheless the evaluators viewed the pharmacokinetic studies as being acceptable as the model was used to simulate plasma steady-state concentrations. This showed that the new regimen leads to rapid achievement of plasma concentrations similar to those achieved with paliperidone-ER.

## Efficacy

There were 7 clinical studies in patients with schizophrenia. Four studies evaluated efficacy for acute treatment over 10-13 weeks. The most important of these studies was **R092670-PSY-3007 (PSY-3007)** as this used a dosage regimen closest to that recommended in this submission. The others were **R092670-PSY-3003 (PSY-3003)** and **R092670-PSY-3004 (PSY-3004)** which followed similar protocols with variations in dose and injection sites and **R092670-SCH-201 (SCH-201)** an earlier study over 10 weeks. The efficacy of paliperidone palmitate for longer term maintenance and recurrence prevention was investigated in **R092670-PSY-3001 (PSY-3001)**. The other studies presented were a comparative study with Risperdal Consta, **R092670-PSY-3002 (PSY-3002)** and **R092670-PSY-3005 (PSY-3005)** which was a cross-over study of injection sites for safety and tolerability purposes.

The acute treatment studies (**PSY-3007, 3003, 3004**) followed essentially the same protocol comprising a 7-day screening, wash-out, tolerability phase and a 13 week double-blind, placebo-controlled phase (Tables 3-5). An oral tolerability test was done if subjects had not previously been treated with either oral risperidone or oral paliperidone-ER. As there had been some rare cases of allergic and hypersensitivity reactions to risperidone it was important to identify anyone who could not tolerate oral paliperidone before administration of the longer acting IM formulation. Varying doses were used in each study with injections on Days 1, 8, 36 and 64. Differences in protocol for study **PSY-3007** included: treatment initiated with a 150 mg dose into deltoid muscle, further injections either deltoid or gluteal administration, and specified needle length based on subject's weight.

Diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental disorders, version four (DSM IV) criteria for at least one year was necessary for inclusion in all studies and a positive and negative syndrome scale (PANSS) total score of between 70 and 120 at screening was also required.<sup>5</sup> The lower limit was higher than the 60 used historically to ensure that subjects were experiencing an acute exacerbation of schizophrenic symptoms. The upper limit of 120 was chosen to balance severity with the ability to provide informed consent. All studies excluded subjects with a history of or current significant physical illness, active substance abuse, treatment resistance, clinically significant laboratory results, risk of suicide, history of neuroleptic malignant syndrome, severe allergic reactions, recent exposure to experimental agents, malignancy within 5 years and females who were pregnant, breastfeeding or planning to become pregnant, involuntary subjects and those not able to provide consent.

---

<sup>5</sup> **Positive and Negative Syndrome Scale (PANSS).** The PANSS is a 30-item scale that was designed to assess various symptoms of schizophrenia including delusions, grandiosity, blunted affect, poor attention and poor impulse control. The 30 symptoms are rated on a 7-point scale that ranges from 1 (absent) to 7 (extreme psychopathology). This scale has been shown to be sensitive to medication treatment, provide a balanced representation of positive and negative symptoms, and gauge their relationship to one another and to global psychopathology. The PANSS interview process typically takes between 30 and 40 minutes to complete.

*PSY-3007: A randomised, double-blind, placebo-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed doses (25 mg eq., 100 mg eq., and 150 mg eq.) of paliperidone palmitate in subjects with schizophrenia.*

This study was conducted in 72 centres in the USA, Russia, Romania, Ukraine, Taiwan, Korea, Malaysia and Serbia (Table 3). The primary objectives were to evaluate the efficacy and safety of 3 fixed doses of paliperidone palmitate (25, 100 and 150 mg) administered IM after an initial dose of 150 mg in the deltoid muscle followed by either deltoid or gluteal injections for a total of 13 weeks of treatment as compared with placebo (PBO) (Table 3). The primary efficacy variable was the change from baseline to endpoint in the PANSS total scores. Secondary objectives were to assess the benefits in personal and social functioning and global improvement in severity of illness with paliperidone palmitate compared to PBO; and to assess dose-response and exposure-response relationships for paliperidone palmitate. Various secondary efficacy measures included changes from baseline in Personal and Social Performance scale (PSP), Clinical Global Impression Severity (CGI-S) scores, PANSS subscales and items, and PANSS responder rates.<sup>6,7</sup>

Study completion rates were: 43% PBO, 52% paliperidone palmitate 25 mg, 54% paliperidone palmitate 100 mg, and 55% paliperidone palmitate 150 mg. The primary reason for withdrawal was lack of efficacy for PBO or lack of efficacy and withdrawn consent for all paliperidone palmitate groups. The demographic and other baseline characteristics (sex, age, race, ethnicity, weight, height, BMI, smoker) and psychiatric history and disease characteristics (schizophrenic subtype, age at diagnosis, baseline PANSS and CGI-S scores, prior hospitalisations) were similar across treatment groups. The majority of subjects had used psychotropic medications prior to study entry (98%), particularly atypical antipsychotics (70%), benzodiazepines (62%) and typical antipsychotics (42%) in similar proportions of patients across groups. During treatment, concomitant medication other than benzodiazepines was 67% - largely zolpidem and paracetamol. Benzodiazepine use was 59%, mainly lorazepam as allowed per protocol, in similar proportions of patients across groups.

Table 3: Efficacy Study R092670-PSY-3007

No of subjects with age and sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Efficacy
n= 652 randomised n= 636 ITT PBO: n=160, 106M, 54F, 40y (19-67) PANSS baseline 87 ± 10	M or F, aged 18-65 years, diagnosed with schizophrenia (DSM IV) for ≥ 1 year, PANSS total between 70-120 on screening & 60-120 at	Pharmacokinetics: Plasma PAL measured by LC-MS/MS.  <b>Primary Efficacy:</b> Change in PANSS total score from baseline to end point for each group v PBO (ANCOVA, ITT, LOCF analysis). Dunnett-Bonferroni based parallel gate-keeping procedure to	Pharmacokinetics: Data used in population analysis (vol 19).  <b>Primary efficacy measure:</b> The mean changes in total PANSS were: -2.9, PBO; -8.0, 25 mg; -11.6, 100 mg & -13.2, 150 mg. All 3 PALP doses were significantly better than PBO (p=0.034, p<0.001 & p<0.001 respectively).  <b>Secondary Measures:</b> Both PALP 100 & 150 mg groups were significantly better than PBO for change from baseline to endpoint for PSP (p=0.007, p<0.001 respectively). Both PALP

<sup>6</sup> **CGI-S = Clinical Global Impression - Severity.** The investigator rates the severity of a subject's condition on a 7-point scale 1=not ill, 2=very mild, 3=mild, 4=moderate, 5=marked, 6=severe, and 7=extremely severe.

<sup>7</sup> **PSP = Personal and Social Performance scale.** The PSP is a validated, clinician-based rating instrument that provides an overall rating of personal and social functioning on a scale of 0 to 100 (higher score indicates better functioning). A single rating is based on 4 domains of functioning: socially useful activities, including work and study; personal and social relationships; self-care; and disturbing and aggressive behaviour.

<p>PALP 25 mg/d: n=155, 111M, 44F, 40y (20- 63)</p> <p>PANSS baseline</p> <p>87 ± 12</p> <p>PALP 100 mg/d: n=161, 107M, 54F, 39y (18-70)</p> <p>PANSS baseline</p> <p>86 ± 11</p> <p>PALP 150 mg/d: n=160, 103M, 57F, 39y (18-69)</p> <p>PANSS baseline</p> <p>88 ± 12</p>	<p>baseline. BMI ≥ 17.</p> <p>Antipsychotics not allowed: RISPC &lt;6 weeks, PALP &lt; 10 months, CLOZ &lt; 3 months, depot antipsychotics &lt;1 Rx cycle. All others stopped on Day -1.</p> <p>Subjects were hospitalised for at least the first 7 days.</p>	<p>adjust for multiplicity.</p> <p><b>Secondary Efficacy:</b></p> <p>Change in CGI-S (LOCF ANCOVA) &amp; PSP scores (LOCF Dunnett-Bonferroni) from baseline to end point. Change in PANSS factors &amp; subscale scores from baseline to end point.</p> <p>Change in PANSS total scores from baseline to each visit. PANSS responders defined as ≥ 30% &amp; ≥ 20% decrease from baseline to end point (CMH). Change to endpoint in sleep VAS ratings (LOCF, ANCOVA).</p>	<p>100 &amp; 150 mg groups were significantly better than PBO for change from baseline to endpoint for CGI-S, (p=0.005 &amp; p&lt;0.001 respectively). Changes from baseline to endpoint were significantly better than PBO for all 5 PANSS factors, all 3 subscales for 100, 150 mg, &amp; for negative symptoms, disorganised thoughts, general psycho-pathology for 25 mg (p&lt;0.05). % PANSS responders (≥ 30%): 34%, 25 mg; 41%, 100 mg; 40%, 150 mg groups. All 3 doses significantly better than PBO (20%); p=0.007, p&lt;0.001 &amp; p&lt;0.001 respectively.</p> <p>% PANSS responders (≥ 20%): 50%, 25 mg; 52%, 100 mg; 58%, 150 mg groups. All doses significantly better than PBO (33%); p=0.003, p=0.001, p&lt;0.001 respectively. Quality of sleep (VAS) change from baseline was significantly better than PBO for 100, 150 mg groups (p&lt;0.001. p=0.026).</p> <p>OC analyses in general confirm LOCF results.</p>
--	---	---	--

For the primary efficacy endpoint, the change from baseline to endpoint in the PANSS total scores, there was a significant difference in favour of all paliperidone palmitate dose groups [least squares mean differences: 25 mg -5.1, 95% CI (-9.01, -1.10) p=0.034 adjusted for multiple comparisons, 100 mg -8.7 (-12.62, -4.78) p<0.001, 150 mg -9.8 (-13.71, -5.85) p<0.001] compared to PBO. There was a dose-response pattern with increase in effect sizes with increasing dose but there were no treatment by country or treatment by baseline PANSS interactions. Post-hoc analyses of treatment by baseline BMI suggested that the treatment effect relative to PBO was smaller in the obese category and that this effect was greatest for US sites.

The secondary efficacy analysis of change from baseline to endpoint in PSP found that paliperidone palmitate was significantly better than PBO for both 100 and 150 mg doses with improved functioning in all treatment groups and a dose related response for the paliperidone palmitate groups. Similarly for the change from baseline to endpoint in CGI-S, paliperidone palmitate was significantly better than PBO for both 100 and 150 mg doses (Table 3). The change in PANSS total score from baseline to each visit showed that there was a decrease in scores over the course of the study for all groups. There were significant differences compared to PBO for all 3 paliperidone palmitate groups from Day 22 and as early as Day 8 for paliperidone palmitate 25 and 150 mg. The proportion of PANSS responders (defined as a decrease from baseline of ≥30%) was significantly greater for all paliperidone palmitate groups than PBO (Table 3). Change from baseline for the 5 PANSS factor scores (positive symptoms, negative symptoms, disorganised thoughts, uncontrolled hostility/excitement and anxiety/depression) were significantly better than PBO for 100 and 150 mg paliperidone palmitate but only negative symptoms and disorganised thoughts were significant for 25 mg paliperidone palmitate. The change from baseline in PANSS subscales scores (positive, negative, general psychopathology) were also significantly better than PBO for 100 and 150 mg paliperidone palmitate but only general psychopathology for 25 mg paliperidone palmitate. Sleep visual analogue scores for quality of sleep and daytime drowsiness were analysed from baseline to endpoint. Quality of sleep was significantly improved in both the 100 and 150 mg

paliperidone palmitate subjects whilst decreases in daytime drowsiness occurred particularly in the PBO group but there were no significant differences across groups.

The primary efficacy analysis was positive for all 3 doses of paliperidone palmitate. One of the secondary analyses (PANSS responders) was also positive for all doses and all other measures were positive for the 100 and 150 mg doses including those measuring personal and social functioning, global improvement and sleep quality.

*PSY-3003: A randomised, double-blind, placebo-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed doses (50 mg eq., 100 mg eq., and 150 mg eq.) of paliperidone palmitate in subjects with schizophrenia.*

This study was conducted at 36 centres in the USA, Malaysia, Korea, Taiwan and Ukraine. The primary objectives were to evaluate the efficacy and safety of 3 fixed doses of paliperidone palmitate when administered at 4 week intervals after 2 initial doses, compared with PBO (Table 4). The secondary objectives of this study were practically the same as for Study **PSY-3007**. Study completion rates were: 38% PBO, 50% paliperidone palmitate 50 mg, 55% paliperidone palmitate 100 mg, and 40% paliperidone palmitate 150 mg. The primary reason for withdrawal was lack of efficacy for all treatment groups. The demographic and other baseline characteristics and psychiatric history and disease characteristics were similar across treatment groups. The majority of subjects had used psychotropic medications prior to study entry (97%), particularly atypical antipsychotics (74%), benzodiazepines (69%) and typical antipsychotics (32%) in similar proportions of patients across groups. During treatment, concomitant medication other than benzodiazepines was 80% - mainly paracetamol and ibuprofen. Benzodiazepine use was 79%, largely lorazepam as allowed per protocol, in similar proportions of patients across groups. Due to a medication kit allocation error, the PBO group ended up with a larger number of subjects and the 150 mg group a smaller number than planned (30 instead of 90).

For the primary efficacy endpoint, the change from baseline to endpoint in the PANSS total scores, there was a significant difference in favour of the 100 mg paliperidone palmitate dose group [least squares mean differences: -6.9, 95% CI (-12.12, -1.68)  $p=0.019$  adjusted for multiplicity, compared to PBO. Since the 50 mg paliperidone palmitate dose was not significantly different to PBO [-3.5 (-8.73, 1.77)], the 150 mg was not tested for significance<sup>8</sup>. There was a treatment by country interaction partly explained by a higher baseline PANSS and a higher proportion of BMI  $\geq 30$  for US subjects, however there was insufficient evidence to confirm a qualitative interaction in comparison to PBO.

Table 4: Efficacy Study R092670-PSY-3003

No of subjects with age and sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Efficacy
n= 388 randomised n= 349 ITT PBO: n=132, 94M, 38F,	M or F, aged 18-65 years, diagnosed with schizophrenia (DSM IV)	Pharmacokinetics: Plasma PAL measured by LC-MS/MS.  <b>Primary Efficacy:</b> Change in PANSS total score from	Pharmacokinetics: PAL plasma concentrations were not dose proportional but 150 mg had limited numbers. Low PAL concentrations in high BMI group for higher doses. Data used in population analysis (vol 19).  <b>Primary efficacy measure:</b>

<sup>8</sup> The statistical analysis pre-specified that only if both of the 50 and 100 mg doses were significantly better than PBO, would the 150 mg have been tested against PBO.

41y (18-68) PANSS baseline 92 ± 13 PALP 50 mg/d: n=93, 65M, 28F, 39y (18-61) PANSS baseline 90 ± 11 PALP 100 mg/d: n=94, 61M, 33F, 39y (20-68) PANSS baseline 90 ± 12 PALP 150 mg/d: n=30, 22M, 8F, 41y (22-67) PANSS baseline 92 ± 12	for ≥ 1 year, PANSS total between 70-120 on screening & at baseline. BMI ≥ 17. Anti- psychotics not allowed: PALP, depot <60 days, oral anti- psychotics stopped by Day -2. Subjects were hospitalised for at least the first 7 days.	baseline to end point for each group v PBO (ANCOVA, ITT, LOCF analysis). Stepwise procedure used to identify effective doses while adjusting for multiplicity. <b>Secondary Efficacy:</b> Change in CGI-S & PSP scores from baseline to end point. Change in PANSS factor & subscale scores from baseline to end point. Change in PANSS total scores from baseline to each visit. PANSS responders defined as ≥ 30% & ≥ 20% decrease from baseline to end point.	The mean changes in total PANSS were: -4.1, PBO; - 7.9, 50 mg; -11.0, 100 mg & -5.5, 150 mg. PALP 100 mg was significantly better than PBO (p=0.019). <b>Secondary Measures:</b> Both PALP 50 & 100 mg groups were significantly better than PBO for change from baseline to endpoint for PSP (LOCF, 50 mg p=0.004 & 100 mg p<0.001). PALP 100 mg was significantly better than PBO for CGI-S scores (LOCF, p=0.010). PALP 100 mg was significantly better than PBO for change from baseline to endpoint for all PANSS 5 factor & 3 subscale scores (LOCF, p<0.01) while 50 mg was better for positive subscale, disorganised thoughts & uncontrolled hostility/excitement (p=0.035, p=0.031, p=0.020 respectively). % PANSS responders (≥ 30%): 34%, 50 mg; 39%, 100 mg; 23%, 150 mg groups. Only 100 mg significantly better than PBO (24%); p=0.012. % PANSS responders (≥ 20%): 50%, 50 mg; 54%, 100 mg; 30%, 150 mg groups. Both 50 & 100 mg significantly better than PBO (34%); p=0.028, p=0.003. There were no differences between PBO & 150 mg PALP for any efficacy analyses but only 30 subjects in this group.
--	---	---	---

The secondary efficacy analysis of change from baseline to endpoint in PSP found that paliperidone palmitate was significantly better than PBO for both 50 and 100 mg doses. For the change from baseline to endpoint in CGI-S, paliperidone palmitate was significantly better than PBO for only the 100 mg dose (Table 4). The change in PANSS total score from baseline to each visit showed that there were significant differences compared to PBO for 100 mg paliperidone palmitate from Day 36. The proportion of PANSS responders (defined as a decrease from baseline of ≥30%) was significantly greater for 100 mg paliperidone palmitate than PBO (Table 4) but when defined as a ≥20% decrease, both 50 and 100 mg were significantly better than PBO. Change from baseline for each of the 5 PANSS factor scores were significantly better than PBO for 100 mg paliperidone palmitate but only disorganised thoughts and uncontrolled hostility/excitement achieved significance for 50 mg paliperidone palmitate. The change from baseline in PANSS subscales scores was also significantly better than PBO for 100 mg paliperidone palmitate but only the positive subscale for 50 mg paliperidone palmitate.

The primary efficacy analysis and all of the secondary efficacy measures were positive for the 100 mg dose of paliperidone palmitate. Some of the secondary analyses (PSP, PANSS responder's ≥ 20%) were also positive for 50 mg dose. The number of subjects in the 150 mg group (n=30) precluded any realistic analysis of this data.

*PSY-3004: A randomised, double-blind, placebo-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed doses (25 mg eq., 50 mg eq., and 100 mg eq.) of paliperidone palmitate in subjects with schizophrenia.*

This study was conducted at 38 centres in the USA, South Africa, Bulgaria, Romania and Russia. The primary and secondary objectives of this study were the same as for Study **PSY-3003** (Table 5). Study completion rates were: 38% PBO, 53% paliperidone palmitate 25 mg, 54% paliperidone palmitate 50 mg, and 57% paliperidone palmitate 100 mg. The primary reason for withdrawal was lack of efficacy for all treatment groups. The demographic and other baseline characteristics and psychiatric history and disease characteristics were similar across treatment groups. The majority of subjects had used psychotropic medications prior to study entry (99%), particularly benzodiazepines (75%), atypical antipsychotics (70%), and typical antipsychotics (50%) in similar proportions of patients across groups. During treatment, concomitant medication other than benzodiazepines was 63% mainly paracetamol and ibuprofen. Benzodiazepine use was 71%, largely lorazepam as allowed per protocol in similar proportions of patients across groups.

For the primary efficacy endpoint, the change from baseline to endpoint in the PANSS total scores, there was a significant difference in favour of all paliperidone palmitate dose groups [least squares mean differences: 25 mg -6.6, 95% CI (-11.40, -1.73)  $p=0.015$  adjusted for multiplicity, 50 mg -5.97 (-10.76, -1.07)  $p=0.017$ , 100 mg -9.2 (-14.07, -4.43)  $p<0.001$ ] compared to PBO. There was a treatment by country interaction partly explained by a differential treatment effect by BMI category with larger improvements in subjects treated with paliperidone palmitate with a normal BMI compared to those who were overweight or obese. However there was insufficient evidence to confirm a qualitative interaction in comparison to PBO.

The secondary efficacy analysis of change from baseline to endpoint in PSP found improved functioning in all treatment groups but no significant differences for any the paliperidone palmitate groups compared to PBO. However, for the change from baseline to endpoint in CGI-S, all paliperidone palmitate groups were significantly better than PBO (Table 5). The change in PANSS total score from baseline to each visit showed that there was a decrease in scores over the course of the study for all groups. There were significant differences compared to PBO for all 3 paliperidone palmitate groups from Day 36. Change from baseline for the PANSS factor scores positive symptoms and negative symptoms, and positive and general psychopathology subscales were significantly better than PBO for all 3 doses of paliperidone palmitate, whereas uncontrolled hostility/excitement was significant for paliperidone palmitate 50 and 100 mg, and anxiety/depression and negative subscale were significant for 25 and 100 mg paliperidone palmitate. The proportion of PANSS responders (defined as a decrease from baseline of  $\geq 30\%$ ) was significantly greater for 25 and 100 mg paliperidone palmitate than PBO (Table 5) but when defined as a  $\geq 20\%$  decrease, all doses were significantly better than PBO.

Table 5: Efficacy Study R092670-PSY-3004

No of subjects with age and sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Efficacy
n= 518 randomised n= 514 ITT PBO: n=125, 78M, 47F, 41y (18-74) PANSS baseline 91 ± 12 PALP 25 mg/d: n=130, 85M, 45F, 41y (18-68) PANSS baseline 91 ± 12 PALP 50 mg/d: n=128, 94M, 34F, 39y (18-64) PANSS baseline 91 ± 12 PALP 100 mg/d: n=131, 85M, 46F, 42y (19-66) PANSS baseline 91 ± 12	M or F, aged 18-65 years, diagnosed with schizophrenia (DSM IV) for ≥ 1 year, PANSS total between 70-120 on screening & at baseline. BMI ≥ 15. Anti-psychotics not allowed: PALP, depot <60 days, oral anti-psychotics stopped by Day -2. Subjects were hospitalised for at least the first 7 days.	Pharmacokinetics: Plasma PAL measured by LC-MS/MS.  <b>Primary Efficacy:</b> Change in PANSS total score from baseline to end point for each group v PBO (ANCOVA, ITT, LOCF analysis). Stepwise procedure used to identify effective doses while adjusting for multiplicity.  <b>Secondary Efficacy:</b> Change in CGI-S & PSP scores from baseline to end point. Change in PANSS factor & subscale scores from baseline to end point. Change in PANSS total scores from baseline to each visit. PANSS responders defined as ≥ 30% & ≥ 20% decrease from baseline to end point.	Pharmacokinetics: PAL plasma concentrations were not dose proportional with lower than expected concentrations for 100 mg. Data used in population analysis (vol 19).  <b>Primary efficacy measure:</b> The mean changes in total PANSS were: -7.0, PBO; -13.6, 25 mg; -13.2, 50 mg & -16.1, 100 mg. All 3 PALP doses were significantly better than PBO (p=0.015, p=0.017 & p<0.001 respectively).  <b>Secondary Measures:</b> None of the PALP groups were significantly better than PBO for change from baseline to endpoint for PSP.  All PALP doses were significantly better than PBO for CGI-S scores (LOCF, p=0.003, p=0.006, p=0.002 respectively).  Changes from baseline to endpoint were significantly better than PBO for: positive & negative symptoms, positive & general psychopathology subscales for all 3 doses; uncontrolled hostility/excitement for 50, 100 mg; anxiety/depression & negative subscale for 25, 100 mg (p<0.05).  % PANSS responders (≥ 30%): 46%, 25 mg; 38%, 50 mg; 52%, 100 mg groups. Both 25 & 100 mg significantly better than PBO (31%); p=0.015, p<0.001.  % PANSS responders (≥ 20%): 57%, 25 mg; 54%, 50 mg; 61%, 100 mg groups. All doses significantly better than PBO (41%); p=0.008, p=0.029, p<0.001 respectively.

The primary efficacy analysis was positive for all three doses of paliperidone palmitate. One of the secondary analyses (CGI-S) was also positive for all doses and other measures were positive for the 25 and 150 mg doses.

*SCH-201: A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of 50 and 100 mg eq. of paliperidone palmitate in subjects with schizophrenia.*

This Phase 2 study was conducted at 30 centres in the USA, Russia, Bulgaria, Poland, Ukraine and India and included an open-label one-week oral run-in phase prior to a 10 week double blind phase (Table 6). The primary objectives of the study were to evaluate the efficacy and safety of two fixed dosages of long-acting injections of paliperidone palmitate compared to PBO using PANSS total scores. Secondary objectives were to assess the global improvement in



severity of illness and to explore the pharmacokinetic profiles of oral paliperidone-ER, oral paliperidone-IR and IM paliperidone palmitate. Study completion rates were: 32% PBO, 59% paliperidone palmitate 50 mg, and 61% paliperidone palmitate 100 mg. The primary reason for withdrawal was lack of efficacy for all treatment groups. The demographic and other baseline characteristics and psychiatric history and disease characteristics were similar across treatment groups. The majority of subjects had used psychotropic medications prior to study entry (75%), most commonly haloperidol (25%), risperidone (19%) and chlorpromazine (18%) in similar proportions of patients across groups. During treatment, concomitant medication other than benzodiazepines was 42% mainly paracetamol. Benzodiazepine use was 53%, largely lorazepam as allowed per protocol in similar proportions of patients across groups.

Table 6: Efficacy Study R092670-SCH-201

No of subjects with age and sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Efficacy
<p>n= 266 enrolled n= 247 randomised n= 197 ITT PBO: n=66, 39M, 27F, 41y (18-60) PANSS baseline 88 ± 14 PALP 50 mg/d: n=63, 41M, 22F, 40y (19-59) PANSS baseline 88 ± 12 PALP 100 mg/d: n=68, 42M, 26F, 37y (18-62) PANSS baseline 85 ± 11</p>	<p>M or F, aged 18-65 years, diagnosed with schizophrenia (DSM IV) for ≥ 1 year, PANSS total between 70-120 on screening and 60-120 at randomisation, BMI 15-35. Anti-psychotics not allowed: RISPC &lt; 100 days, PALP &lt; 10 mos, CLOZ &lt; 3 mos, depot antipsychotics &lt; 4 weeks.</p> <p>Subjects were hospitalised for at least the first 14 days.</p>	<p>Pharmacokinetics: Plasma PAL, R078543, R078544, RISP &amp; PALP measured by LC-MS/MS. <math>C_{max, ss}</math>, <math>t_{max}</math>, <math>C_{min, ss}</math>, <math>t_{1/2}</math>, <math>AUC_{last}</math>, <math>C_{ss, av}</math> &amp; CL/F derived using non-compartment methods.</p> <p><b>Primary Efficacy:</b> Change in PANSS total score from baseline to end point for each group v PBO (ANCOVA, ITT, LOCF analysis).</p> <p><b>Secondary Efficacy:</b> PANSS total score, factor &amp; subscale scores, change from baseline at each time point; change in PANSS total score from baseline to Day 8; PANSS responders defined as ≥ 30% decrease from baseline to week 10; also ≥20% decrease to week 10 analysed. CGI-S change from baseline to end.</p>	<p>Pharmacokinetics: Dose proportionality shown for both ER &amp; IR PAL. Exposure to PAL was similar for 2mg IR &amp; 6 mg ER; &amp; for 4mg IR &amp; 12 mg ER. Ratios of enantiomers were similar for ER &amp; IR PAL approx 1.6-1.8. Dose proportionality was established for PALP doses. Exposure was slightly lower for both doses of PALP cf oral dosing. Ratio of enantiomers was approx 1.6 for PALP. PALP detected in 4.5% samples, highest 3.9 ng/mL.</p> <p><b>Primary efficacy measure:</b></p> <p>The mean changes in total PANSS were: 6.2, PBO; -5.2, 50 mg; -7.8, 100 mg. Both PALP groups were significantly better than PBO (50, p=0.001; 100, p&lt;0.0001).</p> <p><b>Secondary Measures:</b></p> <p>PANSS total score change from baseline was significantly different to PBO for both PALP 50 &amp; 100 mg from Day 8 until week 10 (p&lt;0.10, LOCF), (OC ns 50 mg Day 22, 29). % PANSS responders (≥ 30%): 33% for 50 mg, 37% for 100 mg groups. Both were significantly better than PBO (14%); p=0.007, p=0.002. % responders (≥20%) for both doses were also significantly better than PBO (26%, 47% &amp; 15%). Both PALP 50 &amp; 100 mg groups were significantly better than PBO for change from baseline to endpoint for all PANSS factor scores and subscale scores (LOCF, p&lt;0.10). Both 50 mg (p=0.004) and 100 mg (p&lt;0.001) were significantly better than PBO for CGI-S scores (LOCF; OC 50 mg p=0.056, 100 mg p=0.005). In a post-hoc analysis of change in total PANSS scores, only normal weight group (BMI) was remained significant. Note: smaller numbers in overweight/obese groups.</p>

For the primary efficacy endpoint, the change from baseline to endpoint in the PANSS total scores, there was a significant difference in favour of both paliperidone palmitate dose groups

[least squares mean differences: 50 mg -11.2 (-16.85, -5.57)  $p=0.001$ , 100 mg -14.0 (-19.51, -8.58)  $p<0.000$ ] compared to PBO. There were significant differences compared to PBO for both paliperidone palmitate groups from Day 8. The secondary efficacy analyses: PANSS responders (defined as a decrease from baseline of  $\geq 30\%$ ), PANSS responders (defined as a decrease from baseline of  $\geq 20\%$ ) and change from baseline to endpoint in CGI-S were all significantly greater for both 50 and 100 mg paliperidone palmitate than PBO (Table 6). In addition, change from baseline for the 5 PANSS factor scores and the 3 subscales were significantly better than PBO for both doses of paliperidone palmitate.

The primary efficacy analysis was positive for both doses of paliperidone palmitate. All of the secondary analyses were also positive for both 50 and 100 mg doses. The study has been published (Kramer et al 2009).<sup>9</sup>

The evaluators concluded that overall, the four acute treatment studies were well designed, appropriate for their objectives and met with the TGA-adopted EU guideline.<sup>10</sup> Standard criteria for diagnosis of schizophrenia, assessment of severity of symptoms and appropriate inclusion/exclusion criteria were used. The efficacy variables specified were disorder-specific (PANSS and its subscales) and global (CGI). The three more recent studies also included a measure of personal and social functioning (PSP). The measurement tools, PANSS and CGI, are well-validated and clinically relevant assessments of outcome and are the accepted standard primary efficacy outcome measures used in recent clinical trials of new antipsychotics. Other design elements such as randomisation, double-blind and placebo were appropriate with blinding achieved by using a designated study drug administrator to administer injections who was not involved in ratings and randomisation was implemented using an interactive voice response system. Gender balance, age range, sample size, length of trial and statistical analyses were appropriate. In addition to establishing statistical significance over PBO, studies should also demonstrate clinically significant superiority over PBO. The PANSS response rates were based on a  $\geq 30\%$  decrease from baseline which is a clinically relevant assessment of response which is the standard used in other studies.

*PSY-3001: A randomised, double-blind, placebo-controlled, parallel-group study evaluating paliperidone palmitate in the prevention of recurrence in subjects with schizophrenia.*

This study was conducted at 56 centres in the USA, Russia, Ukraine, Romania, Korea, Taiwan, South Africa, Costa Rica and Mexico and consisted of 5 phases: screening, 9 week open-label transition, 24 week open-label maintenance, double-blind recurrence prevention of variable length determined by recurrence events and an optional open-label extension phase of up to 52 weeks (Table 7). PANSS total scores of less than 120 at screening and less than 75 at the start of maintenance and double-blind phases were required for inclusion. For the double-blind phase, eligible subjects were assigned randomly to either PBO or paliperidone palmitate at the last dose used during the maintenance phase (25, 50 or 100 mg). The definition of recurrence included an increase in PANSS of 25% or more, hospitalisation or the development of other clinically significant symptomatology (Table 7). The primary objectives were to evaluate the efficacy of paliperidone palmitate compared with PBO in the prevention of recurrence of the symptoms of schizophrenia, and to assess the safety and tolerability of paliperidone palmitate in subjects with schizophrenia. Secondary objectives included evaluation of: the improvement of

<sup>9</sup> Kramer M, Litman R, Hough D, Lane R, Lim P, Liu Y, Eerdeken M. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomised, double-blind, placebo-controlled efficacy and safety study. *Internat J Neuropsychopharmacol* 2009; doi:10.1017/S1461145709990988.

<sup>10</sup> EMEA, Committee for Proprietary Medical Products (CPMP), 26 February 1998. Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia, CPMP/EWP/559/95.

positive and negative symptoms, global improvement in severity, benefits to personal and social functioning with paliperidone palmitate compared to PBO; and assessment of symptom reduction and stability of symptoms during the transition and maintenance phases. The objective of the open-label extension phase was to evaluate the long-term safety and tolerability of paliperidone palmitate.

The protocol pre-specified an interim analysis conducted by an independent data monitoring committee which if positive allowed for the study enrolment to be stopped early. Eighty percent of subjects completed the transition phase and continued to the maintenance phase with the majority of subjects receiving either 50 mg or 100 mg paliperidone palmitate. Sixty percent of these subjects completed the maintenance phase with the majority receiving 100 mg paliperidone palmitate (mean dose 83mg). The most common reason for discontinuation was subject choice (8%) or lack of efficacy (7%). A further 11% were in this phase when the study was stopped due to the positive interim analysis (and were eligible to proceed to the open-label extension phase). The interim analysis set included 312 subjects, with 34% of PBO subjects experiencing a relapse compared to 10% for paliperidone palmitate. Of the final ITT set, 53% completed the double-blind phase, 32% experienced a recurrence and 14% withdrew. At the time of study cessation, 38% of the PBO and 67% of the paliperidone palmitate group remained in the study compared with 48% of the PBO and 18% of the paliperidone palmitate group who experienced a relapse. Seventy-four percent of subjects completed the open-label extension of 52 weeks with subject choice being the main reason for withdrawal during this phase (13%). The mean dose was approx 76 mg.

Table 7: Efficacy Study R092670-PSY-3001

No of subjects with age and sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Efficacy
n= 849 phase 2 n= 684 phase 3, n=410 randomised phase 4 n= 408 ITT PBO: n=203, 111M, 92F, 39y (18-63) PANSS baseline 53 ± 12 PALP: n=205,	M or F, aged 18-65 years, diagnosed with schizophrenia (DSM IV) for ≥ 1 year, PANSS total < 120 on screening and < 75 at start of phases 3& 4, BMI ≥ 15.  Anti-psychotics not allowed: RISP- C < 5 weeks, PALP < 10 months, depot anti-psychotics < 28 days. All others	<b>Primary Efficacy:</b>  Time from randomisation to time of first recurrence defined as psychiatric hospitalisation due to schizophrenic symptoms, ↑ 25% PANSS or > 10↑ in PANSS for 2 consecutive ratings depending on randomisation PANSS, suicidal ideation/aggressive behaviour /violent behaviour, PANSS items P1, P2, P3, P6, P7 or G8 ↑≥ 5/6 depending on randomisation score.  Pre-specified interim analysis (after the 68 <sup>th</sup> recurrence event) included in protocol. (Cox proportional hazards model, Kaplan Meier curves, ITT)  <b>Secondary Efficacy:</b> Change from randomisation to end point in PANSS total	<b>Primary efficacy measure:</b>  The time to recurrence was significantly longer in the PALP group compared with PBO (interim ITT, n=312; ITT, both p<0.0001). 48% PBO compared with 18% PALP subjects had recurrence event. The risk of recurrence for PBO was 3.6 X that of PALP (Cox proportional hazards ratio, ITT p<0.0001).  <b>Secondary Measures:</b>  PANSS total score change from baseline to end point was significantly greater for the PBO group (worsening) compared with PALP (p<0.0001, LOCF).  There was a significant difference for change in CGI-S scores in favour of PALP (p<0.0001, LOCF). 75% PALP compared with 56% PBO subjects were either scored as mild, very mild or not ill.  There was a significant difference for change in PSP scores in favour of PALP (p<0.0001, LOCF).  There was a significant difference for change in SQLS scores in favour of PALP (p=0.002, LOCF).

109M, 96F,  39y (18- 66)  PANSS baseline 52 ± 12  n=388  phase 5	stopped on Day -2.	score, factor & subscale scores, CGI-S, PSP & SQLS. (ANCOVA, LOCF).	The PALP group was significantly better than PBO for change from baseline to endpoint for all 5 PANSS factor & 3 subscales (LOCF, p=0.002 to p<0.0001).  <b>Open label phase:</b> Mean change in total PANSS was -4.3, there was no change in CGI-S scores, PSP scores indicated improvement with a mean change of 3.7 as did the mean change in SLQL of - 3.3.
--	-----------------------	---	--

The demographic and other baseline characteristics and psychiatric history and disease characteristics were similar for the all treated, not randomised and the randomised PBO and paliperidone palmitate groups. The majority of subjects had used psychotropic medications prior to study entry (96%), most commonly atypical antipsychotics (75%), benzodiazepines (34%) and typical antipsychotics (34%) in similar proportions of patients across groups. During double-blind treatment, concomitant medication other than benzodiazepines was 47% - mainly zolpidem. Benzodiazepine use was 28% in the PBO group and 19% in the paliperidone palmitate group, largely lorazepam as allowed per protocol.

Since the study was terminated early, the interim analysis was considered the primary analysis. Time to recurrence was significantly longer for paliperidone palmitate compared to PBO (p<0.0001) and this was confirmed by the final analysis ITT data (Table 7). The most common reason for recurrence was an increase of over 25% in total PANSS score. The risk of recurrence of schizophrenia symptoms for PBO subjects was 3.6 times that of paliperidone palmitate subjects. The risk of recurrence was not influenced by age, gender, region or BMI.

The mean PANSS total score decreased during the transition and maintenance phase for all subjects. PBO-treated subjects experienced a significant greater increase in PANSS ratings compared to the paliperidone palmitate group during the double-blind phase. CGI-S, PSP and Schizophrenia Quality of Life Scale-revision 4 (SQLS) changes were consistent with PANSS changes with significant differences in favour of the paliperidone palmitate group (Table 7). Study **PSY-3001** also included an open-label extension phase of up to 52 weeks (Table 13). Seventy four percent of subjects completed the study with the main reason for withdrawal being subject choice. The mean dose during the study was 77 mg. Efficacy evaluations during the open-label extension showed that paliperidone palmitate continued to be effective as shown by improvement or no change in PANSS, CGI-S and PSP ratings.

The primary analysis for the double-blind phase showed that paliperidone palmitate was more effective than PBO in preventing a recurrence of schizophrenic symptoms. All secondary efficacy analyses were in favour of paliperidone palmitate during this phase and there was a clinically meaningful improvement in symptoms during the transition, maintenance and extension phases. The study has been published (Hough et al 2010).<sup>11</sup>

The evaluators noted that the study was designed to mimic clinical practice, that is, transition patient to new medication with flexible dosing then maintain this over 6 months. Overall, the design of this study appears to be appropriate in terms of diagnostic and rating instruments, length of treatment period to ensure clinical stability prior to randomisation to the 2 parallel groups, gender balance, age range, sample size and statistical analyses. Currently there is no

<sup>11</sup> Hough D, Lindenmayer J-P, Gopal S, Melkote R, Lim P, Herben V, Yuen E, Eerdekens M. Safety and tolerability of deltoid and gluteal injections of paliperidone palmitate. *Prog Neuro-Psychopharmacol Biol Psych* 2009; 33: 1022-1031.

universally recognised definition of recurrence; however the criteria chosen in this study seem reasonable and are consistent with similar studies.

*PSY-3002: A randomised, double-blind, placebo-controlled, parallel-group comparative study of flexibly dosed paliperidone palmitate (25, 50, 75, or 100 mg eq.) administered every 4 weeks and flexibly dosed Risperdal Consta (25, 37.5, or 50 mg) administered every 2 weeks in subjects with schizophrenia.*

This study was conducted at 108 centres in Australia, Austria, Belgium, Luxembourg, Canada, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Lithuania, Netherlands, New Zealand, Poland, Spain, USA, Sweden and Switzerland and compared paliperidone palmitate initial dose 50 mg with Risperdal Consta initial dose 25 mg over 53 weeks with dosage adjustments after Day 36 allowed every 4 weeks (Table 8). A PANSS total score of 60-120 at screening was required for inclusion. The primary objective of this study was to demonstrate that paliperidone palmitate is not clinically inferior to Risperdal Consta for the treatment of schizophrenia. The safety and tolerability of paliperidone palmitate was also assessed. Secondary assessments included: global improvement of severity, benefits to personal and social functioning, symptomatic remission, and exploration of the relationship between pharmacokinetics and efficacy parameters.

Study completion rates for the all randomised subjects set were: 41% paliperidone palmitate and 50% Risperdal Consta, and for the per protocol population (PPP) 50% and 61% respectively. The primary reason for withdrawal was lack of efficacy (paliperidone palmitate) and withdrawal of consent (Risperdal Consta) for both data sets. The demographic and other baseline characteristics and psychiatric history and disease characteristics were similar across treatment groups. The majority of subjects had used psychotropic medications prior to study entry (97%), most commonly atypical antipsychotics (79%), benzodiazepines (49%) and typical antipsychotics (30%) in similar proportions of patients across groups. During treatment, concomitant medication other than benzodiazepines was 75% with paracetamol, zolpidem and biperiden the only drugs used in  $\geq 10\%$  of subjects. Benzodiazepine use was 51%, largely lorazepam as allowed per protocol in similar proportions of patients across groups. The mean dose of paliperidone palmitate over the study was 66 mg whilst Risperdal Consta was 33 mg, whilst the mean final doses received were 77 and 36 mg respectively.

Table 8: Efficacy Study R092670-PSY-3002

No of subjects with age & sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Efficacy
n=749 randomised n= 674 ITT n= 570 PPP PALP: n=379, 215M,	M or F, aged 18-65 years, diagnosed with schizophrenia (DSM IV) for $\geq 1$ year, PANSS total 60-120.	Pharmacokinetics: Plasma PAL & RISP measured by LC/MS/MS.  <b>Primary Efficacy:</b>  Non-inferiority analysis using PPP (defined as subjects who had received $\geq 4$ injections with no longer than 35d between them & had baseline & $\geq 1$ PANSS rating). Change in PANSS total score from baseline to end point for each	Pharmacokinetics: PAL plasma concentrations had reached steady-state by Day 204 for all doses. Median dose-normalised PAL concentrations were comparable between BMI categories. Data used in population analysis (vol 19).  <b>Primary efficacy measure:</b>  The mean change in total PANSS was -11.6 for PALP & -14.4 for RISPC. The difference between groups was -2.6 (-5.84, 0.61) (Least squares means, 95% CI). Non-inferiority was not demonstrated. This was confirmed using the ITT population with the difference being -3.8 (-6.96, -0.74). Non-

<p>164F, 41y (18-76) PANSS baseline 82 ± 13 RISPC: n=370, 229M, 139F, 41y (18-84) PANSS baseline 81 ± 13</p>	<p>BMI ≥15. Anti-psychotics not allowed: RISPC &lt; 5 weeks, PALP ever, depot anti-psychotics &lt; 1 injection interval. All others stopped on Day -2.</p>	<p>group (LOCF, ANCOVA) provided point estimate &amp; 95% CI of difference between groups. Non-inferiority demonstrated if 95% CI lower limit exceeded -5. <b>Secondary Efficacy:</b> Change from baseline to each visit &amp; end point in PANSS factors &amp; subscale scores, CGI-S &amp; PSP (ITT ANCOVA). PANSS responders defined as ≥ 30% decrease from baseline to week 53; remission defined as scores of mild or less on PANSS items (P1-3, N1, N4, N6, G5, G9) over last 6 months of double-blind period.</p>	<p>inferiority was suggested in normal weight/overweight subjects (lower CI limit -4.01) but not in obese subjects (-5.29). <b>Secondary Measures:</b> The mean change in CGI-S was -0.4 for PALP &amp; -0.6 for RISPC. The mean change in PSP was 3.7 for PALP &amp; 5.2 for RISPC. % PANSS responders (≥ 30%) were 44% for PALP &amp; 54% for RISPC. PALP &amp; RISPC were similar in effect on PANSS negative symptoms, negative subscale &amp; disorganised thoughts but RISPC was associated with numerically larger effect on positive symptoms, uncontrolled hostility/excitement, anxiety/depression, positive subscale &amp; general psychopathology subscale. % symptomatic remission was 24% for PALP &amp; 29% for RISPC.</p>
--	--	--	---

For the primary efficacy endpoint, the change from baseline to endpoint in the PANSS total scores, the difference between paliperidone palmitate and Risperdal Consta was -2.6 (least squares mean difference) with a 95% CI of (-5.84, -0.61). The lower limit was less than -5, the predetermined margin for non-inferiority, hence non-inferiority was not demonstrated. This was confirmed using the ITT population (Table 8). There was no treatment by country or region interaction but there was a treatment by BMI effect which approached significance whereby obese subjects improved less on paliperidone palmitate than normal or overweight subjects. Combining the normal and overweight groups lead to a non-inferiority finding compared to Risperdal Consta (Table 8). There was no difference in response to treatment in the normal, overweight or obese groups for Risperdal Consta. The secondary efficacy analysis of change from baseline to endpoint in CGI-S and PSP scores, and PANSS responders were similar for paliperidone palmitate and Risperdal Consta (Table 8). There was improvement for all PANSS factors and subscales and symptomatic remission was numerically similar for both groups.

The primary analysis did not support the primary objective of demonstrating paliperidone palmitate to be non-inferior to Risperdal Consta. Further analyses with regard to BMI found that paliperidone palmitate was non-inferior to Risperdal Consta in normal and overweight subjects but not in obese subjects. It is likely that non-inferiority was not demonstrated as initial doses of paliperidone palmitate on both Days 1 and 8 were only 50 mg resulting in low concentrations of paliperidone and a higher rate of drop-outs due to lack of efficacy. As a consequence of this and other studies, the recommended initial dose is now 150 mg on Day 1 and 100 mg on Day 8<sup>12</sup>. Secondary efficacy measures were similar for paliperidone palmitate and Risperdal Consta treated groups with Risperdal Consta having a numerically greater response on most measures but none that were statistically significant.

The evaluators noted that the overall design of this study was appropriate in terms of diagnostic and rating instruments, length of treatment, gender balance, age range and sample size. The choice of a non-inferiority margin of 5 points on the PANSS was based on a PBO-controlled study of Risperdal Consta where the lower limit of the confidence interval for the treatment

<sup>12</sup> This regimen was used in study **PSY-3006**, a 13 week comparison of paliperidone palmitate with Risperdal Consta. Mean changes in PANSS were -18.6 and -17.9 respectively. The pre-specified non-inferiority margin of -5 was met (full data not given). This study was not part of this submission. Data was obtained from [http://www.jnj.com/connect/news/all/20091210\\_090000](http://www.jnj.com/connect/news/all/20091210_090000).

benefit was 5.94 (Study RIS-USA-121) in line with *The Guideline on the choice of the non-inferiority margin (CPMP/EWP/2158/99)* and clinical experience of the sponsor and other experts that an effect of less than or equal to 5 points in the primary endpoint is considered an unimportant difference and represents no real loss of efficacy. The evaluators agreed that this was appropriate.

### **Efficacy Summary**

Paliperidone palmitate has been shown to be efficacious in the treatment of moderate to severe schizophrenia in 4 acute treatment studies. Efficacy has been demonstrated for the primary variable in all studies evaluating 25 and 100 mg, 2 of the studies for 50 and one study of the 150 mg dosages. Efficacy was seen across all PANSS factors and subscales especially for the higher doses 100 and 150 mg and was shown for disorder-specific, global and functional measures. The functional measures were indicative of considerable impairment in personal and social function at baseline, with improvements over time which were significant in 2 studies. Response to treatment was as early as Day 8 in study **PSY-3007** which used the 150 mg initiation dosage. Factors including age, sex, race and baseline PANSS did not influence effect with the exception of geographic region and BMI. In addition, recurrence prevention was demonstrated in subjects who had achieved symptom control during a prior open-label phase of treatment and therapeutic effect was maintained over a year of open-label treatment. Efficacy was confirmed over all domains investigated including all PANSS factors, subscales, CGI, PSP and SQLS. The majority of subjects were treated with 100 mg. Paliperidone palmitate was shown to be non-inferior to Risperdal Consta in normal and overweight subjects but not in the overall group. This may be because of the dosing regime used.

The sponsor's *Clinical Overview* includes data on dose related effect sizes calculated as standardised differences in least-squares means in total PANSS change from baseline to endpoint between paliperidone and PBO. Meta-analytic estimates of combined effect sizes were approx. 0.3 for both 25 and 50 mg, approx. 0.5 for 100 mg and between 0.5 and 0.6 for 150 mg. A recent review has calculated numbers needed to treat (NNT) which is also a measure of effect size from the PANSS response rates for the 4 acute studies (Citrome 2010).<sup>13</sup> NNTs for 25 mg were 7 (**PSY-3004**) and 8 (**PSY-3007**), 50 mg 6 (**SCH-201**), 10 (**PSY-3003**) and 15 (**PSY-3004**), 100 mg 5 (**PSY-3004**, **PSY-3007**, **SCH-201**) and 7 (**PSY-3003**), and 150 mg 5 (**PSY-3007**). The NNT for the recurrence prevention study was 3 (**PSY-3001**). The lower the NNT the larger the effect size with all single digit NNTs significantly better than PBO. NNT has been recommended as a measure of effect size which best reflects clinical significance (Kraemer & Kupfer 2006).<sup>14</sup>

### **Safety**

The six efficacy studies discussed in the previous section also provided safety data. The acute treatment studies (**SCH-201**, **PSY-3007**, **3003** and **3004**) were comparisons of several doses of paliperidone palmitate and PBO for 10-13 weeks. The objectives of these studies included the assessment of tolerability and safety of paliperidone palmitate in comparison to PBO. The recurrence prevention study (**PSY-3001**) also included an open-label extension of up to one year which primarily focussed on safety and tolerability. **PSY-3002** compared the safety and tolerability of paliperidone palmitate with Risperdal Consta. The seventh study, **PSY-3005** was a cross-over study of injection sites again primarily for safety and tolerability purposes. The

<sup>13</sup> Citrome L. Paliperidone palmitate - review of the efficacy, safety and cost of a new second-generation depot antipsychotic medication. *Internat J Clin Prac* 2010; 64: 216-239.

<sup>14</sup> Kraemer H, Kupfer D. Size of treatment effects and their importance to clinical research and practice. *Biological Psychiatry* 2006; 59: 990-996.

individual reports are summarised in Tables 9-16. The combined number of subjects evaluated for safety from these phase 2/3 studies was 2770 with a cumulative exposure of 1375.53 patient-years. Sixty-five percent of subjects (1809) were exposed to at least 12 weeks, 27% (755) at least 6 months and 19% (536) 1 year or more of treatment with paliperidone palmitate.

In all studies safety was assessed using adverse event reports and clinical laboratory evaluations, vital signs, electrocardiograms (ECGs), weight and BMI. Studies investigated changes in mean values over time and treatment emergent clinically important abnormalities. Extra-pyramidal symptoms (EPS) were examined using the Simpson-Angus scale (SAS), the abnormal involuntary movements scale (AIMS), the Barnes akathisia rating scale global assessment score (BARS) and the use of anticholinergic medications.<sup>15,16,17</sup> Tolerability at the injection site was also assessed in all studies by both patient and clinician. Patients who received at least one dose of study medication and provided post-baseline safety data were included in the safety populations.

In study **SCH-201**, which was conducted at 30 centres in the USA, Russia, Bulgaria, Poland, Ukraine and India, the majority of subjects (93%) received oral run-in medication and 42% of the PBO group received all 3 scheduled injections compared with 65-66% of subjects receiving paliperidone palmitate 50 or 100 mg. The majority of patients experienced at least one AE in the double-blind phase of the study (Table 9). The incidence of adverse effects (AEs) was similar across paliperidone palmitate and PBO groups. The most common AE was insomnia at similar rates across groups. Most AEs were mild to moderate in severity. There were no deaths. Serious adverse events (SAEs) (7% PBO, 10% 50, 6% 100) and discontinuation adverse events (DAEs) (10% PBO, 3% 50, 2% 100) were similar across all treatment groups with the most common being psychiatric disorders particularly worsening of schizophrenia or psychosis. Few SAEs were thought probably or possibly drug-related. For AEs of clinical interest (suicidality, somnolence, EPS-related, seizure and convulsions, neuroleptic malignant syndrome, cardiovascular-related including orthostatic hypotension, metabolic events including potentially prolactin-related) only orthostatic hypotension and EPS-related events were greater for paliperidone palmitate than for PBO (Table 9). Anti-EPS medication use was 7% PBO, 10% 50 and 21% 100. There were no statistically significant differences between the paliperidone palmitate groups and PBO in the median changes from baseline to study end for any of the neurological scales (SAS, AIMS, and BARS). However, the incidence of both Parkinsonism and akathisia as assessed by the SAS and BARS respectively was higher for paliperidone palmitate than PBO particularly for the paliperidone palmitate 100 mg group.

---

<sup>15</sup> The Simpson-Angus scale was devised to measure drug-induced parkinsonism, providing standardised ratings for rigidity, tremor and salivation. The scale is entirely sign led. It contains 10 items, each rated on a 5-point scale (0-4), with descriptive anchors for each point and a clearly described examination procedure for each item. Six of the 10 items rate rigidity: arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness and neck rigidity. There is a single item for gait, which is the only measure for bradykinesia, and is in fact a compound item incorporating gait, posture and loss of arm swing. The other three items measure tremor, glabellar tap and salivation.

<sup>16</sup> The Abnormal Involuntary Movement Scale (AIMS) is a rating scale that was designed in the 1970s to measure involuntary movements known as tardive dyskinesia (TD). The AIMS test has a total of twelve items rating involuntary movements of various areas of the patient's body. These items are rated on a five-point scale of severity from 0-4. The scale is rated from 0 (none), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe). Two of the 12 items refer to dental care.

<sup>17</sup> The Barnes Akathisia Scale (commonly known as BAS or BARS) is a rating scale that is administered by physicians to assess the severity of drug-induced akathisia. The Barnes Akathisia Scale is the most widely used rating scale for akathisia. This scale includes objective and subjective items such as the level of the patient's restlessness.



Table 9: Safety Study – R092670-SCH-201

No of subjects with age and sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Results
n= 266 enrolled n= 247 randomised n= 197 ITT PBO: n=66, 39M, 27F, 41y (18-60) PANSS baseline 88 ± 14 PALP 50 mg/d: n=63, 41M, 22F, 40y (19-59) PANSS baseline 88 ± 12 PALP 100 mg/d: n=68, 42M, 26F, 37y (18-62) PANSS baseline 85 ± 11	M or F, aged 18-65 years, diagnosed with schizophrenia (DSM IV) for ≥ 1 year, PANSS total between 70-120 on screening and 60-120 at randomisation. BMI 15-35. Anti-psychotics not allowed: RISP C < 100 days, PALP < 10 months, CLOZ < 3 months, depot anti-psychotics < 4 weeks. Subjects were hospitalised for at least the first 14 days.	AEs assessed at each visit. HR & BP at screening & days -7, -1, 1, 8, 15, 36, 43 & 64. Injection site assessments Days 1, 8 36. Clinical laboratory tests, ECGs & EPS (SAS, AIMS, BARS) at screening, Day -7, 1, 8, 15, 36 & 64. Weight & physical exam at screening & end.	Treatment-emergent adverse effects (TEAEs) reported by 43% subjects with few differences across doses & formulation during oral run-in. Most common: insomnia (9%), somnolence (8%), headache (7%). TEAEs reported by 64% (PBO), 65% (PALP 50) & 60% (PALP 100) subjects. Most common insomnia (18%), headache (7%). There were no deaths. SAEs reported by 7% (PBO), 10% (PALP 50) & 6% (PALP 100) subjects. Most common: psychiatric disorders. DAEs reported by 10% (PBO), 3% (PALP 50) & 2% (PALP 100) subjects. Most common: psychiatric disorders. AEs of clinical interest: Few cases of suicidality, aggression/agitation, somnolence, prolactin-related, glucose-related or cardiovascular related events other than orthostatic hypotension (4% PBO, 6% PALP 50, 11% PALP 100). EPS-related events more common for PALP v PBO as assessed by TEAEs (7%, 10%, 17%) anti-EPS medication use (7%, 10%, 21%) & rating scales however there was no significant difference between groups for change in SAS, BARS & AIMS ratings (ANOVA). There were no clinically relevant mean changes from baseline for clinical laboratory tests & few TE markedly abnormal individual values for either PBO or PALP (no group >5% inc glucose, lipids). Increased prolactin as expected for PALP groups. Incidence of abnormal vital signs (>5%): ↑standing (st) pulse (≥15bpm & >100)15% PBO, 10% 50 mg, 15% 100 mg; ↑ supine (su) pulse 11% PBO, 4% 50 mg, 7% 100 mg; TE orthostatic hypotension 4% PBO, 6% 50 mg, 11% 100 mg. Weight & BMI were significantly increased in both PALP groups compared with PBO (normal weight group). Clinically important weight gain (≥7%) 4% PBO, 8% 50 mg, 6% 100 mg. Incidence of abnormal ECG values: ↑HR 8% PBO, 22% 50 mg, 12% 100 mg; ↓ HR 5% PBO, 6% 50 mg, 5% 100 mg. Incidence of QTcLD change >30 ms (milliseconds) few & similar across groups. Injection site (investigator): redness, pain, swelling & induration were higher for PALP compared with PBO but rated as mild. Few severe reactions, moderate pain PALP 100 Day 36 (12%), PBO 6% Days 1 & 8.

For the laboratory variables, mean changes from baseline to end of study were minimal for any haematology, clinical chemistry or urinalysis parameter and generally similar across groups with the exception of prolactin. Prolactin increased approximately 70-80% during the oral run-in phase such that baseline values were already elevated before the start of the double-blind phase. Few subjects experienced clinically significant abnormalities with no groups showing an incidence of >5% for any parameter including glucose and lipids. Changes from baseline in mean standing and supine systolic, diastolic blood pressure and pulse rate were minor for all groups. Clinically important changes occurring in >5% of any group are listed in Table 9. Treatment emergent clinical important increases in pulse were similar in both paliperidone palmitate groups and PBO as were rates of clinically important changes in BP. Treatment emergent clinical important orthostatic increases in pulse were more frequent with paliperidone palmitate (4% PBO, 6% 50, 11% 100).

There were statistically significant mean increases in weight and BMI for both paliperidone palmitate groups compared to PBO. Paliperidone palmitate 100 was associated with the largest mean increase in both parameters in all BMI subgroups. Clinically important weight gain (≥7%)

was more common for paliperidone palmitate than PBO (4% PBO, 8% 50, 6% 100). There were no differences in mean changes from pre-dose values for either paliperidone palmitate group and PBO for any ECG parameters (heart rate, PR interval, QRS interval, QT interval and dispersion, RR interval and QTc interval). Treatment emergent clinically important increases in heart rate were seen in all groups but these were more frequent for both the paliperidone palmitate groups (8% PBO, 22% 50, 12% 100) and clinically important decreases in HR were similar across groups. There were no subjects with a linear derived QTc correction (QTcLD) change > 60 milliseconds (ms), similar numbers in each group (2-4%) with changes > 30 ms, no subjects had a QTcLD interval of >500 ms and 2 PBO subjects with a QTcLD >450 ms.

Investigator evaluations of the injection site were performed within 30 minutes after injection for redness, pain, swelling and induration. The majority of subjects in all groups did not experience any injection side effects. In general, the paliperidone palmitate groups experienced more mild-moderate symptoms than the PBO subjects however the only severe reactions were 3 reports of severe pain (2 paliperidone palmitate 50, 1 paliperidone palmitate 100). Paliperidone palmitate 100 subjects also experienced an increased rate (12%) of moderate pain after the third injection. Subjects' assessment of the area of injection pain and injection pain using visual analogue scales did not show any clear differences between groups.

In study **PSY-3003**, conducted at 36 centres in the USA, Malaysia, Korea, Taiwan and Ukraine, 37% of subjects received an oral tolerability test. Forty-one percent of the PBO group received all 4 scheduled injections compared with 47-55% of subjects receiving paliperidone palmitate 50, 100 or 150 mg. The majority of patients experienced at least one AE in the double-blind phase of the study (Table 10). The incidence of AEs was similar for paliperidone palmitate 50 and PBO groups but higher for paliperidone palmitate 100 and 150 groups. The most common AE was headache at similar rates across groups. Most AEs were mild to moderate in severity. There were no deaths. SAEs (19% PBO, 17% 50, 10% 100, 20% 150) and DAEs (10% PBO, 9% 50, 2% 100, 7% 150) were lower for the paliperidone palmitate 100 group but similar across the other treatment groups with the most common being psychiatric disorders particularly schizophrenia and psychosis. Few SAEs were thought probably or possibly drug-related. Most AEs of clinical interest were of similar incidence between PBO and paliperidone palmitate groups (Table 10). EPS-related AEs were greater for paliperidone palmitate than PBO as was anti-EPS medication use: 19% 50, 15% 100, 30% 150 and 15% PBO. There were no statistically significant differences between the paliperidone palmitate groups and PBO in the median changes from baseline to study end for any of the neurological scales. The incidence of Parkinsonism and akathisia as assessed by the SAS and BARS respectively was similar or lower for paliperidone palmitate than PBO.

Table 10: Safety Study – R092670-PSY-3003

No of subjects with age and sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Results
n= 388 randomised n= 349 ITT PBO: n=132, 94M, 38F,	M or F, aged 18-65 years, diagnosed with schizophrenia	AEs assessed at each visit.  Clinical laboratory tests &	TEAEs reported by 76% (PBO), 74% (PALP 50), 81% (PALP 100) & 83% (PALP 150) subjects. Most common: PALP headache (22%), insomnia (11%); PBO headache (17%), psychotic disorder (14%), insomnia (10%). There were no deaths. SAEs reported by 19% (PBO), 17% (PALP 50), 10% (PALP 100) & 20% (PALP 150) subjects. Most common psychiatric disorders. DAEs reported by 10% (PBO), 9% (PALP 50), 2% (PALP 100) & 7% (PALP

41y (18-68) PANSS baseline 92 ± 13 PALP 50 mg/d: n=93, 65M, 28F, 39y (18-61) PANSS baseline 90 ± 11 PALP 100 mg/d: n=94, 61M, 33F, 39y (20-68) PANSS baseline 90 ± 12 PALP 150 mg/d: n=30, 22M, 8F, 41y (22-67) PANSS baseline 92 ± 12	(DSM IV) for ≥ 1 year, PANSS total between 70-120 on screening & at baseline. BMI ≥ 17.  Anti- psychotics not allowed: see Table 12.  Subjects were hospital- ised for at least the first 7 days.	weight at screening, baseline & week 13; vital signs & EPS (SAS, AIMS & BARS) at screening, baseline, week 1 & week 13; ECGs at screening, baseline, weeks 1, 5, 9 & week 13; injection site assessments at baseline, weeks 1, 5, 9; physical exam screening & week 13.	150) subjects. Most common psychiatric disorders.  AEs of clinical interest: Incidence of AEs related to suicidality (4% PBO, 4% combined PALP groups), aggression/agitation (9%, 7%), somnolence (4%, 6%), orthostatic hypotension (0%, <1%), prolactin-related (1%, 1%), glucose-related (2%, 2%), EPS-related (12%, 17%). Anti-EPS medication use (15%, 21%). No significant difference between groups for change in SAS, BARS & AIMS ratings (ANOVA).  There were no clinically relevant mean changes from baseline for clinical laboratory tests & few TE markedly abnormal individual values for either PBO or PALP (no group >5% inc glucose, lipids). Increased prolactin as expected for PALP groups. Incidence of abnormal vital signs (>5%): ↑st pulse (≥15bpm & >100) 15% PBO, 15% 50 mg, 9% 100 mg, 10% 150 mg; ↑su pulse 5% PBO, 4% 50 mg, 4% 100 mg, 0% 150 mg; TE orthostatic hypotension 3% PBO, 1% 50 mg, 1% 100 mg, 0% 150 mg. Weight & BMI were increased in all PALP groups compared with PBO. Clinically important weight gain (≥7%) 2% PBO, 12% 50 mg, 10% 100 mg, 4% 150 mg. Incidence of abnormal ECG values: ↑HR 12% PBO, 11% 50 mg, 13% 100 mg, 13% 150 mg; ↓HR all groups ≤2%. Incidence of max QTcLD >450 ms, 0% PBO, 4% 50 mg, 2% 100 mg, 0% 150 mg; change >30 ms 2% PBO, 2% 50 mg, 4% 100 mg, 0% 150 mg. Observer injection site: no severe reactions, few moderate reactions ≤ 3% redness, ≤7% pain, similar across groups. Self-ratings: injection site pain & injection pain similar across groups.
--	--	--	--

For the laboratory variables, mean changes from baseline to end of study were minimal for haematology, renal function, liver function, glucose and serum lipids and generally similar across groups with the exception of prolactin. Mean changes for prolactin were: males 50 mg 7 ng/mL, 100 mg 15 ng/mL, 150 mg 15 ng/mL; females 32, 40, 62 ng/mL respectively. Few subjects experienced clinically significant abnormalities with no groups showing an incidence of >5% for any parameter including glucose and lipids except for prolactin (males 9% PBO, 35% 50, 56% 100, 53% 150; females 3% PBO, 58% 50, 60% 100, 67% 150). Changes from baseline in mean standing and supine systolic, diastolic blood pressure and pulse rate were minor for all groups. Treatment emergent clinical important increases in pulse (Table 10) were similar in both paliperidone palmitate groups and PBO as were treatment emergent clinical important orthostatic increases in pulse.

There were statistically significant mean increases in weight and BMI for paliperidone palmitate 50 and 100 groups compared to PBO. Clinically important weight gain (≥7%) was more common for paliperidone palmitate than PBO (2% PBO, 12% 50, 10% 100, 4% 150). There were no major differences in mean changes from pre-dose values for either paliperidone palmitate group and PBO for any ECG parameters. Treatment emergent clinically important increases in heart rate were seen in similar rates in all groups as were clinically important decreases in HR. No subjects had a QTcLD change > 60 ms, similar numbers in each group (2-4%) had changes > 30 ms, no subjects had a QTcLD interval of >480 ms and 6 paliperidone palmitate subjects had a QTcLD >450 ms.

Investigator evaluations of the injection site were performed within 60 minutes after injection. The majority of subjects in all groups did not experience any injection side effects.

There were no severe reactions. There were a few reports of moderate pain (2-3% across groups) with paliperidone palmitate 150 subjects reporting an increased rate (7%) after the fourth injection. Subjects' assessment of the injection site pain and injection pain using visual analogue scales did not show any clear differences between groups.

In study **PSY-3004**, conducted at 38 centres in the USA, South Africa, Bulgaria, Romania and Russia, 45% of subjects received an oral tolerability test. Forty-three percent of the PBO group received all 4 scheduled injections compared with 57-64% of subjects receiving paliperidone palmitate 25, 50 or 100 mg. The majority of patients experienced at least one AE in the double-blind phase of the study (Table 11). The most common AE was headache at similar rates across groups. Most AEs were mild to moderate in severity. There were 2 deaths, one subject suicided (paliperidone palmitate 100) and the other had pancreatic carcinoma (PBO). SAEs (18% PBO, 14% 25, 13% 50, 8% 100) were more frequent for the PBO group. DAEs (6% PBO, 6% 25, 2% 50, 5% 100) were similar for all treatment groups with the most common being psychiatric disorders particularly schizophrenia and psychosis. Few SAEs were thought probably or possibly drug-related. Most AEs of clinical interest were of similar incidence between PBO and paliperidone palmitate groups with aggression/agitation and somnolence more common for the paliperidone palmitate groups (Table 11). EPS-related AEs were greater for paliperidone palmitate than PBO but anti-EPS medication use was similar: 10% 25, 7% 50, 8% 100 and 9% PBO. There were no statistically significant differences between the paliperidone palmitate groups and PBO in the median changes from baseline to study end for any of the neurological scales. The incidence of Parkinsonism and akathisia as assessed by the SAS and BARS respectively was similar for paliperidone palmitate and PBO.

There were no clinically relevant mean changes from baseline to end of study for haematology, renal function, liver function, glucose and serum lipids across groups with the exception of prolactin. Mean changes for prolactin were males: 25 mg 4 ng/mL, 50 mg 7 ng/mL, 100 mg 10 ng/mL; females 9, 35, 44 ng/mL respectively. Few subjects experienced clinically significant abnormalities with no groups showing an incidence of >5% for any parameter except for prolactin (males 9% PBO, 24% 25, 30% 50, 37% 100; females 12% PBO, 30% 25, 48% 50, 48% 100). Changes from baseline in mean standing and supine systolic, diastolic blood pressure and pulse rate were not clinically relevant across all groups. Treatment emergent clinical important increases in pulse (Table 11) were similar in the paliperidone palmitate groups and PBO. Treatment emergent clinical important orthostatic increases in pulse were small and similar across groups.

There were statistically significant mean increases in weight and BMI for paliperidone palmitate 50 and 100 groups compared to PBO. Clinically important weight gain ( $\geq 7\%$ ) was more common for paliperidone palmitate than PBO (2% PBO, 6% 25, 7% 50, 11% 100). There were no major differences in mean changes from pre-dose values for either paliperidone palmitate group and PBO for any ECG parameters. Treatment emergent clinically important increases in heart rate occurred more often in the paliperidone palmitate 25 and 100 groups (13% PBO, 21% 25, 10% 50, 16% 100) whereas clinically important decreases in HR were similar across groups. No subjects had a QTcLD change > 60 ms, similar numbers in each group (3-5%) had changes > 30 ms, no subjects had a QTcLD interval of >480 ms and 2 paliperidone palmitate and 4 PBO subjects had a QTcLD >450 ms.

Table 11: Safety Study – R092670-PSY-3004

No of subjects with age and sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Results

<p>n= 518 randomised n= 514 ITT</p> <p>PBO: n=125, 78M, 47F, 41y (18-74)</p> <p>PANSS baseline 91 ± 12</p> <p>PALP 25 mg/d: n=130, 85M, 45F, 41y (18-68)</p> <p>PANSS baseline 91 ± 12</p> <p>PALP 50 mg/d: n=128, 94M, 34F, 39y (18-64)</p> <p>PANSS baseline 91 ± 12</p> <p>PALP 100 mg/d: n=131, 85M, 46F, 42y (19-66)</p> <p>PANSS baseline 91 ± 12</p>	<p>M or F, aged 18-65 years, diagnosed with schizophrenia (DSM IV) for ≥ 1 year, PANSS total between 70-120 on screening &amp; at baseline.</p> <p>BMI ≥ 15.</p> <p>Anti-psychotics not allowed: see Table 13.</p> <p>Subjects were hospitalised for at least the first 7 days.</p>	<p>AEs assessed at each visit.</p> <p>Clinical laboratory tests &amp; weight at screening, baseline &amp; week 13; vital signs &amp; EPS (SAS, AIMS &amp; BARS) at screening, baseline, week 1 &amp; week 13; ECGs at screening, baseline, weeks 1, 5, 9 &amp; week 13; injection site assessments at baseline, weeks 1, 5, 9; physical exam screening &amp; week 13.</p>	<p>TEAEs reported by 72% (PBO), 75% (PALP 25), 66% (PALP 50) &amp; 66% (PALP 100) subjects. Most common: PALP insomnia (14%), headache (10%); PBO insomnia (17%), schizophrenia (16%), headache (11%). There were 2 deaths (PBO, PALP 100 mg). SAEs reported by 18% (PBO), 14% (PALP 25), 13% (PALP 50) &amp; 8% (PALP 100) subjects. Most common psychiatric disorders. DAEs reported by 6% (PBO), 6% (PALP 25), 2% (PALP 50) &amp; 5% (PALP 100) subjects. Most common psychiatric disorders.</p> <p>Clinically relevant AEs: Incidence of AEs related to suicidality (3% PBO, 2% PALP), aggression/agitation (9%, 12%), somnolence (3%, 6%), orthostatic hypotension (0%, 1%), prolactin-related (1%, 1%), glucose-related (1%, 1%), EPS-related (9%, 12%). Anti-EPS medication use (9%, 8%) &amp; no significant difference between groups for change in SAS, BARS &amp; AIMS ratings (ANOVA).</p> <p>There were no clinically relevant mean changes from baseline for clinical laboratory tests &amp; few TE markedly abnormal values for either PBO or PALP (no group &gt;5% inc glucose, lipids). Increased prolactin as expected for PALP groups. Incidence of abnormal vital signs (&gt;5%): ↑st pulse (≥15bpm &amp; &gt;100) 9% PBO, 7% 25 mg, 9% 50 mg, 5% 100 mg; ↑ su pulse 6% PBO, 3% 25 mg, 4% 50 mg, 2% 100 mg; TE orthostatic hypotension 1% PBO, 2% 25 mg, 2% 50 mg, 0% 150 mg. Weight &amp; BMI showed dose-related ↑ for PALP. Clinically important weight gain (≥7%) 2% PBO, 6% 25 mg, 7% 50 mg, 11% 100 mg. Incidence of abnormal ECG values: ↑HR 13% PBO, 21% 25 mg, 10% 50 mg, 16% 100 mg; ↓ HR all groups ≤4%. Incidence of max QTcLD &gt;450 ms, 3% PBO, 0% 25 mg, 1% 50 mg, 1% 100 mg; change &gt;30 ms 5% PBO, 3% 25 mg, 4% 50 mg, 5% 100 mg. Injection site: 1x severe pain (PALP 25 mg), moderate reactions ≤ 3% redness, ≤2% pain, 0% swelling, ≤1% induration, all similar across groups. Self-ratings: injection site pain &amp; injection pain decreased with time &amp; similar across groups.</p>
---	---	---	---

Investigator evaluations of the injection site were performed within 60 minutes after injection. The majority of subjects in all groups did not experience any injection side effects.

There was one report of severe pain for paliperidone palmitate 25 at baseline. There were a few reports of moderate pain (1-2%), redness (1-3%) and induration (1%) across groups. Subjects' assessment of the injection site pain and injection pain showed that the intensity of the pain decreased over time for all groups.

In study **PSY-3007**, conducted at 72 centres in the USA, Russia, Romania, Ukraine, Taiwan, Korea, Malaysia and Serbia, 46% of subjects received an oral tolerability test. Forty-eight percent of the PBO group received all 4 scheduled injections compared with 56-61% of subjects receiving paliperidone palmitate 25, 100 or 150 mg. The majority of patients experienced at least one AE in the double-blind phase of the study (Table 12). The most common AE was insomnia at similar rates across groups. Most AEs were mild to moderate in severity. There was one death in a subject on paliperidone palmitate 150 one week after discontinuation due to a cerebrovascular accident. SAEs (14% PBO, 9% 25, 13% 100, 8% 150) and DAEs (7% PBO, 6% 25, 6% 100, 5% 150) were similar for all treatment groups with the most common being psychiatric disorders, particularly schizophrenia and psychosis. Few SAEs were thought probably or possibly drug-related. Most AEs of clinical interest were of similar incidence between PBO and paliperidone palmitate groups (Table 12). EPS-related AEs and anti-EPS

medication use was similar: 11% 25, 12% 100, 13% 150 and 13% PBO. There were no differences between the paliperidone palmitate groups and PBO in the median changes from baseline to study end for any of the neurological scales. The incidence of Parkinsonism and akathisia as assessed by the SAS and BARS respectively was similar for paliperidone palmitate and PBO.

Table 12: Safety Study – R092670-PSY-3007

No of subjects with age and sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Results
<p>n= 652 randomised n= 636 ITT PBO: n=160, 106M, 54F, 40y (19-67) PANSS baseline 87 ± 10 PALP 25 mg/d: n=155, 111M, 44F, 40y (20-63) PANSS baseline 87 ± 12 PALP 100 mg/d: n=161, 107M, 54F, 39y (18-70) PANSS baseline 86 ± 11 PALP 150 mg/d: n=160, 103M, 57F, 39y (18-69) PANSS baseline 88 ± 12</p>	<p>M or F, aged 18-65 years, diagnosed with schizophrenia (DSM IV) for ≥ 1 yr, PANSS total between 70-120 on screening &amp; 60-120 at baseline BMI ≥17. Anti-psychotics not allowed: see Table 14. Subjects hospitalised for at least the first 7 days</p>	<p>AEs assessed at each visit. Vital signs &amp; SAS, AIMS &amp; BARS at screening, baseline, week 1 &amp; 13; weight at screening, baseline &amp; week 13; clinical laboratory tests at screening, baseline, weeks 5 &amp; 13; ECGs at screening, baseline, weeks 1, 5 &amp; 13; injection site assessments at base-line, weeks 1, 5, 9; physical exam screening &amp; wk 13.</p>	<p>TEAEs reported by 65% (PBO), 63% (PALP 25), 60% (PALP 100) &amp; 63% (PALP 150) subjects. Most common: PALP insomnia (12%); PBO insomnia (17%), schizophrenia (12%). There was 1 death (PALP 150). SAEs reported by 14% (PBO), 9% (PALP 25), 13% (PALP 100) &amp; 8% (PALP 150) subjects. Most common psychiatric disorders. DAEs reported by 7% (PBO), 6% (PALP 25), 6% (PALP 100) &amp; 8% (PALP 150) subjects. Most common psychiatric disorders. Special interest AEs: Incidence of AEs related to suicidality (2% PBO, 2% PALP), aggression/agitation (9%, 6%), somnolence (2%, 4%), orthostatic hypotension (0%, &lt;1%), prolactin-related (1%, 1%), glucose-related (1%, 0%), EPS-related (10%, 10%). Anti-EPS medication use (13%, 12%) &amp; no differences between groups for change in SAS, BARS &amp; AIMS ratings (ANOVA). There were no clinically relevant mean changes from baseline for clinical laboratory tests &amp; few markedly individual abnormalities for either PBO or PALP (no group &gt;5% inc glucose, lipids). Increased prolactin as expected for PALP groups. Incidence of abnormal vital signs (&gt;5%): ↑st pulse (≥15bpm &amp; &gt;100) 6% PBO, 10% 25 mg, 11% 100 mg, 7% 150 mg; ↑ su pulse 2% PBO, 5% 25 mg, 3% 100 mg, 3% 150 mg; TE orthostatic hypotension 2% PBO, 1% 25 mg, 2% 100 mg, 2% 150 mg. Weight &amp; BMI showed dose –related ↑ for PALP. Weight &amp; BMI were increased in all PALP groups cf PBO. Clinically important weight gain (≥7%) 5% PBO, 6% 25 mg, 8% 100 mg, 13% 150 mg. Incidence of abnormal ECG values: ↑HR 9% PBO, 16% 25 mg, 11% 100 mg, 10% 150 mg; ↓ HR all groups ≤4%. Incidence of max QTcLD &gt;450 ms, 0% PBO, 1% 25 mg, 0% 100 mg, 1% 150 mg; change &gt;30 ms 3% PBO, 3% 25 mg, 4% 100 mg, 3% 150 mg. Injection site: severe pain all PALP groups (1-2%), severe induration PALP 25 (1%); moderate reactions ≤ 1% redness, ≤4% pain, ≤2% swelling, ≤2% induration, all similar across groups. Self-ratings: injection pain similar across groups &amp; decreased with time, lower for gluteal compared with deltoid.</p>

There were no clinically relevant mean changes from baseline to end of study for haematology, renal function, liver function, glucose and serum lipids across groups with the exception of prolactin. Mean changes for prolactin were males: 25 mg 4 ng/mL, 100 mg 8 ng/mL, 150 mg 13 ng/mL; females 9, 5, 37 ng/mL respectively. Few subjects experienced clinically significant abnormalities with no groups showing an incidence of >5% for any parameter except for

prolactin (males 4% PBO, 31% 50, 30% 100, 29% 150; females 4% PBO, 23% 50, 21% 100, 16% 150). Changes from baseline in mean standing and supine systolic, diastolic blood pressure and pulse rate were not clinically relevant across all groups. Treatment emergent clinical important increases in pulse (Table 12) were similar in the paliperidone palmitate groups and PBO. Treatment emergent clinical important orthostatic increases in pulse were small and similar across groups.

There were mean increases in weight and BMI for all paliperidone palmitate groups compared to PBO with both showing a dose-related increase. Clinically important weight gain ( $\geq 7\%$ ) was more common for paliperidone palmitate than PBO (5% PBO, 6% 25, 8% 100, 13% 150) with again a dose-related trend apparent. There were no major differences in mean changes from pre-dose values for either paliperidone palmitate group and PBO for any ECG parameters. Treatment emergent clinically important increases in heart rate occurred more often in the paliperidone palmitate 25 group (9% PBO, 16% 25, 11% 100, 10% 150) whereas clinically important decreases in HR were similar across groups. No subjects had a QTcLD change  $> 60$  ms, similar numbers in each group (3-4%) had changes  $> 30$  ms, no subjects had a QTcLD interval of  $> 480$  ms and 2 paliperidone palmitate had a QTcLD  $> 450$  ms.

Investigator evaluations of the injection site were performed within 30 minutes after injection. The majority of subjects in all groups did not experience any injection side effects.

There were a few severe pain reports for all paliperidone palmitate groups (1-2%) and one severe induration report for paliperidone palmitate 25. There were a few reports of moderate pain ( $\leq 4\%$ ), redness ( $\leq 1\%$ ) and induration ( $\leq 2\%$ ) across groups. Subjects' assessment of the injection pain showed that the intensity of the pain decreased over time for all groups. Comparison of gluteal and deltoid sites showed that pain was less for the gluteal site.

In study **PSY-3001** (Table 13), 39% of subjects received an oral tolerability test, 90% received 3 injections during the transition phase and 68% received 6 injections during the maintenance phase. In the double-blind phase, 24% of the PBO group received at least 5 injections compared with 37% of subjects receiving paliperidone palmitate (interim analysis) and 24% and 46% respectively received at least 7 injections (final analysis). The majority of patients experienced at least one AE in the transition/maintenance phase of the study, of a similar rate to those reported in the acute studies (Tables 9-12). SAEs and DAEs were also similar to the acute studies. The rate of AEs reported during the double-blind phase of the study was lower as might be expected after 33 weeks of treatment and was similar for the PBO (44%) and paliperidone palmitate (45%) groups. The most common AE was insomnia for PBO and weight increased for the paliperidone palmitate group. Most AEs were mild to moderate in severity. SAEs were more frequent for the PBO group with the most common being psychiatric disorders, particularly schizophrenia and psychosis. Few SAEs were thought probably or possibly drug-related. DAEs were low for both PBO and paliperidone palmitate groups (Table 13). There were 3 deaths during transition /maintenance: 1 subject suicided, 1 died from natural causes (?stroke) and 1 was accidental. There were a further 2 deaths post treatment: 1 died from ingestion of a toxic substance 19 days after discontinuation and the other due to a heart attack 10 days after discontinuation. Most AEs of clinical interest were infrequent during the transition/maintenance phase and of similar incidence between PBO and paliperidone palmitate groups during the double-blind phase (Table 13). Both EPS-related AEs and anti-EPS medication use were greater for paliperidone palmitate than PBO. There were no statistically significant differences between paliperidone palmitate and PBO in the median changes from baseline to study end for all treatment groups for any of the neurological scales. The incidence of Parkinsonism and akathisia as assessed by the SAS and BARS respectively was similar for paliperidone palmitate and PBO.

There were no clinically relevant mean changes from baseline for either the transition/maintenance or double-blind phases for laboratory analyses with the exception of prolactin as expected from the acute studies. Mean increases of 10 and 25 ng/mL (male, female) were seen in the paliperidone palmitate group during the transition/maintenance phase with 48-49% of subjects with abnormally high levels. Smaller increases were seen during the double-blind phase (males 4 ng/mL, females 13 ng/mL) with 13% above the normal limit in the paliperidone palmitate group. Few subjects experienced other clinically significant abnormalities with no groups showing an incidence of >5% for any parameter including glucose and lipids. Changes from baseline in vital signs were not clinically relevant across all groups for either phase of the study. Treatment emergent abnormally high standing pulse rates were greater for paliperidone palmitate than PBO (Table 13). Treatment emergent clinical important orthostatic increases in pulse were small and similar across groups.

Table 13: Safety Study – R092670-PSY-3001

No of subjects with age and sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Results
n= 849 phase 2 n= 684 phase 3 n=410 randomised phase 4 n= 408 ITT n=388 phase 5 Other details see Table 4.	M or F, aged 18-65 years, diagnosed with schizophrenia (DSM IV) for ≥ 1 yr, PANSS total < 120 on screening and < 75 at start of phases 3 & 4. BMI ≥15.  Anti-psychotics not allowed: see Table 4.	AEs assessed at each visit.  Injection site assessments every visit after Day 1. HR, BP, clinical laboratory tests & ECGs on Days -7, 1, weeks 9, 21, 33, 45, then HR, BP & ECGs every 12 weeks & lab tests every 24 weeks. SAS, AIMS, BARS on Days -7, 1, weeks 9, 33, 45 & every 12 weeks. Physical exam at screening & end. Weight at Days -7, week 33, 45 & every 24 weeks.	Transition/maintenance phases (T/M): TEAEs reported by 67% subjects. Most common: insomnia (15%), anxiety (10%), headache (9%). SAEs reported by 14%, DAEs 6% most common psychiatric disorders. 3 deaths.  Double-blind phase: TEAEs reported by 45% (PBO), 44% (PALP). Most common PBO: insomnia (7%), PALP weight ↑ (7%). SAEs reported by 13% (PBO), 5% (PALP), most common psychiatric disorders. DAEs reported by <1% (PBO) & 1% (PALP) subjects. Clinical interest AEs: Few cases of suicidality (2% T/M, 2% PBO, 2% PALP), aggression/ agitation (5%, 3%, <1%), somnolence (2%, <1%, 1%), prolactin-related (3%, 1%, 3%), glucose-related (3%, 3%, 4%) or cardiovascular related including orthostatic hypotension (<1%, 1%, <1%). EPS-related TEAEs (9%, 2%, 6%), anti-EPS medication (12%, 6%, 10%). No significant difference between groups for change in SAS, BARS & AIMS ratings (ANOVA). There were no clinically relevant mean changes from baseline for clinical laboratory tests in either T/M or DB phases except for prolactin. TE markedly abnormal values were low in incidence for PBO & PALP (no group >5% inc glucose, lipids). There were no clinically relevant mean changes from baseline for vital signs in T/M but significantly higher DBP for PBO v PALP in DB phase. Incidence of abnormal vital signs (>5%): ↑st pulse (≥15bpm & >100) T/M 5%, DB PBO 3%, PALP 6%. TE orthostatic hypotension (1%, 1%, ≤1%). Weight & BMI were increased in both T/M & DB phases with PALP > PBO. Clinically important weight gain (≥7%): T/M 12%, DB 3% PBO, 6% PALP. Incidence of abnormal ECG values: ↑HR T/M 8%, DB PBO 8%, PALP 6%, ↓ HR all groups ≤4%. Incidence of max QTcLD >450 ms: 2% T/M, 0% PBO, <1% PALP; change >30 ms: 4% T/M, 5% PBO, 6% PALP. Injection site: T/M severe pain 1 subject, moderate pain 3%, moderate redness, swelling, induration 1-2 subjects, DB moderate pain 1% PBO, 1% PALP. Subject: T/M no change with time, DB intensity ↓PBO.



There were mean increases in weight and BMI during the transition phase and for the paliperidone palmitate group during the double-blind phase. Clinically important weight gain ( $\geq 7\%$ ) was more common for paliperidone palmitate than PBO (12% transition/maintenance, 3% PBO, 6% paliperidone palmitate). There were no major differences in mean changes from pre-dose values for either phase for any ECG parameters. Treatment emergent clinically important increases in heart rate and clinically important decreases in HR were similar across groups. No subjects had a QTcLD change  $> 60$  ms with similar numbers in each group (4-6%) having changes  $> 30$  ms. There were no subjects with a QTcLD interval of  $> 480$  ms and 2 paliperidone palmitate subjects with a QTcLD  $> 450$  ms during transition/maintenance .

Investigator evaluations of the injection site were performed within 60 minutes after injection. The majority of subjects did not experience any injection side effects. Pain was reported as severe for 1 subject and moderate for  $\leq 3\%$  during the transition/maintenance phase. Moderate redness, swelling and induration occurred in 1-2 subjects. There were no severe reports and only moderate pain (1%) for both groups during the double-blind phase. Subjects' assessment of the injection site pain and injection pain was relatively constant during the transition/maintenance phase. The intensity of pain decreased for both PBO and paliperidone palmitate over time whereas the severity increased for PBO during the double-blind phase.

Study **PSY-3001** also included an open-label extension phase of up to 52 weeks (Table 14). The primary objective was to assess safety and tolerability for subjects treated for more than a year with paliperidone palmitate. Seventy-three percent of subject received 12 injections of paliperidone palmitate and 35% received supplemental paliperidone-ER - largely the PBO/paliperidone palmitate group. A total of 222 subjects were exposed to paliperidone palmitate continuously during all phases of the study for one year. The rate of AEs reported during the open-label phase was similar for all 3 groups and slightly higher than during the double-blind phase of the study. The most common AEs were insomnia, schizophrenia, headache and weight increased. Most AEs were mild to moderate in severity. SAEs were less frequent than during the earlier phases of the study, the most common being psychiatric disorders, particularly schizophrenia which was the reason for the one SAE that was thought probably or possibly drug-related. There were no deaths and DAEs were low and occurred only in the PBO/paliperidone palmitate group (Table 14).

Prolactin concentrations were increased in the PBO/paliperidone palmitate group but remained relatively stable in the other 2 groups during the extension phase. There were no other clinically relevant mean changes from either the transition/ maintenance baseline or the open-label baseline for laboratory analyses. Few subjects experienced clinically significant abnormalities with no groups showing an incidence of  $> 5\%$  for any parameter including glucose and lipids. Across all groups changes from either baseline in vital signs were not clinically relevant. Treatment emergent abnormally high standing pulse rates averaged 6% from open-label baseline and 8% from transition baseline (Table 14). There were mean increases in weight and BMI during the extension phase of 1% (0.9 kg) from extension phase baseline and 3% (2.0 kg) from transition baseline. Clinically important weight gain ( $\geq 7\%$ ) averaged 13% from open-label baseline but increased to 23% from transition baseline (Table 14).

There were no major changes from extension phase baseline values for any ECG parameters. Treatment emergent abnormal increases in heart rate averaged 9% from extension baseline but data was not given for incidence from pre-dose baseline. No subjects had a QTcLD change  $> 60$  ms, 2 subjects had changes  $> 30$  ms, no subjects had a QTcLD interval of  $> 480$  ms and 22 (6%) of subjects had a QTcLD  $> 450$  ms from open-label baseline to study end. The data were similar from pre-dose baseline. Investigator evaluations of the injection site found that the majority of subjects did not experience any injection side effects. There were no reports of

severe injection site reactions and only 1% experienced moderate pain during the extension phase. Subjects' assessment of the injection site pain and injection pain showed that injection site pain decreased for all groups over time whereas there were varied responses for injection pain.

Table 14: Safety Study – R092670-PSY-3001- open-label extension

No of subjects with age and sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Results
n= 388 PBO/PALP: n=153, 78M, 75F, 39y (18-61) PANSS baseline 64 ± 21 PALP/PALP: n=161, 84M, 77F, 37y (19-66) PANSS baseline 55 ± 17 PALP (NODB*)/PALP: n=74, 47M, 27F, 35y (18-62) PANSS baseline 52 ± 12 * no double-blind phase	Subjects who had completed the double-blind phase see table 19, had a recurrence (PALP/PALP & PBO/PALP groups), or had had at least 1 injection of PALP when the study was stopped (no double blind PALP (NODB)/PALP).	AEs & injection site assessments assessed at each visit (monthly). HR, BP & ECGs every 12 weeks & clinical laboratory tests every 24 weeks. EPS (SAS, AIMS, BARS) every 12 weeks. Weight every 24 weeks.	TEAEs reported by 56% (PBO/PALP), 57% (PALP/PALP) & 53% PALP (NODB)/PALP. Most common: insomnia (7%), schizophrenia, nasopharyngitis, headache & weight ↑ (6%). No deaths. SAEs reported by 7% (PBO/PALP), 6% (PALP/PALP) & 3% PALP (NODB)/PALP. Most common schizophrenia. DAEs reported by 4% (PBO/PALP) subjects. Special interest AEs: EPS-related (7% PBO/PALP, 8% PALP/PALP, 1% PALP (NODB)/PALP), prolactin-related (2%, 4%, 5%), glucose-related (4%, 4%, 3%), orthostatic hypotension (1%, 2%, 0%). Median SAS, BARS & AIMS ratings were zero at baseline & end point for all groups. There were no clinically relevant mean changes from extension phase baseline to end point or from transition phase baseline to end point for clinical laboratory tests & few markedly individual abnormalities across groups (no group >5% inc glucose, lipids). There were no clinically relevant mean changes from either extension phase or transition phase baseline to end point for vital signs. Incidence of abnormal vital signs (>5%): ↑st pulse (≥15bpm & >100) 4% (PBO/PALP), 6% (PALP/PALP) & 10% PALP (NODB)/PALP from extension baseline: 6%, 11%, 8% from transition baseline. Clinically important weight gain (≥7%): 17% (PBO/PALP), 8% (PALP/PALP) & 13% PALP (NODB)/PALP from extension baseline: 21%, 23%, 25% from transition baseline. Incidence of abnormal ECG values: ↑HR 8% (PBO/PALP), 10% (PALP/PALP) & 11% PALP (NODB)/PALP from open-label baseline: data not given from transition baseline. Two subjects with max QTcLD >450 ms, none >480 ms. QTcLD changes from extension baseline >30 ms: 8% (PBO/PALP), 5% (PALP/PALP) & 3% PALP (NODB)/PALP, from pre-dose 6%, 6%, 5%, none >60 ms. Injection site: no severe reactions, 1% moderate pain, all other assessments mild or absent. Self-ratings: injection site pain improved with time, injection pain improved for PBO/PALP, other 2 groups slightly worse at end point.

Study **PSY-3002** compared paliperidone palmitate (25, 50, 75 100 mg) with Risperdal Consta (25, 37.5, 50 mg) over a 53 week period (Table 15). Twenty-one percent of subjects received oral tolerability tests. Forty-nine percent of the paliperidone palmitate group received all 27 scheduled injections compared with 59% of subjects receiving Risperdal Consta. The majority of patients experienced at least one AE during the study with overall rates similar between treatment groups. The most common AEs were also similar for both groups (Table 15). Most AEs were mild to moderate in severity. There were 4 deaths: 3 in the paliperidone palmitate group (acute myocardial infarct, unknown cause, food aspiration) and 1 in the Risperdal Consta group (lung neoplasm). None of these were thought related to study drug. SAEs (29% paliperidone palmitate, 22% Risperdal Consta) were greater for paliperidone palmitate and DAEs (7% paliperidone palmitate, 6% Risperdal Consta) were similar with the most common being psychiatric disorders, particularly schizophrenia and psychosis. Few SAEs were thought

probably or possibly drug-related. Most AEs of special interest were of similar incidence between drug groups (Table 15). EPS-related AEs were higher for Risperdal Consta than paliperidone palmitate but anti-EPS medication use was similar and decreased for both groups during the study. There were no significant differences between the groups in the median changes from baseline to study end for any of the neurological scales. The incidence of Parkinsonism and akathisia as assessed by the SAS and BARS respectively was similar for paliperidone palmitate and Risperdal Consta.

Table 15: Safety Study – R092670-PSY-3002

No of subjects with age and sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Results
n=749 randomised n= 674 ITT n= 570 PPP PALP: n=379, 215M, 164F, 41y (18-76) PANSS baseline 82 ± 13 RISPC: n=370, 229M, 139F, 41y (18-84) PANSS baseline 81 ± 13	M or F, aged 18-65 years, diagnosed with schizophrenia (DSM IV) for ≥ 1 year, PANSS total 60-120. 50 aged ≥ 65 years to be enrolled. BMI ≥15. Anti-psychotics not allowed: see Table 11.	AEs assessed at each visit. HR, BP, clinical laboratory tests, EPS (SAS, AIMS & BARS) at screening, baseline, weeks 5, 25 & 53. ECGs at screening, baseline, weeks 5, 9, 25, 37 & 53. Injection site assessments on Days 1, 8 & monthly. Weight at screening, baseline, week 25, 53. GISF at baseline & weeks 25, 53.	TEAEs reported by 76% (PALP), 79% (RISPC). Most common: PALP insomnia (15%), psychotic disorder (14%), schizophrenia (12%), anxiety (10%); RISPC insomnia, anxiety (15%), psychotic disorder (12%), headache (11%). 4 deaths: 3 PALP, 1 RISPC. SAEs reported by 29% (PALP), 22% (RISP). Most common: psychotic disorder, schizophrenia, both groups. DAEs reported by 7% (PALP), 6% (RISPC), most common psychiatric disorders. Special interest AEs: Incidence of AEs related to suicidality (3% PALP, 2% RISPC), aggression/agitation (9%, 7%), somnolence (2%, 3%), orthostatic hypotension (3%, 4%), prolactin-related (3%, 4%), glucose-related (2%, 4%), dermatological (4%, 7%), EPS-related (17%, 22%). Anti-EPS medication use decreased during study (21%-9%, 19%-12%) & no significant difference between groups for change in SAS, BARS & AIMS ratings (ANOVA). There were no clinically relevant mean changes from baseline for clinical laboratory tests & few markedly individual abnormalities for either PALP or RISPC (no group >5% except LDL ↑ 8%, 7%). ↑ prolactin as expected for both groups. Incidence of abnormal vital signs (>5%): ↑st pulse (≥15bpm & >100)11% PALP, 13% RISPC; ↑ su pulse 6% PALP, 4% RISPC; TE orthostatic hypotension 3% PALP, 3% RISPC. Weight & BMI were not changed in both groups. Clinically important weight gain (≥7%) 14% PALP, 15% RISPC. Incidence of abnormal ECG values: ↑HR 12% PALP, 13% RISPC; ↓ HR 7% PALP, 8% RISPC. Four subjects with max QTcLD >450 ms in each group, none >480 ms. QTcLD changes from baseline: none > 60 ms, >30 ms: 5% PALP, 4% RISPC. Injection site: <2% severe pain, redness or induration; moderate pain <5%, redness, swelling, induration <1%. Self-ratings: injection site pain & injection pain improved with time for both groups. No significant difference between groups for change in GISF (ANCOVA, 95% CI).

There were no clinically relevant mean changes from baseline to end of study for haematology, renal function, liver function, glucose and serum lipids across groups with the exception of prolactin. Mean changes for prolactin were males: 7 ng/mL paliperidone palmitate, 9 ng/mL Risperdal Consta; females 23 and 22 ng/mL respectively. Few subjects experienced clinically

significant abnormalities with no groups showing an incidence of >5% for any parameter except for prolactin (males: 31% paliperidone palmitate, 53% Risperdal Consta; females: 42% paliperidone palmitate, 51% Risperdal Consta). Changes from baseline in mean standing and supine systolic, diastolic blood pressure and pulse rate were not clinically relevant across all groups. Treatment emergent clinically important increases in pulse (Table 15) were similar in the both groups as were treatment emergent clinically important orthostatic hypotension.

There were no clinically relevant changes in weight or BMI for either group and clinically important weight gain ( $\geq 7\%$ ) was similar for both groups (14% paliperidone palmitate, 16% Risperdal Consta). There were no major differences in mean changes for either group for any ECG parameters. Treatment emergent clinically important increases in heart rate occurred at a similar rate (12% paliperidone palmitate, 13% Risperdal Consta) as did clinically important decreases in HR. No subjects had a QTcLD change > 60 ms, similar numbers in each group (4-5%) had changes > 30 ms, no subjects with a QTcLD interval of >480 ms and 4 per group with a QTcLD >450 ms.

Investigator evaluations of the injection site were performed within 60 minutes after injection. The majority of subjects did not experience any injection side effects. There were a few severe or moderate reports for either group (Table 15) and in general reactions decreased with time. Subjects' assessment of the injection pain showed that the intensity of the pain decreased over time for both groups. This study included an assessment of sexual function before treatment and on weeks 25 and 53 as measured by the Global Impressions of Sexual Function scale (GISF). There were no significant differences between the groups for any item or total scores on the GISF.

The safety profile for paliperidone palmitate was similar to that of Risperdal Consta as might be expected. The incidences of SAEs related to schizophrenia were higher for paliperidone palmitate. This could be explained by the lower plasma concentrations for paliperidone palmitate compared to Risperdal Consta at start which resulted from the initial doses of 50 mg on Days 1 and 8.

*PSY-3005: A randomised, cross-over study to evaluate the overall safety and tolerability of paliperidone palmitate in the deltoid or gluteus muscle in subjects with schizophrenia.*

This study was conducted at 34 centres in Belgium, Bulgaria, Czech Republic, Germany, Slovak Republic and the USA and the study design involved a fixed dose (50, 75 or 100 mg) over a 25 week period with a cross-over of injection sites after 13 weeks (Table 16). The primary objectives were to evaluate the safety and tolerability of the deltoid site and the safety and tolerability of switching injection sites. The first objective was achieved using a between-group comparison of the incidence of AEs during the first 13 weeks for deltoid versus gluteal injections and the second objective using a within-subject comparison of the incidence of AEs during the last 8 weeks of each dosing sequence.

Twenty-three percent of subjects received oral tolerability tests and one subject developed severe pruritis and hyperhydrosis and was not randomised to the study. Twenty to twenty-five percent of both treatment sequences received all 7 scheduled injections. There were similar incidences of AEs reported for deltoid and gluteal injections in the first study period (Table 16). There were no significant differences between injection sites across all dosages and no dosage dependent increase in incidence of AEs. The proportion of subjects reporting AEs during the last 8 weeks of each treatment period were not significantly different across treatment sequences and dosages (Table 16). The incidence of new AEs during the second study period was also not significantly different across sequences and doses.

The majority of patients experienced at least one AE during the study with overall rates similar between deltoid and gluteal groups (Table 16). The most common AEs were also similar for both groups during period 1. The rate of AEs was lower for period 2 (deltoid 51%, gluteal 46%). Most AEs were mild to moderate in severity. There was 1 death from suicide after 4 gluteal injections of paliperidone palmitate 100. SAEs and DAEs (both 5% deltoid, 4% gluteal) were similar for both injection site groups with the most common being psychiatric disorders, particularly schizophrenia and psychosis. Approximately half the subjects with SAEs had events that were thought probably or possibly drug-related. Most AEs of clinical interest were of low incidence and not differentiated by treatment sequence or injection site (Table 16). EPS-related AEs were 7% overall and anti-EPS medication use was 10%. There were no differences between the groups in the median changes from baseline to study end for any of the neurological scales or in the incidence of Parkinsonism and akathisia as assessed by the SAS and BARS respectively.

There were no clear differences across groups for mean changes from baseline to end of study for any laboratory parameters, vital signs, weight, BMI or ECG values. Mean changes for prolactin across groups were 6-17 ng/mL for males and 0-43 ng/mL for females. Clinically significant abnormalities were similar across groups for laboratory parameters with none showing an incidence of >5% for any parameter except for prolactin which ranged across the groups from 38-58% for males and 36-58% for females. Treatment emergent clinical important increases in standing pulse varied from 13-33% and supine pulse from 5-26% between groups with no clear distinction between treatment sequences. Similarly, clinically important weight gain ( $\geq 7\%$ ) varied from 5-18%, and clinically important increases in heart rate from 3-14%. No subjects had a QTcLD change > 60 ms, similar numbers in each group (1-4) had changes > 30 ms, no subjects with a QTcLD interval of >480 ms and 5 with a QTcLD >450 ms. Investigator evaluations of the injection site for this study were compared for the deltoid and gluteal sites. Overall symptoms were higher for the deltoid site and this was confirmed by the subject's assessment of injection pain. The differences were not considered to be clinically significant.

Table 16: Safety Study – R092670-PSY-3005

No of subjects with age and sex (Mean, range)	Diagnosis and inclusion criteria	Criteria for evaluation	Results
n= 252 randomised n= 249 ITT PALP 50 mg DG: n=42; 25M, 17F; 44y (22-72) PALP 50 mg GD: n=40; 23M, 17F; 42y (20-72) PALP 75 mg DG: n=38; 20M, 18F; 43y (22-66) PALP 75 mg GD: n=43;	M or F, aged >18 years, diagnosed with schizophrenia (DSM IV) for $\geq 1$ year, PANSS total $\leq 70$ , BMI $\geq 17$ . Exclusion criteria: Relapse <90 days or Rx change <45 days. Anti-psychotics not allowed: RISPC < 5 weeks, PALP < 10 months,	<b>Safety:</b> AEs assessed at each visit. Between-groups incidence for first 13 weeks & within-subject incidence weeks 5-13 & weeks 17-25 compared between deltoid v gluteal sites (ITT, 90% CIs). Vital signs & injection site assessments at screening/ baseline, weeks 1, 5, 9, 13, 17, 21, 25. Clinical laboratory tests & ECGs at screening/ baseline & weeks 5, 13, 21, 25. Weight at screening,	<b>Safety:</b> TEAEs reported by 61-71% (deltoid) & 58-65% (gluteal) with no significant difference between injection sites. TEAEs for weeks 5-13: 32-45% deltoid, 29-42% gluteal & for weeks 17-25: 29-42% gluteal, 30-41% deltoid. No significant difference in incidence whether the switch was from deltoid to gluteal or vv. New TEAEs during period 2 were not significantly different for treatment sequences or dosages. No dose –dependent effects or differences between obese/non-obese subjects between treatment sequences. Overall TEAEs: deltoid 59%, gluteal 55%. Most common deltoid period 1: insomnia (14%), anxiety (13%), headache (12%), gluteal period 1: insomnia (15%), headache (10%), agitation (9%). There was 1 death (suicide). SAEs/DAEs deltoid (5%), gluteal (4%) most common psychiatric disorders. Clinical interest AEs: Suicidality (2%), agitation (10%), somnolence (4%), EPS-related (7%), cardiac arrhythmias (8%), orthostatic hypotension (4%), dermatological 5%. There were no differences

<p>25M, 18F; 43y (20-75)</p> <p>PALP 100 mg GD: n=46; 21M, 25F; 43y (19- 76)</p> <p>PALP 100 mg DG: n=40; 27M, 13F; 41y (21- 78)</p>	<p>depot anti- psychotics &lt; 60 days. Others Day - 2</p>	<p>weeks 13 &amp; 25. SAS, AIMS, BARS rated at screening/ baseline &amp; weeks 5, 13, 17, 25.</p> <p><b>Pharmacokinetics:</b> Plasma PAL measured by LC-MS/ MS. Descriptive statistics for all sampling times, ratios of deltoid/ gluteal concentrations.</p> <p><b>Efficacy:</b> PANSS, CGI-S to monitor clinical status.</p>	<p>between doses or treatment sequence/ injection sites in laboratory parameters, vital signs, weight or ECGs. Injection site pain, swelling, induration was higher for deltoid but not clinically significant. There was no difference between groups for changes in SAS, BARS &amp; AIMS ratings.</p> <p><b>Pharmacokinetics:</b> Higher initial plasma PAL for deltoid compared with gluteal injections but at apparent steady-state similar pre-dose median PAL concentrations were observed. Data used in population analysis.</p> <p><b>Efficacy:</b> There were no clinically relevant dose or injection site differences.</p>
--	--	--	---

Overall, there was little difference between the safety and tolerability profile of paliperidone palmitate following injection in deltoid or gluteal sites. Given that the plasma concentrations achieved with deltoid injection were 50% higher, more adverse reactions may have been expected. Clinically important abnormalities varied considerably between the groups with some incidences for increases in standing and supine pulse that were higher than those seen in the previous studies. This may be related to the small numbers in each group. As noted under *Efficacy*, the study has been published (Hough et al 2009).<sup>11</sup>

The evaluators noted that the methodology used to evaluate the safety and tolerability of paliperidone palmitate in these studies was appropriate. Assessments were done at least at baseline and end of treatment. AEs were either volunteered or elicited by non-directional questioning. Laboratory normal ranges and clinically important values were defined in the protocols. All studies used a variety of correction methods for QTc but considered QTcLD as the most appropriate. The assessment of EPS-related events was thorough and included well-established and commonly used ratings scales.

The probability of drug-drug interactions is low based on the pharmacokinetic properties of paliperidone as previously established for oral paliperidone. The systemic exposure following paliperidone palmitate is low and thus its potential to affect other drugs is low. The potential for other drugs to affect paliperidone palmitate is unlikely as no relevant interactions have been reported at the level of the esterases which are responsible for the hydrolysis of the palmitate ester. Interactions previously observed for oral paliperidone would be expected for paliperidone palmitate as noted in the Product Information document.

Safety in pregnancy has not been established. Of the 10 cases reported across studies, there were 3 healthy deliveries, 4 elective abortions, 2 spontaneous abortions and 1 unknown outcome. There were no reported overdoses of paliperidone as expected since the study drugs were administered at each study centre. Paliperidone palmitate will not readily be available to patients hence overdose and abuse potential is minimal. Withdrawal symptoms were evaluated in study **PSY-3001** from newly-emerging AEs during the first injection cycle of the double-blind phase in those subjects randomised to placebo. The most common events were anxiety, insomnia and depression (1% each).

### Safety Summary

These studies of paliperidone palmitate are in keeping with the established safety profile of oral paliperidone. There were no new safety signals from either the acute or long term studies. AEs

were generally similar in frequency to PBO treated subjects and there were no consistent differences across studies for gender, age, BMI or race for incidence of AEs. The most common SAEs were psychiatric disorders such as schizophrenia or psychotic disorder which was frequently an exacerbation of the underlying illness. The sponsor's *Clinical Overview* presented common adverse drug reactions (ADRs) from the pooled acute studies, that is, those AEs that were considered reasonably associated with paliperidone palmitate. Incidences were: PBO 46%, 25 mg 54%, 50 mg 50%, 100 mg 52% and 150 mg 45%. Those ADRs > 5% for any dose were vomiting (25 mg), injection site pain (100, 150 mg), dizziness (25 mg), akathisia (100,150 mg) headache (all groups), somnolence/sedation (25, 50 mg), agitation (PBO, 25, 100, 150 mg) and insomnia (all groups). In study **PSY-3001**, incidences of ADRs were: 20% PBO, 21% paliperidone palmitate with those >5%, weight increased for paliperidone and insomnia for PBO.

Most of the studies found EPS AEs and EPS-medication rates similar for paliperidone palmitate and PBO for low doses but with a trend to higher rates for higher doses. There was a low rate of suicide related events which was similar to that for PBO. Elevations in prolactin were observed for all paliperidone palmitate studies as expected but the incidence of AEs was only 1-3% across studies. In terms of metabolic risk factors commonly observed with other antipsychotics, paliperidone palmitate did not alter either glucose or lipid concentrations either acute or long term in any of the studies. In some studies there was a greater frequency of clinically abnormal increases in pulse but other studies found paliperidone palmitate to be similar to PBO. Incidences of orthostatic hypotension were around 2-3% for paliperidone palmitate and PBO in most studies but higher than PBO in one study (**SCH-201**). Abnormal increases in heart rate were more frequent for paliperidone palmitate than PBO in some studies. Increases in QTc were uncommon but paliperidone palmitate should be used with caution with other drugs known to prolong QTc.

In the acute studies, mean weight increased by 0.4-1.5 kg with paliperidone palmitate treatment and some studies showed a dose dependent increase. Incidences in abnormally increased weight ( $\geq 7\%$ ) were more common for paliperidone palmitate and were also dose-dependent in some studies. During the extension phase of study **PSY-3001** there was a mean increase of 2.0 kg and a mean 23% incidence of abnormally increased weight from study baseline to end of extension phase. Injection site pain was more frequent for paliperidone palmitate than PBO although severe or moderate reactions were few and the majority of subjects rated injection site reactions as mild. Injections in the deltoid muscle were associated with more reactions than gluteal injections but both had acceptable tolerability as did switching between sites.

### Post-Marketing Data

There were no post-marketing data for paliperidone palmitate at the time of this submission, however the available post-marketing data for paliperidone-ER was provided. A search was conducted by the sponsor of SCEPTRE, part of the Benefit Risk Management (a division of Johnson & Johnson Pharmaceutical Research and Development) worldwide safety system to identify all cases reported to the company for paliperidone-ER to 31 October 2008.

Post-marketing exposure for paliperidone-ER was estimated at approx 200,000 person years. There were 1768 spontaneous cases reported with paliperidone-ER as suspect, co-suspect or suspect-interacting drug. Of these, 84% were medically confirmed by a health care professional with 31% considered serious. There were 48 fatal reports with the majority attributed to either from suicide, a cardiac event or unknown. Of the remaining non-fatal reports, all reported AEs were already listed in the Company Core Data Sheet as adverse drug reactions with the



exception of anxiety and insomnia which are often manifestations of the underlying condition.<sup>18</sup> Cases of potential risk were analysed and none were supported by sufficient evidence to be considered ADRs with the exception of priapism which was subsequently added to the company core data sheet. A review of cases of special interest based on medical significance and special populations such as paediatric or geriatric patients did not detect any new or emerging safety concerns. Overall, the review of post-marketing safety data for paliperidone-ER found that the safety profile was consistent with the current company core data sheet.

### Clinical Summary and Conclusions

Paliperidone is a monoaminergic antagonist with effects on dopamine type2 and serotonin type2A receptors which has been formulated as a long-acting IM formulation (paliperidone palmitate). Non-adherence to antipsychotic medication is a major problem in treating schizophrenia hence the development of long-acting injectables (LAIs) which have been shown to reduce the risk of relapse (Citrome 2010).<sup>13</sup> Paliperidone palmitate fits the requirements for a suitable LAI in terms of once-monthly dosing interval, prolonged stable plasma concentrations and injection site tolerability.

Paliperidone palmitate has been shown to be efficacious in the treatment of moderate to severe schizophrenia in 4 acute treatment studies. Efficacy has been demonstrated in at least one study at all dose levels, across all PANSS factors and subscales and for disorder-specific, global and functional measures. Longer term studies demonstrated recurrence prevention in subjects who had achieved symptom control during a prior open-label phase of treatment and therapeutic effect was maintained over a year of open-label treatment. The long term comparative study with Risperdal Consta did not show non-inferiority across all BMI groups. This may have been due to the dosage regimen employed as non-inferiority appears to have been shown over the short term in a study (**PSY-3006**) which has been completed but only a summary of the results is available on the company's website. Further long term studies with the proposed dose regimen would be of interest to establish non-inferiority with Risperdal Consta. There were no new safety or tolerability concerns from the change of formulation apparent in any of the measures examined in either the short or long term studies. The safety profile was similar to that for Risperdal Consta and for paliperidone-ER.

The proposed dosage regime was justified by evidence from the studies submitted and from pharmacokinetic modelling. For the Phase 2/3 acute treatment studies (**SCH-201, PSY-3003, PSY-3004**) there was a consistent finding of higher BMI being associated with poorer treatment response. In these studies lower plasma concentrations were observed early in treatment in the high BMI group. This can be mitigated by initial injections on Days 1/8 of 150/100 mg, initial injection into deltoid muscle is recommended as this achieves higher plasma concentrations than gluteal injection, and use of longer needles for heavier subjects. This initiation regime was confirmed by model simulations to rapidly achieve plasma paliperidone concentrations similar to that of the paliperidone-ER recommended dose of 6 mg. Once steady-state has been reached, BMI was not a factor as shown by the long term study (**PSY-3001**) where the risk of relapse was similar for all BMI groups. The recommended maintenance dose of 75 mg paliperidone palmitate was also shown to produce steady-state plasma concentrations that fell within that of the paliperidone-ER 6 mg range. Data from the long term studies were in agreement with this choice as the mean dose during the double-blind phase of **PSY-3001** was 83 mg whilst that for

---

<sup>18</sup> A Company Core Data Sheet (CCDS) is a company-internal global reference labelling document used to direct the content of local (affiliate) labelling. A Company Core Safety Information (CCSI) is a subset of the CCDS which contains all relevant safety information that a company requires to be listed in all countries where the drug is marketed. It serves as reference information for determining the "listedness" of an adverse reaction.

**PSY-3002** was 66 mg with a final dose of 77 mg. In the latter study however, a larger number of subjects finished the study in the 100 mg dose group. Simulations for various missing dose scenarios showed that  $\pm 2$  days either side of Day 8 and  $\pm 1$  week either side of the regular 4 weekly dosing interval lead to minimal decreases in plasma concentrations. For any intervals longer than 6 weeks, the recommendation is to start with two deltoid injections a week apart at the previously effective maintenance dose. Previous oral antipsychotics can be discontinued at the time of initiation of paliperidone palmitate, long-acting injectable antipsychotics one injection cycle and Risperdal Consta one month prior to starting treatment with paliperidone palmitate. A study investigating switching from oral antipsychotics to paliperidone palmitate is about to commence in the USA.

The proposed initiation regime for paliperidone palmitate leads to rapid attainment of steady-state plasma concentrations which is a significant improvement over other LAIs which require oral cover over the first few weeks. It also has the benefit of requiring use of only one agent for acute and maintenance treatment of schizophrenia. Other advantages include the lack of drug-interaction potential and the possibly lesser effect on some metabolic risk factors compared to other antipsychotics. As for other antipsychotics the risks include weight gain and EPS-related adverse effects. However, the potential to reduce noncompliance and avoid relapse, rehospitalisation or suicide outweigh the risks associated with this medication.

The evaluators recommended approval of the application for the registration of Invega Sustenna (paliperidone palmitate) for the treatment and prevention of recurrence of schizophrenia.

## **V. Pharmacovigilance Findings**

A Risk Management Plan was submitted with this application but the TGA determined it was not a requirement at the time of submission and therefore it was not evaluated.

## **VI. Overall Conclusion and Risk/Benefit Assessment**

The submission was summarised in the following Delegate's overview and recommendations:

### **Quality**

The application was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its March 2010 meeting (see Section II). The PSC concluded that there should be no objection on quality and pharmaceutical grounds to approval of this application provided all outstanding issues were addressed to the satisfaction of the TGA.

### **Nonclinical**

There were no nonclinical findings to preclude approval of registration and that the issues of potential local injection site irritation and general anaphylactoid reactions should be addressed from clinical data.

### **Clinical**

#### **Pharmacology**

The clinical evaluators identified fourteen studies on bioavailability and pharmacokinetics. On the outcome of the bioavailability / pharmacokinetic studies, the evaluators stated that:

- Following a single-dose of IM paliperidone palmitate, plasma paliperidone reaches a peak concentration within 14 days with an apparent half-life ranging from 25-49 days over the dose range of 25-150 mg.
- Both depot formulations (F011 / F013) used for phase 2/3 studies have been shown to result in a controlled release rate of paliperidone, suitable for once-monthly dosing, with

relative bioavailability close to 100% for both formulations (114% for F011 and 126% for F013). Although there was no absolute bioavailability study submitted to compare the new formulation with IV paliperidone, comparison of dose-normalised AUC for paliperidone IV with paliperidone palmitate IM at four doses and from both injection sites found a mean of 94% bioavailability.

- Dose – proportionality was achieved for total exposure ( $AUC_{\infty}$ ) over the recommended dose range for both the deltoid and gluteal IM administration. Steady-state was achieved more rapidly with 2 injections a week apart rather than using a higher loading dose. Deltoid administration resulted in higher peak concentrations than gluteal, thus the recommended initiation regime is 2 injections a week apart into the deltoid muscle.
- The ratio of the enantiomers was consistent at all doses and there was no indication of an effect of CYP 2D6 or CYP 3A4/5 metaboliser status on paliperidone kinetics.
- A population pharmacokinetic assessment, involving 1795 subjects from phases 1, 2 and 3 studies and based on one-compartmental model with first order kinetics, indicates that (a) repeated injections into the deltoid muscle (compared with gluteal) resulted in a faster increase in plasma concentrations and enhanced time to achieve steady-state but did not influence overall exposure; higher doses associated with larger injection volumes increased the apparent half-life which increased time to steady-state (b) a slower rise in plasma concentrations was found for obese subjects which can be mitigated by use of a longer needle in heavier subjects. The latter will avoid possible administration of paliperidone palmitate into adipose tissue and delaying absorption (c) renal impairment required a reduction in dosage.
- The population pharmacokinetic model was also used to simulate expected plasma concentrations using the initiation regimen of deltoid doses of 100 mg IM on Days 1 and 8, which were found to attain potential therapeutic concentrations rapidly, based on plasma concentrations obtained from previous oral paliperidone studies. It was also used to assess the impact of switching injection sites after Day 36, which was found to not have a major effect on maintenance of steady-state concentrations. The model was then revalidated with new data from **R092670-PSY-3007 (PSY-3007)**. The finding was that initiation with a higher dose of 150 mg into the deltoid muscle with appropriate needle length resulted in rapid achievement of target concentrations and estimated model pharmacokinetic parameters remained unchanged.

In addition, the population pharmacokinetic model simulations for the recommended dosage regime for paliperidone palmitate IM showed good agreement with plasma concentration ranges for oral paliperidone-extended release (ER), where the recommended dose of 6 mg/d resulted in 90% of subjects achieving a plasma concentration of paliperidone of between 3.5 and 50 ng/mL, which is probably of more relevance than establishing absolute bioavailability.

- Further population pharmacokinetic simulations showed that the steady-state peaks and troughs for paliperidone palmitate 25, 75, 150 mg were contained within the paliperidone-ER (1, 6, 12 mg/d respectively) exposure window. It should be noted, that none of the studies actually evaluated the pharmacokinetics of paliperidone using the final recommended dosing regime of paliperidone palmitate, that is, Day 1, IM 150 mg, Day 8, 100 mg, both deltoid followed by monthly IM 75 mg (25-150 mg) either deltoid or gluteal. Nonetheless, the pharmacokinetic studies were acceptable as the model was used to simulate plasma steady-state concentrations. This showed that the new regimen

leads to rapid achievement of plasma concentrations similar to those achieved with paliperidone-ER.

### **Efficacy**

The evaluators identified seven studies with efficacy and/or safety data. Four studies (**R092670: PSY-3007, PSY-3003, PSY-3004 and SCH-201**) evaluated efficacy in acute treatment over 10-13 weeks. Study **R092670-PSY-3001** assessed efficacy in long term maintenance and recurrence prevention treatment. **R092670: PSY-3002 and PSY-3005** were comparative, cross over studies with Risperdal Consta assessing injection sites for safety and tolerability purposes.

*Study PSY-3007. A randomised, double-blind, placebo-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed doses (25 mg eq., 100 mg eq., and 150 mg eq.) of paliperidone palmitate in subjects with schizophrenia.*

The primary efficacy variable was the change from baseline to endpoint in the PANSS total scores. Secondary objectives were to assess the benefits in personal and social functioning, global improvement in severity of illness with paliperidone palmitate compared to PBO, dose-response and exposure-response relationships for paliperidone palmitate. The secondary efficacy variables included changes from baseline in Personal and Social Performance scale (PSP), Clinical Global Impression Severity (CGI-S) scores, PANSS subscales and items, and PANSS responder rates.

*Study PSY-3003. A randomised, double-blind, placebo-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed doses (50 mg eq., 100 mg eq., and 150 mg eq.) of paliperidone palmitate in subjects with schizophrenia.*

The primary efficacy variable, the secondary objectives / efficacy variables and statistical analyses were as for **Study PSY-3007**.

*Study PSY-3004. A randomised, double-blind, placebo-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed doses (25 mg eq., 100 mg eq., and 150 mg eq.) of paliperidone palmitate in subjects with schizophrenia.*

The primary and secondary objectives, drug dose / administration / site, study duration and statistical analyses were as for **study PSY-3003**.

*R092670-SCH-201. A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of 50 and 100 mg eq. of paliperidone palmitate in subjects with schizophrenia.*

The primary objectives of the study were to evaluate the efficacy and safety of 2 fixed doses of long-acting injections of paliperidone palmitate compared to PBO using PANSS total scores. Secondary objectives were to assess the global improvement in severity of illness and to explore the pharmacokinetic profiles of oral paliperidone-ER, oral paliperidone-IR and IM paliperidone palmitate. Intramuscular injection was into the gluteal muscle on Days 1, 8 and 36 of study duration.

*Study PSY-3001. A randomised, double-blind, placebo-controlled, parallel-group, study evaluating paliperidone palmitate in the prevention of recurrence in subjects with schizophrenia (DSM IV) for  $\geq 1$  year, PANSS total  $< 120$  on screening and  $< 75$  at start of phases 3 and 4.*

The primary objectives were to evaluate the efficacy of paliperidone palmitate compared with PBO in the prevention of recurrence of the symptoms of schizophrenia, and to assess the safety and tolerability of paliperidone palmitate in subjects with schizophrenia. Secondary objectives included evaluation of: the improvement of positive and negative symptoms, global improvement in severity, benefits to personal and social functioning with paliperidone palmitate

compared with PBO; and assessment of symptom reduction and stability of symptoms during the transition and maintenance phases. The objective of the open-label extension phase was to evaluate the long-term safety and tolerability of paliperidone palmitate.

*Study PSY-3001. A randomised, double-blind, placebo-controlled, parallel-group, study evaluating paliperidone palmitate in the prevention of recurrence in subjects with schizophrenia (DSM IV) for  $\geq 1$  year, PANSS total < 120 on screening and < 75 at start of phases 3 and 4.*

The primary objectives were to evaluate the efficacy of paliperidone palmitate compared with PBO in the prevention of recurrence of the symptoms of schizophrenia, and to assess the safety and tolerability of paliperidone palmitate in subjects with schizophrenia. Secondary objectives included evaluation of: the improvement of positive and negative symptoms, global improvement in severity, benefits to personal and social functioning with paliperidone palmitate compared with PBO; and assessment of symptom reduction and stability of symptoms during the transition and maintenance phases. The objective of the open-label extension phase was to evaluate the long-term safety and tolerability of paliperidone palmitate.

*Study PSY-3002. A randomised, double-blind, active-controlled, parallel-group comparative study of flexibly dosed paliperidone palmitate (25, 50, 75, or 100 mg eq.) administered every 4 weeks and flexibly dosed Risperdal Consta (25, 37.5, or 50 mg) administered every 2 weeks in subjects with schizophrenia (DSM IV) for  $\geq 1$  year, PANSS total score 60 – 120.*

The primary objective of the study was to demonstrate that paliperidone palmitate is not clinically inferior to Risperdal Consta for the treatment of schizophrenia. The safety and tolerability of paliperidone palmitate was also assessed. Secondary assessments included: global improvement of severity, benefits to personal and social functioning, symptomatic remission, and exploration of the relationship between pharmacokinetics and efficacy parameters.

Based on the above studies, the evaluators summarised the efficacy outcome as follows:

- Paliperidone palmitate has been shown to be efficacious in the treatment of moderate to severe schizophrenia in 4 acute treatment studies. Efficacy has been demonstrated for the primary variable in all studies evaluating 25 and 100 mg, 2 of the studies for 50 and one study of the 150 mg dosages.
- Efficacy was seen across all PANSS factors and subscales especially for the higher doses 100 and 150 mg and was shown for disorder-specific, global and functional measures. The functional measures were indicative of considerable impairment in personal and social function at baseline, with improvements over time which were significant in 2 studies. Response to treatment was as early as Day 8 in study **PSY-3007** which used the 150 mg initiation dosage.
- Factors including age, sex, race and baseline PANSS did not influence effect with the exception of geographic region and BMI. In addition, recurrence prevention was demonstrated in subjects who had achieved symptom control during a prior open-label phase of treatment and therapeutic effect was maintained over a year of open-label treatment.
- Efficacy was confirmed over all domains investigated including all PANSS factors, subscales, CGI, PSP and SQLS. The majority of subjects were treated with 100 mg. Paliperidone palmitate was shown to be non-inferior to Risperdal Consta in normal and overweight subjects but not in the overall group. This may be because of the dosing regime used.

## Safety

The evaluators summarised that:

- The studies of paliperidone palmitate are in keeping with the established safety profile of oral paliperidone. There were no new safety signals from either the acute or long term studies. AEs were generally similar in frequency to PBO treated subjects and there were no consistent differences across studies for gender, age, BMI or race for incidence of AEs. The most common SAEs were psychiatric disorders such as schizophrenia or psychotic disorder which was frequently an exacerbation of the underlying illness.
- The sponsor's *Clinical Overview* presented common adverse drug reactions (ADRs) from the pooled acute studies, that is, those AEs that were considered reasonably associated with paliperidone palmitate. Incidences were: PBO 46%, 25 mg 54%, 50 mg 50%, 100 mg 52% and 150 mg 45%. Those ADRs > 5% for any dose were vomiting (25 mg), injection site pain (100, 150 mg), dizziness (25 mg), akathisia (100, 150 mg) headache (all groups), somnolence/sedation (25, 50 mg), agitation (PBO, 25, 100, 150 mg) and insomnia (all groups). In study PSY-3001, incidences of ADRs were: 20% PBO, 21% paliperidone palmitate with those >5% for paliperidone weight increased and insomnia for PBO.
- Most of the studies found EPS AEs and EPS-medication rates similar for paliperidone palmitate and PBO for low doses but with a trend to higher rates for higher doses. There was a low rate of suicide related events which was similar to that for PBO.
- Elevations in prolactin were observed for all paliperidone palmitate studies as expected but the incidence of AEs was only 1-3% across studies. In terms of metabolic risk factors commonly observed with other antipsychotics, paliperidone palmitate did not alter either glucose or lipid concentrations either acute or long term in any of the studies.
- In some studies there was a greater frequency of clinically abnormal increases in pulse but other studies found paliperidone palmitate to be similar to PBO. Incidences of orthostatic hypotension were around 2-3% for paliperidone palmitate and PBO in most studies but higher than PBO in one study (**SCH-201**). Abnormal increases in heart rate were more frequent for paliperidone palmitate than PBO in some studies. Increases in QTc were uncommon but paliperidone palmitate should be used with caution with other drugs known to prolong QTc.
- In the acute studies, mean weight increased by 0.4-1.5 kg with paliperidone palmitate treatment and some studies showed a dose dependent increase. Increases in abnormally increased weight ( $\geq 7\%$ ) were more common for paliperidone palmitate and were also dose-dependent in some studies. During the extension phase of study **PSY-3001** there was a mean increase of 2.0 kg and a mean 23% incidence of abnormally increased weight from study baseline to end of extension phase.
- Injection site pain was more frequent for paliperidone palmitate than PBO although severe or moderate reactions were few and the majority of subjects rated injection site reactions as mild. Injections in the deltoid muscle were associated with more reactions than gluteal injections but both had acceptable tolerability as did switching between sites.

## Risk-Benefit Analysis

Overall, the evaluators recommended acceptance of the submission.

The quality evaluator has no objection to the products' registration and the Delegate accepted the sponsor's response to the issues raised by the quality evaluator for consideration by the Delegate. In particular, (a) any inadvertent intravascular injection should not result in a fatal outcome while potentially exaggerating treatable overdose symptoms, (b) replacing figure 1 in the proposed PI with the sponsor's proposed statement has better clarified the purpose /intention of the figure, which was essentially a simulation of plasma steady state concentrations of paliperidone palmitate post IM deltoid 150 mg Day 1 and IM deltoid 100 mg Day 8 (not the complete recommended dosing regimen), over those achieved with paliperidone-ER ( 2,6,12 mg/day) and (c) extrapolated pharmacokinetic data not involving properly conducted intravenous studies can only be used to state the probable extent, as opposed to absolute bioavailability, of a drug and in such case reference to absolute bioavailability cannot be made in the PI.

The nonclinical evaluator supported the product's registration. The issues of local injection site reaction /pain and probable anaphylactic reaction to paliperidone are already documented in the PI.

The clinical evaluator also supported the product's registration in line with the proposed indication.

The Delegate indicated that there was sufficient efficacy evidence (more so that the oral formulation is already approved) with a reasonable safety margin, and that there is a clinical role for the injectable form of paliperidone to recommend approval of the application for the proposed indication:

*Acute and maintenance treatment of schizophrenia in adults.*

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended approval for the indication:

*Acute and maintenance treatment of schizophrenia in adults*

In making this recommendation, the ACPM considered advice from the PSC that the submitted data has adequately resolved the previous population pharmacokinetic concerns. In addition, the ACPM noted the PSC concerns regarding the switch from a BMI-based to a weight-based needle selection and requested that the appropriate correlation be adequately addressed in the Administration section of the PI.

The ACPM agreed with the Delegate that safety and efficacy has been sufficiently demonstrated and that the approval is subject to the finalisation of issues relating to the PI to the satisfaction of the TGA.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Invega Sustenna containing paliperidone (as palmitate) 25 mg, 50 mg, 75 mg, 100 mg and 150 mg modified release injection pre-filled syringe for:

*Acute and maintenance treatment of schizophrenia in adults*

**Attachment 1. Product Information**

The following Product Information was approved at the time this AusPAR was published.  
For the current Product Information please refer to the TGA website at [www.tga.gov.au](http://www.tga.gov.au).



---

# INVEGA SUSTENNA<sup>®</sup>

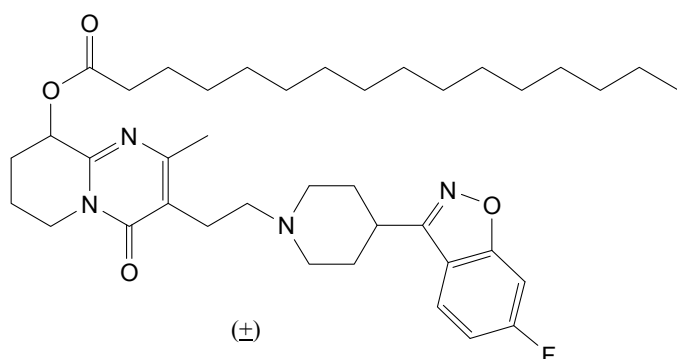
## PRODUCT INFORMATION

---

### NAME OF THE MEDICINE

Paliperidone palmitate.

The chemical name is (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoate.



CAS: 199739-10-1

C<sub>39</sub>H<sub>57</sub>FN<sub>4</sub>O<sub>4</sub>

MW=664.89

### DESCRIPTION

The active ingredient, paliperidone palmitate, is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. INVEGA SUSTENNA<sup>®</sup> contains a racemic mixture of (+)- and (-)- paliperidone palmitate. Paliperidone palmitate is very slightly soluble in ethanol and methanol; practically insoluble in water, polyethylene glycol 400 and propylene glycol; and slightly soluble in ethyl acetate.

INVEGA SUSTENNA<sup>®</sup> is available as a white to off-white sterile modified release aqueous suspension for intramuscular injection in dose strengths of 25 mg, 50 mg, 75 mg, 100 mg and 150 mg paliperidone (as palmitate). The inactive ingredients are polysorbate 20, macrogol 4000, citric acid monohydrate, sodium phosphate - dibasic anhydrous, sodium phosphate - monobasic monohydrate, sodium hydroxide, and water for injection.

INVEGA SUSTENNA<sup>®</sup> is provided in a pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper and tip cap (bromobutyl rubber). The kit contains 2 safety needles (a 1 ½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle).

### PHARMACOLOGY

#### Mechanism of Action

Paliperidone palmitate is hydrolyzed to paliperidone (see **Pharmacokinetics**). Paliperidone is the major active metabolite of 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 dopamine Type 2 (D<sub>2</sub>) and serotonin Type 2 (5HT<sub>2A</sub>) receptor antagonism.

## Pharmacodynamics

Paliperidone is a centrally active dopamine Type 2 (D<sub>2</sub>) receptor antagonist and a serotonin Type 2 (5HT<sub>2A</sub>) receptor antagonist. Paliperidone is also active as an antagonist at  $\alpha_1$  and  $\alpha_2$  adrenergic receptors and H<sub>1</sub> histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone has no affinity for cholinergic muscarinic or  $\beta_1$ - and  $\beta_2$ -adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar *in vitro*.

## Pharmacokinetics

### Absorption and Distribution:

Due to its extremely low water solubility, paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. Following a single intramuscular dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median  $t_{max}$  of 13 days. The release of the drug starts as early as day 1 and lasts for as long as 126 days.

Following intramuscular injection of single doses (25 mg -150 mg) in the deltoid muscle, on average, a 28% higher  $C_{max}$  was observed compared with injection in the gluteal muscle. The two initial deltoid intramuscular injections of 150 mg on day 1 and 100 mg on day 8 help attain therapeutic concentrations rapidly. The release profile and dosing regimen of INVEGA SUSTENNA<sup>®</sup> results in sustained therapeutic concentrations. The AUC of paliperidone following INVEGA SUSTENNA<sup>®</sup> administration was dose-proportional over a 25 mg -150 mg dose range, and less than dose-proportional for  $C_{max}$  for doses exceeding 50 mg. The mean steady-state peak:trough ratio for a INVEGA SUSTENNA<sup>®</sup> dose of 100 mg was 1.8 following gluteal administration and 2.2 following deltoid administration.

Following administration of paliperidone palmitate the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6–1.8.

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

### Metabolism and Elimination:

In a study with oral immediate-release <sup>14</sup>C-paliperidone, one week following administration of a single oral dose of 1 mg immediate-release <sup>14</sup>C-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 have been identified *in vivo*, none of which accounted for more than 10% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernable difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

*In vitro* studies have shown that paliperidone is a 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.

The median apparent half-life of paliperidone following INVEGA SUSTENNA<sup>®</sup> single-dose administration over the dose range of 25 mg -150 mg ranged from 25 days - 49 days.

## Modified Release Paliperidone Palmitate Injection versus Oral Modified-Release Paliperidone:

INVEGA SUSTENNA<sup>®</sup> is designed to deliver paliperidone over a monthly period while modified-release oral paliperidone is administered on a daily basis. Figure 1 presents the median pharmacokinetic profiles for paliperidone for 5 weeks following INVEGA SUSTENNA<sup>®</sup> administration using the recommended initiation regimen compared to the administration of an oral modified-release tablet (6 mg or 12 mg). The initiation regimen for INVEGA SUSTENNA<sup>®</sup> (150 mg/100 mg in the deltoid muscle on Day 1/Day 8) was designed to rapidly attain steady-state paliperidone concentrations when initiating therapy without the use of oral supplementation.

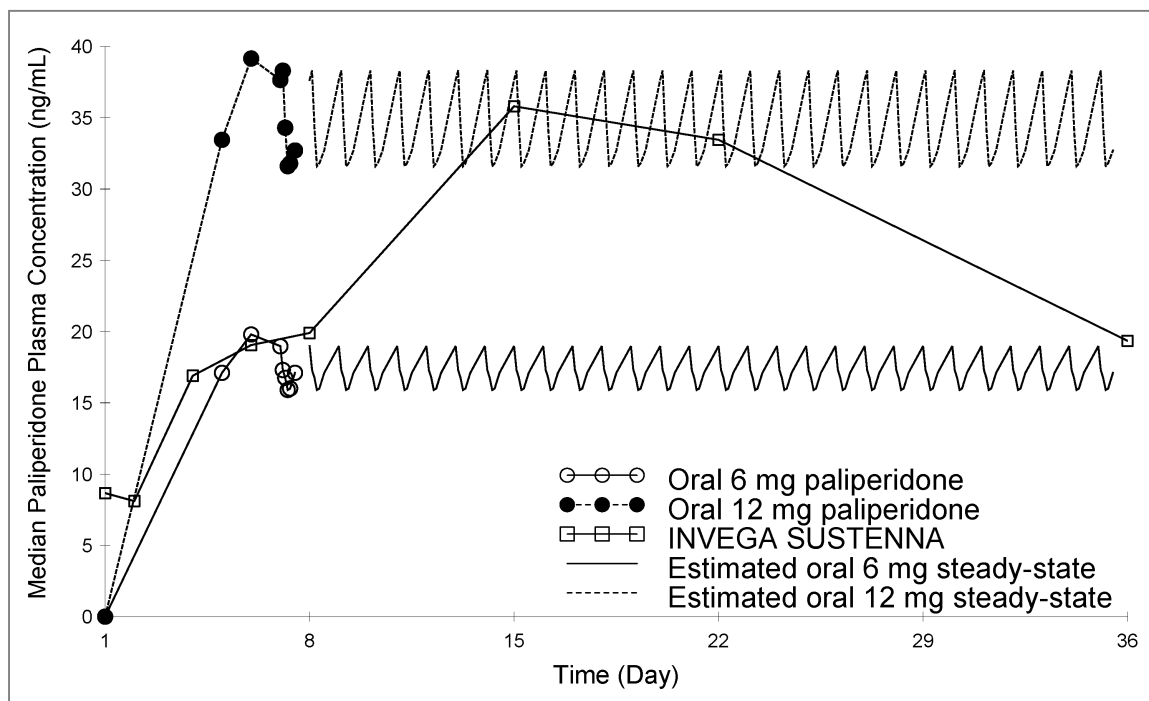


Figure 1. Median plasma concentration-time profiles following median pharmacokinetic profiles for paliperidone for 5 weeks following INVEGA SUSTENNA<sup>®</sup> administration using the recommended initiation regimen (initiating with paliperidone palmitate equivalent to paliperidone 150 mg/100 mg in the deltoid muscle on Day 1/Day 8), compared to the daily administration of an oral modified-release tablet (6 mg or 12 mg).

In general, overall initiation plasma levels with INVEGA SUSTENNA<sup>®</sup> were within the exposure range observed with 6-12 mg modified-release oral paliperidone. The use of the INVEGA SUSTENNA<sup>®</sup> initiation regimen allowed patients to stay in this exposure window of 6-12 mg modified-release oral paliperidone even on trough pre-dose days (Day 8 and Day 36). The intersubject variability for paliperidone pharmacokinetics following delivery from INVEGA SUSTENNA<sup>®</sup> was lower relative to the variability determined from modified-release oral paliperidone tablets. Because of the difference in median pharmacokinetic profiles between the two products, caution should be exercised when making a direct comparison of their pharmacokinetic properties.

### Special Populations

#### Renal Impairment:

INVEGA SUSTENNA<sup>®</sup> has not been systematically studied in patients with renal impairment. The dose of INVEGA SUSTENNA<sup>®</sup> should be reduced in patients with mild renal impairment; INVEGA SUSTENNA<sup>®</sup> is not recommended for use in patients with moderate or severe renal impairment (see **DOSE AND ADMINISTRATION**). Although INVEGA SUSTENNA<sup>®</sup> was not studied in patients with moderate or severe renal impairment, the disposition of a single oral dose paliperidone 3 mg modified-release tablet was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing estimated creatinine clearance.

Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% on average in mild (CrCl = 50 mL/min to < 80 mL/min), 64% in moderate (CrCl = 30 mL/min to < 50 mL/min), and 71% in severe (CrCl = 10 mL/min to < 30 mL/min) renal impairment, corresponding to an average increase in exposure ( $AUC_{inf}$ ) of 1.5 fold, 2.6 fold, and 4.8 fold, respectively, compared to healthy subjects. Based on a limited number of observations with INVEGA SUSTENNA® in subjects with mild renal impairment and pharmacokinetic simulations, the recommended initiation of INVEGA SUSTENNA® for patients with mild renal impairment is with a dose of 100 mg on treatment day 1 and 75 mg one week later; thereafter, follow with monthly injections of 50 mg (see **DOSAGE AND ADMINISTRATION**).

#### Hepatic Impairment:

INVEGA SUSTENNA® has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone in subjects with moderate hepatic impairment (Child-Pugh Class B), no dose adjustment is required in patients with mild or moderate hepatic impairment (see **DOSAGE AND ADMINISTRATION**). In the study with oral paliperidone in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects, although total paliperidone exposure decreased because of a decrease in protein binding. Paliperidone has not been studied in patients with severe hepatic impairment.

#### Elderly:

No dosage adjustment is recommended based on age alone. However, dose adjustment may be required because of age-related decreases in creatinine clearance (see Hepatic Impairment above and **DOSAGE AND ADMINISTRATION**).

#### Race:

No dosage adjustment is recommended based on race. No differences in pharmacokinetics were observed between Japanese and Caucasians.

#### Gender:

No dosage adjustment is recommended based on gender, although slower absorption was observed in females in a population pharmacokinetic analysis.

#### Smoking:

No dosage adjustment is recommended based on smoking status. Based on *in vitro* studies utilizing human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone.

### Clinical trials

A total of 2652 patients with schizophrenia were included in the five pivotal studies with INVEGA SUSTENNA®, of whom 2142 received INVEGA SUSTENNA®.

The efficacy of INVEGA SUSTENNA® was evaluated in both acute treatment and recurrence prevention of symptoms of schizophrenia.

The efficacy of INVEGA SUSTENNA® in the acute treatment of schizophrenia was established in four short-term (one 9-week and three 13-week) double-blind, randomized, placebo-controlled, fixed-dose studies of acutely relapsed adult patients who met DSM-IV criteria for schizophrenia. The fixed doses of INVEGA SUSTENNA® in these studies were given on days 1, 8, and 36 in the 9-week study, and additionally on day 64 of the 13-week studies, i.e., at a weekly interval for the initial two doses and then every 4 weeks for maintenance.

The efficacy of INVEGA SUSTENNA® in recurrence prevention of symptoms of schizophrenia was established in one longer-term double-blind, placebo-controlled study involving adult patients who met DSM-IV criteria for schizophrenia. The study included flexible dosing of INVEGA SUSTENNA® (25, 50, and 100 mg) during the maintenance phase and fixed dosing (25, 50, and 100 mg) during the double-blind phase.

Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS), a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. Functioning was evaluated using the Personal and Social Performance (PSP) scale. The PSP is a validated clinician rated scale that measures personal and social functioning in the domains of socially useful activities: work and study, personal and social relationships, self-care, and disturbing and aggressive behaviors. The severity of dysfunctioning in social, personal, and self-care is measured by level of difficulty (absent, mild, manifest, marked, severe) in performing such activities with and without the help of other people. Similarly, severity of dysfunctioning in aggressive behaviors is measured by the presence or absence of aggressive behaviors (e.g., rudeness, insulting others in public, breaking objects, verbal threats, physical assault) and the frequency in which these behaviors occur.

In a 13-week study (R092670 PSY-3007) (n=636) comparing three fixed doses of INVEGA SUSTENNA<sup>®</sup> (initial deltoid injection of 150 mg followed by 3 gluteal or deltoid doses of either 25 mg/4 weeks, 100 mg/4 weeks or 150 mg/4 weeks) to placebo, all three doses of INVEGA SUSTENNA<sup>®</sup> were superior to placebo in improving the PANSS total score (Note: This is the key study demonstrating recommended dosing initiation). These results support efficacy across the entire duration of treatment and improvement in PANSS and was observed as early as day 4 with significant separation from placebo in the 25 mg and 150 mg INVEGA SUSTENNA<sup>®</sup> groups by day 8. The study also assessed functionality as defined by the PSP scale, the key secondary outcome measure. The baseline range of scores suggested a moderate to marked difficulty in areas of socially useful activities, personal and social relationships, self-care, and/or disturbing and aggressive behavior. The PSP scores for the 100 mg/4 weeks and the 150 mg/4 weeks, but not the 25 mg/4 weeks, treatment groups demonstrated statistical superiority to placebo.

In another 13-week study (R092670-PSY-3003) (n=349) comparing three fixed doses of INVEGA SUSTENNA<sup>®</sup> (50 mg/4 weeks, 100 mg/4 weeks, and 150 mg/4 weeks) to placebo, only 100 mg/4 weeks of INVEGA SUSTENNA<sup>®</sup> was superior to placebo in improving the PANSS total score. The functionality of subjects was measured using the PSP scale, with improvements in the PSP score from baseline to end point being statistically superior to placebo for both 100 mg/4 weeks and 50 mg/4 weeks doses of INVEGA SUSTENNA<sup>®</sup>. Although a 150 mg dose was included in this study, there were insufficient numbers of subjects receiving this dose to allow definitive conclusions concerning the efficacy of this dose.

In a third 13-week study (R092670-PSY-3004) (n=513) comparing three fixed doses of INVEGA SUSTENNA<sup>®</sup> (25 mg/4 weeks, 50 mg/4 weeks, and 100 mg/4 weeks) to placebo, all three doses of INVEGA SUSTENNA<sup>®</sup> were superior to placebo in improving the PANSS total score. In this study, none of the INVEGA SUSTENNA<sup>®</sup> dose groups achieved statistical significance when compared with placebo for the PSP score.

In the 9-week study (R092670-SCH-201) (n=197) comparing two fixed doses of INVEGA SUSTENNA<sup>®</sup> (50 mg/4 weeks and 100 mg/4 weeks) to placebo, both doses of INVEGA SUSTENNA<sup>®</sup> were superior to placebo in improving PANSS total score. Statistical superiority of both INVEGA SUSTENNA<sup>®</sup> groups relative to placebo was achieved by Day 8 for the change in PANSS total score. 50 mg or 100 mg INVEGA SUSTENNA<sup>®</sup> administered in the gluteal muscle on Days 1, 8, and 36 of the double-blind period, demonstrated statistically superior improvement compared to placebo for the primary efficacy variable.

The efficacy of INVEGA SUSTENNA<sup>®</sup> in maintaining response and then in the prevention of recurrence of psychotic symptoms in subjects with schizophrenia was established in a longer-term double-blind, placebo-controlled, flexible-dose study (R092670-PSY-3001) involving adult subjects who met DSM-IV criteria for schizophrenia. The study included a 9 week open-label acute treatment followed by a 24 week maintenance of response period. Eligible subjects were then randomized to a double blind placebo-controlled recurrence prevention phase with variable duration as this was determined by advent of a recurrent episode. During the variable length double-blind phase, 410 stabilized patients were randomized to either the same dose of INVEGA

SUSTENNA® (median duration 171 days [range 1 day - 407 days]) they received during the maintenance phase, i.e., 25 mg, 50 mg, or 100 mg administered every 4 weeks, or to placebo (median duration 105 days [range 8 days - 441 days]) until they experienced a recurrence of schizophrenia symptoms. Recurrence was pre-defined as time to first emergence of one or more of the following: psychiatric hospitalization,  $\geq 25\%$  increase (if the baseline score was  $> 40$ ) or a 10-point increase (if the baseline score was  $\leq 40$ ) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation, or a score of  $\geq 5$  (if the maximum baseline score was  $\leq 3$ ) or  $\geq 6$  (if the maximum baseline score was 4) on two consecutive assessments of the individual PANSS items P1 (Delusions), P2 (Conceptual disorganization), P3 (Hallucinatory behavior), P6 (Suspiciousness/persecution), P7 (Hostility), or G8 (Uncooperativeness). The primary efficacy variable was time to a recurrence event. A pre-planned interim analysis (after 68 recurrence events occurred), showed a significantly longer time to recurrence in patients treated with INVEGA SUSTENNA® compared to placebo ( $p < 0.001$ ), and the study was stopped early because maintenance of effect was demonstrated. See [Figure 2](#).

An examination of population subgroups did not reveal any clinically significant differences in responsiveness on the basis of gender, age, or race.

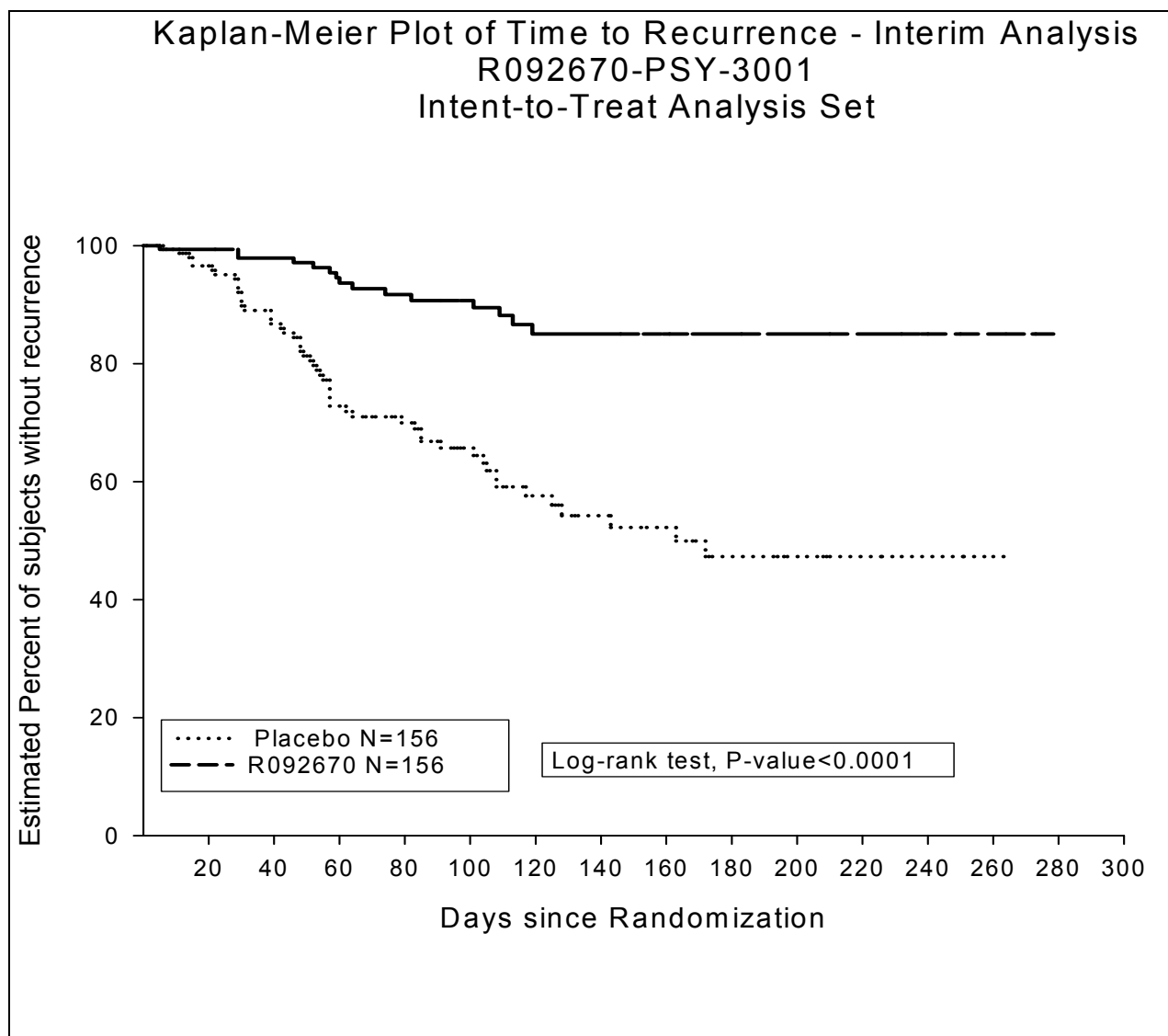


Figure 2: Kaplan Meier Plot of Time to Recurrence

There was a significant difference ( $p < 0.0001$  based on the log-rank test) between the treatment groups in the time to recurrence in favor of paliperidone palmitate; subjects who continued treatment on paliperidone palmitate experienced recurrence later than subjects who switched to placebo. This difference exceeded the threshold for significance (i.e., the p-value was less than  $p < 0.0106$ ) resulting in the IDMC recommendation to stop the study early.

## INDICATIONS

INVEGA SUSTENNA<sup>®</sup> is indicated for the acute and maintenance treatment of schizophrenia in adults.

## CONTRAINDICATIONS

Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone and paliperidone. Paliperidone palmitate is converted to paliperidone, which is a metabolite of risperidone and is therefore contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in the INVEGA SUSTENNA<sup>®</sup> formulation.

## PRECAUTIONS

### Use in the elderly

Clinical studies of INVEGA SUSTENNA<sup>®</sup> did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with renal impairment (see **PHARMACOLOGY** – Special Populations), who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **DOSAGE AND ADMINISTRATION**).

### Use in elderly patients with dementia

#### Overall Mortality:

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. INVEGA SUSTENNA<sup>®</sup> (paliperidone palmitate) is not approved for the treatment of dementia-related psychosis.

#### Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis:

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. Oral paliperidone and INVEGA SUSTENNA<sup>®</sup> were not marketed at the time these studies were performed and are not approved for the treatment of patients with dementia-related psychosis.

### Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including paliperidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated

extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.

## QT Prolongation

Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

The effects of oral paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

In the QT study (n = 141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release ( $C_{max\ ss} = 113$  ng/mL) was more than 2-fold the exposure observed with the maximum recommended 150 mg dose of INVEGA SUSTENNA<sup>®</sup> administered in the deltoid muscle (predicted median  $C_{max\ ss} = 50$  ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which  $C_{max\ ss} = 35$  ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.

In the three fixed-dose efficacy studies of oral paliperidone modified release, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the oral paliperidone 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec).

In the four fixed-dose efficacy studies of INVEGA SUSTENNA<sup>®</sup>, no subject experienced a change in QTcLD exceeding 60 msec and no subject had a QTcLD value of > 500 msec at any time point. In the long-term recurrence prevention study, no subject had a QTcLD change > 60 msec, and one subject had a QTcLD value of 507 msec (Bazett's QT corrected interval [QTcB] value of 483 msec); this latter subject also had a heart rate of 45 beats per minute.

## Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop



the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop after relatively brief treatment periods at low doses, although this is uncommon.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome and may thus mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, INVEGA SUSTENNA<sup>®</sup> should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with INVEGA SUSTENNA<sup>®</sup>, drug discontinuation should be considered. However, some patients may require treatment with INVEGA SUSTENNA<sup>®</sup> despite the presence of the syndrome.

## Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials, and there have been few reports of hyperglycemia or diabetes in trial subjects treated with INVEGA SUSTENNA<sup>®</sup>. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because INVEGA SUSTENNA<sup>®</sup> was not marketed at the time these studies were performed, it is not known if INVEGA SUSTENNA<sup>®</sup> is associated with this increased risk.

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. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

## Weight Gain

Weight gain has been observed with INVEGA SUSTENNA<sup>®</sup> and other atypical antipsychotics. In the 13-week study involving 150 mg initiation dosing, the proportion of subjects with an abnormal weight increase  $\geq 7\%$  showed a dose-related trend, with a 5% incidence rate in the placebo group compared with rates of 6%, 8%, and 13% in the INVEGA SUSTENNA<sup>®</sup> 25 mg, 100 mg, and 150 mg groups, respectively. In the two 13-week, fixed-dose, double-blind, placebo-controlled trials

(pooled data), the proportions of subjects meeting a weight gain criterion of 7% of body weight were 6%, 9%, and 10% in the INVEGA SUSTENNA<sup>®</sup> 25 mg, 50 mg, and 100 mg groups, respectively, compared with 2% in the placebo group. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, 8% and 6% in the INVEGA SUSTENNA<sup>®</sup> 50 mg and 100 mg groups, respectively, met this criterion compared with 4% in the placebo group.

During the 33-week open-label period (9-week flexible-dose transition phase followed by a 24-week maintenance phase flexible-dose and minimum 12-week fixed dose) of the maintenance trial, 12% of INVEGA SUSTENNA<sup>®</sup>-treated subjects met this criterion; the mean (SD) weight change from open-label baseline was +0.7 (4.79) kg. In the variable length double-blind phase, this criterion (weight gain of 7% from double-blind phase to endpoint) was met by 6% of INVEGA SUSTENNA<sup>®</sup>-treated subjects compared with 3% of placebo-treated subjects; the mean weight change from double-blind baseline was +0.5 kg for INVEGA SUSTENNA<sup>®</sup> compared with -1.0 kg for placebo. In the open-label extension phase of the study, the mean (SD) weight change was 0.9 (4.26) kg and the mean incidence of weight gain of  $\geq 7\%$  from open-label baseline was 13%. The mean (SD) weight change from the start of the study (transition baseline) to the end of the one-year extension phase was 2.0 (6.91) kg and mean incidence of weight gain of  $\geq 7\%$  was 23%.

## Hyperprolactinemia

Like other drugs that antagonize dopamine D<sub>2</sub> receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats (see **PRECAUTIONS** – Carcinogenicity). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

## Orthostatic Hypotension and Syncope

Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. Syncope was reported in < 1% (4/1293) of subjects treated with INVEGA SUSTENNA<sup>®</sup> in the recommended dose range of 25 mg to 150 mg in the four fixed-dose, double-blind, placebo-controlled trials compared with 0% (0/510) of subjects treated with placebo. In the four fixed-dose efficacy studies, orthostatic hypotension was reported as an adverse event by < 1% (2/1293) of INVEGA SUSTENNA<sup>®</sup>-treated subjects compared to 0% (0/510) with placebo. Incidences of orthostatic hypotension and syncope in the long-term studies were similar to those observed in the short-term studies.

INVEGA SUSTENNA<sup>®</sup> should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

## Leukopenia, Neutropenia, and Agranulocytosis

Class Effect: In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including oral form of paliperidone. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of INVEGA SUSTENNA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count  $<1000/\text{mm}^3$ ) should discontinue INVEGA SUSTENNA® and have their WBC followed until recovery.

## Potential for Cognitive and Motor Impairment

Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA SUSTENNA® (see **ADVERSE EFFECTS**). Antipsychotics, including INVEGA SUSTENNA®, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

## Seizures

In the four fixed-dose double-blind placebo-controlled studies,  $<1\%$  (1/1293) of subjects treated with INVEGA SUSTENNA® in the recommended dose range of 25 mg –150 mg experienced an adverse event of convulsion compared with  $<1\%$  (1/510) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

Like other antipsychotic drugs, INVEGA SUSTENNA® should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

## Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. INVEGA SUSTENNA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

## Suicide

The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy.

## Priapism

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Although no cases of priapism have been reported in clinical trials with INVEGA SUSTENNA®, priapism has been reported with oral paliperidone during postmarketing surveillance. Severe priapism may require surgical intervention.

## Thrombotic Thrombocytopenic Purpura (TTP)

No cases of TTP were observed during clinical studies with oral paliperidone or INVEGA SUSTENNA<sup>®</sup>. Although cases of TTP have been reported in association with risperidone administration, the relationship to risperidone therapy is unknown

## Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA SUSTENNA<sup>®</sup> to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

## Administration

INVEGA SUSTENNA<sup>®</sup> is intended for intramuscular injection, and care must be taken to avoid inadvertent injection into a blood vessel (see **DOSAGE AND ADMINISTRATION**).

## Antiemetic Effect

An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdose with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

## Use in Patients with Concomitant Illness

Clinical experience with INVEGA SUSTENNA<sup>®</sup> in patients with certain concomitant illnesses is limited.

Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

INVEGA SUSTENNA<sup>®</sup> has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with INVEGA SUSTENNA<sup>®</sup>, caution should be observed in patients with known cardiovascular disease (see **PRECAUTIONS** – Orthostatic Hypotension and Syncope).

## Monitoring: Laboratory Tests

No specific laboratory tests are recommended.

## Use in patients with renal impairment

INVEGA SUSTENNA<sup>®</sup> has not been systematically studied in patients with renal impairment (see **PHARMACOLOGY** – Special Populations). A reduced dose is recommended in patients with mild renal impairment; INVEGA SUSTENNA<sup>®</sup> is not recommended in patients with moderate or severe renal impairment (see **DOSAGE AND ADMINISTRATION**).

## Use in patients with hepatic impairment

INVEGA SUSTENNA<sup>®</sup> has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment.

## Use in Children and adolescents younger than 18 years

Safety and effectiveness of INVEGA SUSTENNA® in patients < 18 years of age have not been established.

## Effects on fertility

Fertility studies of paliperidone palmitate have not been performed.

Mating and fertility of male and female rats was not affected at oral paliperidone doses up to 2.5 mg/kg/day (twice the maximum recommended oral clinical dose based on body surface area (mg/m<sup>2</sup>)). The 2.5 mg/kg/day dose produced slight maternal toxicity, increased pre-implantation loss and slightly reduced the number of live embryos; the no-effect dose was 0.63 mg/kg/day.

In rat fertility studies with risperidone, which is extensively converted to paliperidone in rats and humans, mating (but not fertility) was impaired at doses 0.2 to 5 times the maximum human dose on a mg/m<sup>2</sup> basis, by an effect on females. In repeat dose toxicity studies in beagle dogs, risperidone at doses of 1 to 17 times the maximum human dose on a mg/m<sup>2</sup> basis was associated with adverse effects on the male reproductive system (inhibited ejaculation, incomplete spermatogenesis, reduced sperm motility and concentration, reduced gonadal and prostatic weight, prostatic immaturity, decreased serum testosterone). Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. No-effect doses were not determined in either rat or dog.

## Use in pregnancy – Category B3

The safety of INVEGA SUSTENNA® during human pregnancy has not been established. Reversible extrapyramidal symptoms in the neonate have been observed following the use of risperidone during the last trimester of pregnancy. Risperidone is extensively converted to paliperidone in humans. It is not known whether neonatal extrapyramidal effects will occur following the use of paliperidone palmitate near the end of pregnancy.

No teratogenicity was observed following a single intramuscular treatment of pregnant rats with paliperidone palmitate in early gestation. The highest dose (160 mg/kg) was maternotoxic and resulted in paliperidone exposure 4-fold the maximal anticipated clinical exposure based on plasma AUC. No teratogenic effect was noted in rats and rabbits following oral administration of paliperidone during the period of organogenesis at respective exposures up to 28- and 17-fold the maximal anticipated clinical exposure, based on plasma AUC. Maternotoxic doses in rabbits were associated with increased fetal mortality. Studies with risperidone also found no teratogenic effects in rats and rabbits following oral administration of risperidone during the period of organogenesis at doses up to nine times the human dose on a mg/m<sup>2</sup> basis. INVEGA SUSTENNA® should only be used during pregnancy if the benefits outweigh the risks.

## Use in lactation

In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Therefore, women receiving INVEGA SUSTENNA® should not breast-feed infants.

Oral administration of paliperidone to rats from early gestation to lactation was associated with adverse effects in pups (clinical signs, reduced body weight gain and survival, impaired righting reflex) during lactation at doses similar to the maximal recommended clinical dose on mg/m<sup>2</sup> basis; the no-effect dose was less than the clinical dose. In risperidone studies in rats, oral administration of risperidone during late gestation and lactation was associated with increased pup deaths during early lactation at doses 0.2 to 5 times the maximum human dose on a mg/m<sup>2</sup> basis (a no effect dose was not determined) and with reduced pup weight gain at doses fivefold or greater than the maximal recommended human dose on a mg/m<sup>2</sup> basis. There were also increases in stillborn rat pups at an oral risperidone dose 2.5 to 5 times the maximum human dose on a mg/m<sup>2</sup> basis. It is not known

whether these effects of risperidone and paliperidone resulted from a direct effect on the fetuses and pups and/or to an effect on the dams.

## Alcohol

Given the primary CNS effects of paliperidone, patients should be advised to avoid alcohol while taking this medicine.

## Carcinogenicity

The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in a long-term study in rats. There was an increase in mammary gland adenocarcinomas in female rats at 10, 30, and 60 mg /kg/month, associated with respective exposures (plasma AUC) of 0.4, 1.6 and 3 times clinical exposure at the maximum recommended 150 mg dose of INVEGA SUSTENNA<sup>®</sup>. A no-effect dose was not established. Male rats showed an increase in total mammary gland tumours at 30 and 60 mg /kg/month, associated with respective exposures (plasma AUC) of 1 and 2 times clinical exposure. A carcinogenicity study in mice has not been conducted with paliperidone palmitate.

Carcinogenicity studies of risperidone, which is extensively converted to paliperidone in rats, mice, and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats, equivalent to 0.3, 1.3 and 5 times (mice) and 0.6, 2.5 and 10 times (rats) the maximum human dose on a mg/m<sup>2</sup> basis. There were statistically significant increases in pituitary gland adenomas in female mice and endocrine pancreas adenomas in male rats at the two highest dose levels, and in mammary gland adenocarcinomas at all dose levels in female mice and female rats and at the highest dose in male rats. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D<sub>2</sub>-receptor antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents in terms of human risk is unknown (see **PRECAUTIONS** – Hyperprolactinemia).

## Genotoxicity

Paliperidone palmitate was not genotoxic in *in vitro* tests for bacterial reverse gene mutation and forward mutation in mammalian cells (mouse lymphoma). Paliperidone was also not genotoxic in these tests, or in an *in vivo* test for clastogenicity (rat micronucleus assay).

## Interactions with other medicines

Since paliperidone palmitate is hydrolyzed to paliperidone (see **PHARMACOLOGY**) results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

### Potential for INVEGA SUSTENNA<sup>®</sup> to Affect Other Drugs:

Given the primary CNS effects of paliperidone (see **ADVERSE EFFECTS**), INVEGA SUSTENNA<sup>®</sup> should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

Because of its potential for inducing orthostatic hypotension, an additive effect may be observed when INVEGA SUSTENNA<sup>®</sup> is administered with other therapeutic agents that have this potential (see **PRECAUTIONS** – Orthostatic Hypotension and Syncope).

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that

are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

Paliperidone is a weak inhibitor of P-glycoprotein (P-gp) at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

#### Potential for Other Drugs to Affect INVEGA SUSTENNA<sup>®</sup>:

Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19, so that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, *in vivo* studies do not show decreased elimination by these isozymes and they contribute to only a small fraction of total body clearance. *In vitro* studies have shown that paliperidone is a P-gp substrate.

Co-administration of oral paliperidone modified release once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state  $C_{max}$  and AUC of paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone. A minor decrease in the amount of drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. On initiation of carbamazepine, the dose of INVEGA SUSTENNA<sup>®</sup> should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA SUSTENNA<sup>®</sup> should be re-evaluated and decreased if necessary.

Paliperidone is metabolized to a limited extent by CYP2D6 (see **PHARMACOLOGY** – Pharmacokinetics). In an interaction study in healthy subjects in which a single 3 mg dose of oral paliperidone modified release was administered concomitantly with 20 mg per day of paroxetine (a potent CYP2D6 inhibitor), paliperidone exposures were on average 16% (90% CI: 4, 30) higher in CYP2D6 extensive metabolizers. Higher doses of paroxetine have not been studied. 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 INVEGA SUSTENNA<sup>®</sup>, a clinically significant interaction would not be expected between divalproex sodium and INVEGA SUSTENNA<sup>®</sup> intramuscular injection.

#### **Effect on ability to drive or operate machinery**

As INVEGA SUSTENNA<sup>®</sup> has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that INVEGA SUSTENNA<sup>®</sup> therapy does not affect them adversely (see **PRECAUTIONS** – Potential for Cognitive and Motor Impairment).

## **ADVERSE EFFECTS**

### **Clinical Trial Data**

The most common adverse reactions (reported by  $\geq 5\%$  in any INVEGA SUSTENNA<sup>®</sup> dose group in the four fixed-dose, double-blind, placebo-controlled trials) were: insomnia, headache, agitation, somnolence/sedation, dizziness, injection site pain, akathisia, and vomiting.

The most common adverse reaction that was associated with discontinuation from double-blind, placebo-controlled trials was agitation (caused discontinuation in 0.5% of INVEGA SUSTENNA<sup>®</sup>-treated subjects) (see **ADVERSE EFFECTS** – Discontinuation Due to Adverse Reactions).

The data described in this section are derived from a clinical trial database consisting of a total of 3817 subjects with schizophrenia who received at least one dose of INVEGA SUSTENNA<sup>®</sup> in the recommended dose range of 25 mg to 150 mg and a total of 510 subjects with schizophrenia who received placebo. Among the 3817 INVEGA SUSTENNA<sup>®</sup>-treated subjects, 1293 received INVEGA SUSTENNA<sup>®</sup> in four fixed-dose, double-blind, placebo-controlled trials (one 9-week and three 13-week studies), 849 received INVEGA SUSTENNA<sup>®</sup> in the long-term recurrence prevention trial (of whom 205 continued to receive INVEGA SUSTENNA<sup>®</sup> during the double-blind placebo-controlled phase of this study), and 1675 received INVEGA SUSTENNA<sup>®</sup> in five non-placebo controlled trials (three noninferiority active-comparator trials, one long-term open-label pharmacokinetic and safety study, and an injection site [deltoid-gluteal] cross-over trial). One of the 13-week studies (PSY-3007) included a 150 mg INVEGA SUSTENNA<sup>®</sup> initiation dose followed by treatment with either 25 mg, 100 mg, or 150 mg every 4 weeks.

Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of INVEGA SUSTENNA<sup>®</sup> (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for INVEGA SUSTENNA<sup>®</sup> often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The majority of all adverse reactions were mild to moderate in severity.

#### **Double-Blind, Placebo-Controlled Data**

Table 1 lists the adverse reactions reported in 2% or more of INVEGA SUSTENNA<sup>®</sup>-treated subjects with schizophrenia in the four fixed-dose, double-blind, placebo-controlled trials.



**Table 1. Adverse Reactions in ≥ 2% of INVEGA SUSTENNA®-Treated Subjects with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials**

System/Organ Class Adverse Reaction	Placebo <sup>a</sup> (N=510)	25 mg (N=130)	50 mg (N=302)	INVEGA SUSTENNA®			
				100 mg (N=312)	150/25 mg <sup>b</sup> (N=160)	150/100 mg <sup>b</sup> (N=165)	150/150 mg <sup>b</sup> (N=163)
<b>Total percentage of subjects with adverse reaction</b>	70	75	68	69	63	60	63
<b>Gastrointestinal disorders</b>							
Abdominal discomfort/Abdominal pain upper	2	2	4	4	1	2	4
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
<b>General disorders and administration site conditions</b>							
Asthenia	0	2	1	<1	0	1	1
Fatigue	1	1	2	2	1	2	1
Injection site reaction	2	0	4	6	9	7	10
<b>Infections and infestations</b>							
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
<b>Injury, poisoning and procedural complications</b>							
Skin laceration	<1	2	<1	0	1	0	0
<b>Investigations</b>							
Alanine aminotransferase increased	2	0	2	1	1	1	1
Weight increased	1	4	4	1	1	1	2
<b>Musculoskeletal and connective tissue disorders</b>							
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
<b>Nervous system disorders</b>							
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
<b>Psychiatric disorders</b>							
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
<b>Respiratory, thoracic and mediastinal disorders</b>							
Cough	1	2	3	1	0	1	1
<b>Vascular disorders</b>							
Hypertension	1	2	1	1	1	1	0

Percentages are rounded to whole numbers. Table includes adverse events that were reported in 2% or more of subjects in any of the INVEGA SUSTENNA® groups and which occurred at greater incidence than in the placebo group.

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

<sup>b</sup> Initial deltoid injection of 150 mg followed by either 25 mg, 100 mg, or 150 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (25 mg, 50 mg, and 100 mg) are from studies involving only gluteal injection.

Adverse events for which the INVEGA SUSTENNA® incidence was equal to or less than placebo are not listed in the table, but included the following: dyspepsia, psychotic disorder, schizophrenia, and tremor. The following terms were combined: somnolence/sedation, breast tenderness/breast pain, abdominal discomfort/abdominal pain upper/stomach discomfort, and tachycardia/sinus tachycardia/heart rate increased. All injection site reaction-related adverse events were collapsed and are

grouped under "Injection site reactions".

### **Adverse Reactions Observed During the Clinical Trial Evaluation of INVEGA SUSTENNA<sup>®</sup> and Not Listed in Table 1**

The following additional adverse reactions occurred in INVEGA SUSTENNA<sup>®</sup>-treated subjects in the above four fixed-dose, double-blind, placebo-controlled trials, in the double-blind phase of the maintenance trial, or in INVEGA SUSTENNA<sup>®</sup>-treated subjects with schizophrenia who participated in other clinical trials, and were not reported in Table 1. They were determined to be adverse reactions based upon reasons to suspect causality such as timing of onset or termination with respect to drug use, plausibility in light of the drug's known pharmacology, occurrence at a frequency above that expected in the treated population or occurrence of an event typical of drug-induced adverse reactions

**Table 2. Adverse Reactions Observed During the Clinical Trial Evaluation of INVEGA SUSTENNA<sup>®</sup> and Not Listed in Table 1**

<p><b>Cardiac disorders:</b> Atrioventricular block first degree, bradycardia, bundle branch block, electrocardiogram QT prolonged, palpitations, postural orthostatic tachycardia syndrome, tachycardia</p> <p><b>Ear and labyrinth disorders:</b> Vertigo</p> <p><b>Endocrine disorders:</b> Hyperprolactinemia</p> <p><b>Eye disorders:</b> Eye movement disorder, eye rolling, oculogyric crisis, vision blurred</p> <p><b>Gastrointestinal disorders:</b> Salivary hypersecretion</p> <p><b>Immune system disorders:</b> Hypersensitivity</p> <p><b>Investigations:</b> Blood cholesterol increased, blood glucose increased, blood triglycerides increased, electrocardiogram abnormal</p> <p><b>Metabolism and nutrition disorders:</b> Decreased appetite, hyperglycemia, hyperinsulinemia, increased appetite</p> <p><b>Musculoskeletal and connective tissue disorders:</b> Joint stiffness, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, nuchal rigidity</p> <p><b>Nervous system disorders:</b> Bradykinesia, cerebrovascular accident, convulsion, dizziness postural, drooling, dysarthria, dyskinesia, dystonia, hypertonia, lethargy, neuroleptic malignant syndrome, oromandibular dystonia, parkinsonism, psychomotor hyperactivity, syncope, tardive dyskinesia</p> <p><b>Psychiatric disorders:</b> Restlessness</p> <p><b>Reproductive system and breast disorders:</b> Amenorrhea, breast discharge, erectile dysfunction, galactorrhea, gynecomastia, menstrual disorder, menstruation delayed, menstruation irregular, sexual dysfunction</p> <p><b>Skin and subcutaneous tissue disorders:</b> Drug eruption, pruritus, pruritus generalized, rash, urticaria</p> <p><b>Vascular disorders:</b> Orthostatic hypotension</p>
---

## Discontinuations Due to Adverse Reactions

The percentages of subjects who discontinued due to adverse events in the four fixed-dose, double-blind, placebo-controlled trials were 5.0% and 7.8% in INVEGA SUSTENNA<sup>®</sup>- and placebo-treated subjects, respectively.

## Dose-Related Adverse Reactions

Based on the pooled data from the four fixed-dose, double-blind, placebo-controlled trials, among the adverse reactions that occurred at  $\geq 2\%$  incidence in the subjects treated with INVEGA SUSTENNA<sup>®</sup>, only akathisia, increased with dose. Hyperprolactinemia also exhibited a dose relationship, but did not occur at  $\geq 2\%$  incidence in INVEGA SUSTENNA<sup>®</sup>-treated subjects from the four fixed-dose studies.

## Demographic Differences

An examination of population subgroups in the double-blind placebo-controlled trials did not reveal any evidence of differences in safety on the basis of age, gender, or race alone; however, there were few subjects  $\geq 65$  years of age.

## Extrapyramidal Symptoms (EPS)

Pooled data from the two double-blind (R092670-PSY-3003, R092670-PSY-3004), placebo-controlled, 13-week, fixed-dose trials provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline or score at the end of trial) which broadly evaluates Parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline or score at the end of trial) which evaluates akathisia, (3) use of anticholinergic medications to treat emergent EPS, (4) the Abnormal Involuntary Movement Scale scores (mean change from baseline or scores at the end of trial) ([Table 3](#)), and (5) incidence of spontaneous reports of EPS ([Table 4](#)).

**Table 3.** Treatment-Emergent Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication

Scale	Percentage of Subjects			
	Placebo (N=262)	25 mg (N=130)	50 mg (N=223)	100 mg (N=228)
Parkinsonism <sup>a</sup>	9	12	10	6
Akathisia <sup>b</sup>	5	5	6	5
Dyskinesia <sup>c</sup>	3	4	6	4
Use of Anticholinergic Medications <sup>d</sup>	12	10	12	11

a: For Parkinsonism, percent of subjects with Simpson-Angus Total score  $> 0.3$  at endpoint (Total score defined as total sum of items score divided by the number of items)

b: For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score  $\geq 2$  at endpoint

c: For Dyskinesia, percent of subjects with a score  $\geq 3$  on any of the first 7 items or a score  $\geq 2$  on two or more of any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint

d: Percent of subjects who received anticholinergic medications to treat emergent EPS

**Table 4.** Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term

EPS Group	Percentage of Subjects			
	Placebo (N=262)	INVEGA SUSTENNA®		
		25 mg (N=130)	50 mg (N=223)	100 mg (N=228)
Overall percentage of subjects with EPS-related adverse events	10	12	11	11
Parkinsonism <sup>a</sup>	5	6	6	4
Hyperkinesia <sup>b</sup>	2	2	2	4
Tremor	3	2	2	3
Dyskinesia <sup>c</sup>	1	2	3	1
Dystonia <sup>d</sup>	0	1	1	2

a: Parkinsonism group includes: Extrapyramidal disorder, hypertonia, musculoskeletal stiffness, parkinsonism, drooling, masked facies, muscle tightness, hypokinesia

b: Hyperkinesia group includes: Akathisia, restless legs syndrome, restlessness

c: Dyskinesia group includes: Dyskinesia, choreoathetosis, muscle twitching, myoclonus, tardive dyskinesia

d: Dystonia group includes: Dystonia, muscle spasms

The results across all phases of the long-term recurrence prevention trial exhibited comparable findings. In the 9-week, fixed-dose, double-blind, placebo-controlled trial (R092670-SCH-201) the proportions of Parkinsonism and akathisia assessed by incidence of rating scales were higher in the INVEGA SUSTENNA® 100 mg group (18% and 11%, respectively) than in the INVEGA SUSTENNA® 50 mg group (9% and 5%, respectively) and placebo group (7% and 4%, respectively).

In the 13-week study (R092670-PSY-3007) involving 150 mg initiation dosing, the incidence of any treatment-emergent EPS-related adverse events was similar to that of the placebo group (8%), but exhibited a dose-related pattern with 6%, 10%, and 11% in the INVEGA SUSTENNA® 150/25 mg, 150/100 mg, and 150/150 mg groups, respectively. Hyperkinesia was the most frequent category of EPS-related adverse events in this study, and was reported at a similar rate between the placebo (4.9%) and INVEGA SUSTENNA® 150/100 mg (4.8%) and 150/150 mg (5.5%) groups, but at a lower rate in the 150/25 mg group (1.3%).

## Dystonia

**Class Effect:** Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

## Laboratory Test Abnormalities

In the pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials (R092670-PSY-3003, R092670-PSY-3004), a between-group comparison revealed no medically important differences between INVEGA SUSTENNA® and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no differences between INVEGA SUSTENNA® and placebo in the incidence of discontinuations due to changes in hematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements. However, INVEGA SUSTENNA® was associated with increases in serum prolactin (see **PRECAUTIONS** – Hyperprolactinemia). The results from the 13-week study involving 150 mg initiation dosing (R092670-PSY-3007), the 9-week, fixed-dose, double-blind, placebo-controlled trial (R092670-SCH-201) and the double-blind phase of the recurrence prevention trial (R092670-PSY-3001) exhibited comparable findings.

## Pain Assessment and Local Injection Site Reactions

In the pooled data from the two 13-week, fixed-dose, double-blind, placebo-controlled trials (R092670-PSY-3003, R092670-PSY-3004), the mean intensity of injection pain reported by subjects using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 10.9 to 9.8; 25 mg: 10.3 to 7.7; 50 mg: 10.0 to 9.2; 100 mg: 11.1 to 8.8). The results from both the 9-week, fixed-dose, double-blind, placebo-controlled trial and the double-blind phase of the recurrence prevention trial exhibited comparable findings.

In the 13-week study (R092670-PSY-3007) involving 150 mg initiation dosing, occurrences of induration, redness, or swelling, as assessed by blinded study personnel, were infrequent, generally mild, decreased over time, and similar in incidence between the INVEGA SUSTENNA<sup>®</sup> and placebo groups. Investigator ratings of injection pain were similar for the placebo and INVEGA SUSTENNA<sup>®</sup> groups. Investigator evaluations of the injection site after the first injection for redness, swelling, induration, and pain were rated as absent for 69-100% of subjects in both the INVEGA SUSTENNA<sup>®</sup> and placebo groups. At Day 92, investigators rated absence of redness, swelling, induration, and pain in 95-100% of subjects in both the INVEGA SUSTENNA<sup>®</sup> and placebo groups.

## Adverse Reactions Reported in Clinical Trials with Oral Paliperidone

The following is a list of additional adverse reactions that have been reported in clinical trials with oral paliperidone:

Cardiac disorders:	bundle branch block left, sinus arrhythmia
Gastrointestinal disorders:	abdominal pain, flatulence, small intestinal obstruction
General disorders and administration site conditions:	edema, edema peripheral
Immune system disorders:	anaphylactic reaction
Infections and infestations:	rhinitis
Musculoskeletal and connective tissue disorders:	arthralgia, musculoskeletal pain, torticollis, trismus
Nervous system disorders:	cogwheel rigidity, grand mal convulsion, parkinsonian gait, transient ischemic attack
Psychiatric disorders:	sleep disorder
Reproductive system and breast disorders:	breast engorgement, breast tenderness/breast pain, retrograde ejaculation
Respiratory, thoracic and mediastinal disorders:	nasal congestion, pharyngolaryngeal pain, pneumonia aspiration
Skin and subcutaneous tissue disorders:	rash papular
Vascular disorders:	hypotension, ischemia

## Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of paliperidone; because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency: angioedema, priapism, swollen tongue, urinary incontinence, urinary retention.

## Adverse Events Reported With Risperidone

Paliperidone is the major active metabolite of risperidone. Adverse events reported with oral risperidone long-acting injection can be found in the ADVERSE EFFECTS section of the Product Information for those products.

## DOSAGE AND ADMINISTRATION

### Use with Oral Paliperidone or with Risperidone

Concomitant use of INVEGA SUSTENNA<sup>®</sup> with oral paliperidone or oral or injectable risperidone has not been studied. Since paliperidone is the major active metabolite of risperidone, consideration should be given to the additive paliperidone exposure if any of these medications are coadministered with INVEGA SUSTENNA<sup>®</sup>.

### Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching from other antipsychotics to INVEGA SUSTENNA<sup>®</sup>, or concerning concomitant administration with other antipsychotics.

#### Switching from Oral Antipsychotics:

For patients who have never taken oral paliperidone or oral or injectable risperidone, it is recommended to establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA<sup>®</sup>. Previous oral antipsychotics can be discontinued at the time of initiation of treatment with INVEGA SUSTENNA<sup>®</sup> (see, **DOSAGE AND ADMINISTRATION - Recommended Dosing**)

#### Switching from Long-Acting Injectable Antipsychotics:

When switching patients from previous long-acting injectable antipsychotics, initiate INVEGA SUSTENNA<sup>®</sup> therapy in place of the next scheduled injection. INVEGA SUSTENNA<sup>®</sup> should then be continued at monthly intervals. The one-week initiation dosing regimen as described under **DOSAGE AND ADMINISTRATION – Recommended Dosing** is not required.

Patients previously stabilised on different doses of RISPERDAL CONSTA prolonged release suspension for intramuscular injection can attain similar paliperidone steady-state exposure during maintenance treatment with INVEGA SUSTENNA<sup>®</sup> monthly doses according to the following:

#### **Doses of RISPERDAL CONSTA and INVEGA SUSTENNA<sup>®</sup> needed to attain similar paliperidone exposure at steady-state**

Previous RISPERDAL CONSTA Dose	INVEGA SUSTENNA <sup>®</sup> Injection
25 mg every 2 weeks	50 mg monthly
37.5 mg every 2 weeks	75 mg monthly
50 mg every 2 weeks	100 mg monthly

Note: This recommended dosing for switch from RISPERDAL CONSTA to INVEGA SUSTENNA<sup>®</sup> is derived from pharmacokinetic modeling.

If INVEGA SUSTENNA<sup>®</sup> is discontinued, its prolonged-release characteristics must be considered. As recommended with other antipsychotic medications, the need for continuing existing extrapyramidal symptoms (EPS) medication should be re-evaluated periodically.

### Recommended Dosing

For patients who have never taken oral paliperidone or oral or injectable risperidone, it is recommended to establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA SUSTENNA®.

Recommended initiation of INVEGA SUSTENNA® is with a dose of 150 mg on treatment day 1 and 100 mg one week later (day 8), both administered in the deltoid muscle. The recommended subsequent monthly dose is 75 mg; this can be increased or decreased in the range of 25 to 150 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.

Adjustment of the maintenance dose may be made monthly. When making dose adjustments, the prolonged-release characteristics of INVEGA SUSTENNA® should be considered (see **PHARMACOLOGY** – Pharmacokinetics), as the full effect of the dose adjustment may not be evident for several months.

## Dosage in Special Populations

### Renal Impairment

INVEGA SUSTENNA® has not been systematically studied in patients with renal impairment (see **PHARMACOLOGY** – Pharmacokinetics). For patients with mild renal impairment (creatinine clearance  $\geq 50$  mL/min to  $< 80$  mL/min), recommended initiation of INVEGA SUSTENNA® is with a dose of 100 mg on treatment day 1 and 75 mg one week later, both administered in the deltoid muscle. Thereafter, follow with monthly injections of 50 mg in either the deltoid or gluteal muscle.

INVEGA SUSTENNA® is not recommended in patients with moderate or severe renal impairment (creatinine clearance  $< 50$  ml/min).

### Hepatic Impairment

INVEGA SUSTENNA® has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment (see **PHARMACOLOGY** – Pharmacokinetics).

### Elderly

In general, recommended dosing of INVEGA SUSTENNA® for elderly patients with normal renal function is the same as for younger adult patients with normal renal function. As elderly patients may have reduced renal function, see Renal Impairment above for dosing recommendations in patients with renal impairment.

## Maintenance Therapy

INVEGA SUSTENNA® has been shown to be effective in delaying time to recurrence of symptoms of schizophrenia in long-term use. It is recommended that responding patients be continued on treatment at the lowest dose needed. Patients should be periodically reassessed to determine the need for continued treatment.

## Missed Doses

### Avoiding Missed Doses

It is recommended that the second initiation dose of INVEGA SUSTENNA® 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 (day 8) timepoint. 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 timepoint.

### Missed Dose (1 Month to 6 Weeks)

After initiation, the recommended injection cycle of INVEGA SUSTENNA® is monthly. If less than 6 weeks have elapsed since the last injection, then the previously stabilized dose should be administered as soon as possible, followed by injections at monthly intervals.

#### Missed Dose (> 6 Weeks to 6 Months)

If more than 6 weeks have elapsed since the last injection of INVEGA SUSTENNA®, **resume the same dose the patient was previously stabilized on (unless the patient was stabilized on a dose of 150 mg, then the first two injections should each be 100 mg)** in the following manner: 1) a deltoid injection as soon as practically possible, followed by 2) another deltoid injection (same dose) one week later, and 3) resumption of either deltoid or gluteal dosing at monthly intervals.

#### Missed Dose (> 6 Months)

If more than 6 months have elapsed since the last injection of INVEGA SUSTENNA®, initiate dosing as described above - see **DOSAGE AND ADMINISTRATION - Recommended Dosing**.

### Administration Instructions

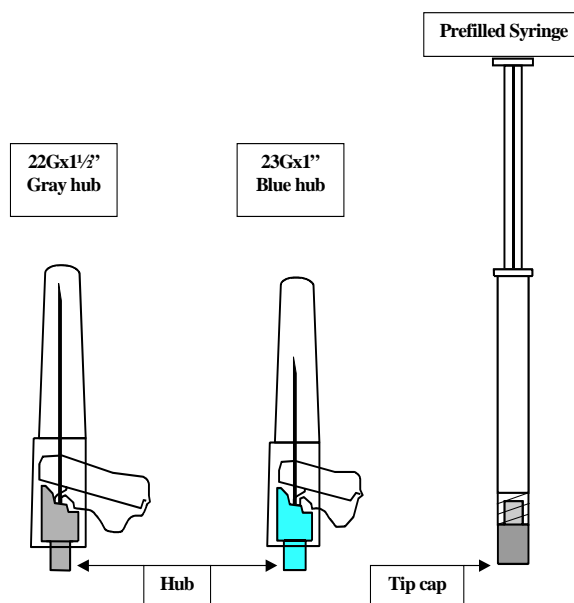
INVEGA SUSTENNA® is intended for intramuscular use only. Inject slowly, deep into the muscle. Care should be taken to avoid inadvertent injection into a blood vessel. Each injection should be administered by a health care professional. Administration should be in a single injection. Do not administer the dose in divided injections. Do not administer intravascularly or subcutaneously.

The recommended needle size for administration of INVEGA SUSTENNA® into the deltoid muscle is determined by the patient's weight. For those  $\geq 90$  kg ( $\geq 200$  lb), the 1½ inch, 22-gauge needle is recommended. For those  $< 90$  kg ( $< 200$  lb), the 1-inch, 23 gauge needle is recommended. Deltoid injections should be alternated between the two deltoid muscles.

The recommended needle size for administration of INVEGA SUSTENNA® into the gluteal muscle is the 1½-inch, 22 gauge needle. Administration should be made into the upper-outer quadrant of the gluteal area. Gluteal injections should be alternated between the two gluteal muscles.

### Instructions for Use

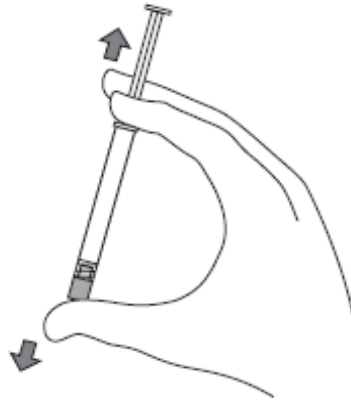
The kit contains a prefilled syringe and 2 safety needles (a 1½-inch 22 gauge needle and a 1-inch 23 gauge needle) for intramuscular injection.





INVEGA SUSTENNA® is for single use only.

1. Shake the syringe vigorously for a minimum of 10 seconds to ensure a homogeneous suspension.

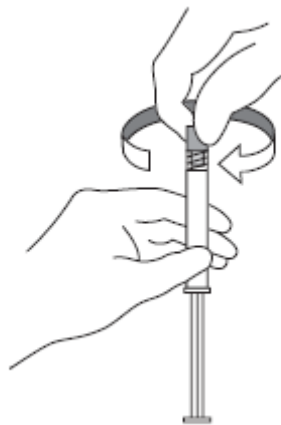


2. Select the appropriate needle.

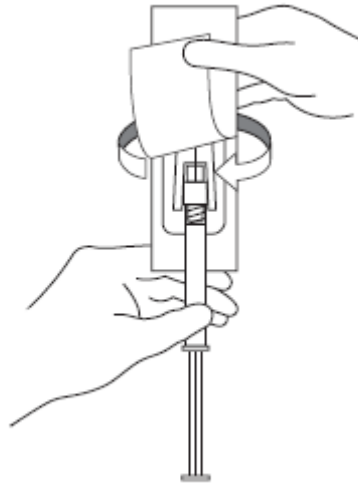
For DELTOID injection, if the patient weighs < 90 kg (< 200 lb), use the 1-inch **23** gauge needle (needle with **blue** colored hub); if the patient weighs ≥ 90 kg (≥ 200 lb), use the 1 ½-inch **22** gauge needle (needle with **gray** colored hub).

For GLUTEAL injection, use the 1 ½-inch **22** gauge needle (needle with **gray** colored hub).

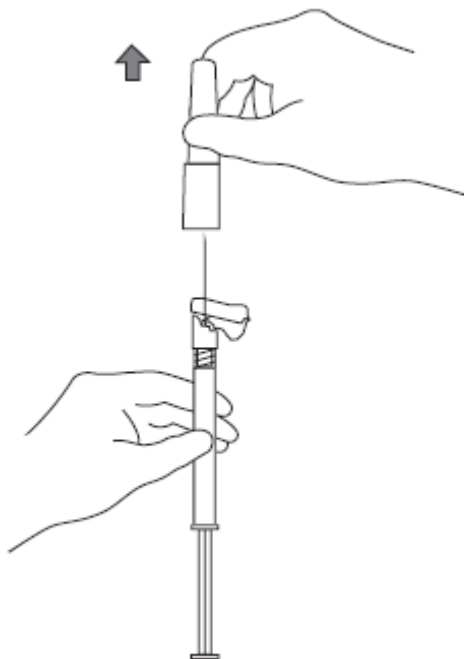
3. While holding the syringe upright, remove the rubber tip cap with an easy clockwise twisting motion.



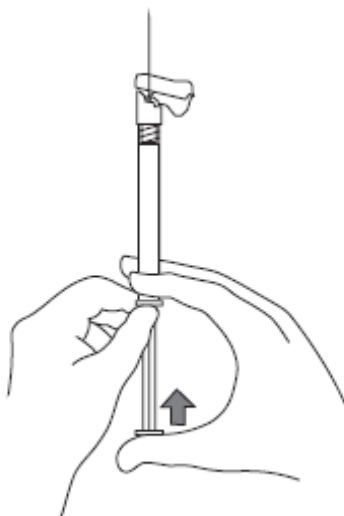
4. Peel the safety needle pouch half way open. Grasp the needle sheath using the plastic peel pouch. Attach the safety needle to the luer connection of the syringe with an easy clockwise twisting motion.



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.

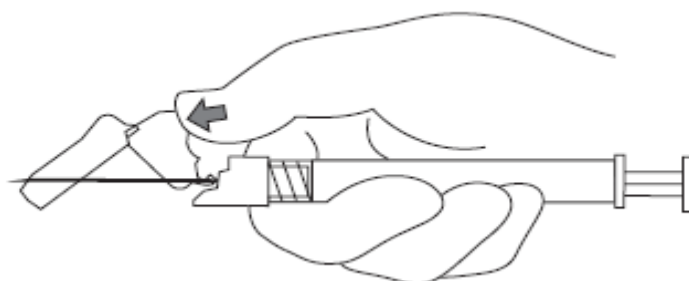


6. Bring the syringe with the attached needle in upright position to de-aerate. De-aerate the syringe by moving the plunger rod carefully forward.

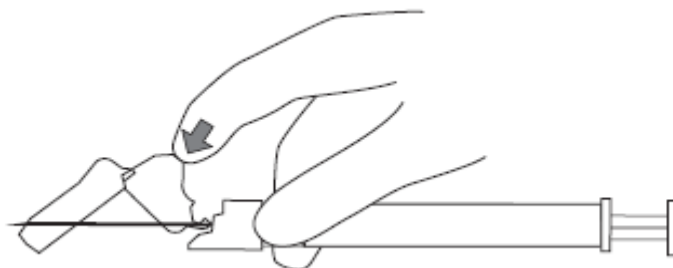


7. Inject the entire contents intramuscularly into the selected deltoid or gluteal muscle of the patient. **Do not administer intravascularly or subcutaneously.**
8. After the injection is complete, use either thumb or finger of one hand (8a, 8b) or a flat surface (8c) to activate the needle protection system. The needle protection system is fully activated when a 'click' is heard. Discard the syringe with needle appropriately.

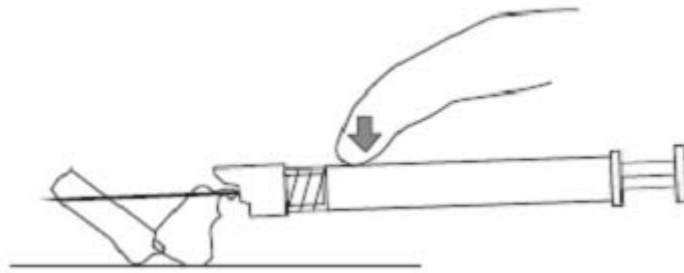
8a



8b



8c



## OVERDOSAGE

No cases of overdose were reported in premarketing studies with INVEGA SUSTENNA<sup>®</sup>. Because INVEGA SUSTENNA<sup>®</sup> is to be administered by health care professionals, the potential for overdose by patients is low.

While experience with paliperidone overdose is limited, among the few cases of overdose reported in premarketing trials with oral paliperidone, the highest estimated ingestion was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and QT prolongation. Torsade de pointes and ventricular fibrillation have been reported in a patient in the setting of overdose with oral paliperidone.

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the OVERDOSAGE section of the risperidone Product Information.

### Management of Overdosage

There is no specific antidote to paliperidone, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consideration should be given to the prolonged-release characteristics of INVEGA SUSTENNA<sup>®</sup> and the long apparent half-life of paliperidone when assessing treatment needs and recovery. Multiple drug involvement should also be considered.

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of paliperidone. Similarly the alpha-blocking properties of bretylium might be additive to those of paliperidone, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of paliperidone-induced alpha

blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

## **PRESENTATION AND STORAGE CONDITIONS**

INVEGA SUSTENNA<sup>®</sup> is available in dosage strengths equivalent to 25 mg, 50 mg, 75 mg, 100 mg and 150 mg paliperidone (as palmitate).

INVEGA SUSTENNA<sup>®</sup> is provided in a pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper and tip cap (bromobutyl rubber). The kit contains 2 safety needles (a 1 ½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle).

Store at room temperature (25°C). Excursions between 15 and 30°C are permitted.

## **POISON SCHEDULE**

S4 - Prescription Only Medicine

## **SPONSOR**

Janssen-Cilag Pty Ltd  
1-5 Khartoum Road, North Ryde, NSW, 2113, AUSTRALIA

New Zealand Office:  
Janssen-Cilag (New Zealand) Ltd  
Ground Floor, 105 Carlton Gore Road, Newmarket  
Auckland, NEW ZEALAND

Date of TGA approval: 20 July 2010

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia

Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605

**[www.tga.gov.au](http://www.tga.gov.au)**