
INVEGA SUSTENNA[®]

Paliperidone palmitate

AUSTRALIAN PRODUCT INFORMATION

1. NAME OF THE MEDICINE

Paliperidone palmitate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient, paliperidone palmitate, is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. INVEGA SUSTENNA contains a racemic mixture of (+)- and (-)-paliperidone palmitate. INVEGA SUSTENNA is available in dose strengths of 25 mg, 50 mg, 75 mg, 100 mg and 150 mg paliperidone (as palmitate).

For the full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

INVEGA SUSTENNA is available as a white to off-white sterile modified release aqueous suspension for intramuscular injection.

INVEGA SUSTENNA paliperidone (as palmitate) 25 mg modified release injection pre-filled syringe: Each 0.25 mL prefilled syringe contains 25 mg of paliperidone as 39 mg paliperidone palmitate.

INVEGA SUSTENNA paliperidone (as palmitate) 50 mg modified release injection pre-filled syringe: Each 0.5 mL prefilled syringe contains 50 mg of paliperidone as 78 mg paliperidone palmitate.

INVEGA SUSTENNA paliperidone (as palmitate) 75 mg modified release injection pre-filled syringe: Each 0.75 mL prefilled syringe contains 75 mg of paliperidone as 117 mg paliperidone palmitate.

INVEGA SUSTENNA paliperidone (as palmitate) 100 mg modified release injection pre-filled syringe: Each 1.0 mL prefilled syringe contains 100 mg of paliperidone as 156 mg paliperidone palmitate.

INVEGA SUSTENNA paliperidone (as palmitate) 150 mg modified release injection pre-filled syringe: Each 1.5 mL prefilled syringe contains 150 mg of paliperidone as 234 mg paliperidone palmitate.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

INVEGA SUSTENNA is indicated for the acute and maintenance treatment of schizophrenia in adults.

4.2 DOSE AND METHOD OF ADMINISTRATION

Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to INVEGA SUSTENNA 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. Previous oral antipsychotics can be gradually discontinued at the time of initiation of treatment with INVEGA SUSTENNA. INVEGA SUSTENNA should be initiated as described under section 4.2 Dose and Method of Administration - Recommended Dosing.

Switching from Long-Acting Injectable Antipsychotics

When switching patients currently at steady-state on a long-acting injectable antipsychotic, initiate INVEGA SUSTENNA therapy in place of the next scheduled injection. INVEGA SUSTENNA should then be continued at monthly intervals. The one-week initiation dosing regimen as described under section 4.2 Dose and Method of 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 monthly doses according to the following:

Doses of RISPERDAL CONSTA and INVEGA SUSTENNA needed to attain similar paliperidone exposure at steady-state

Previous RISPERDAL CONSTA Dose	INVEGA SUSTENNA 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 is derived from pharmacokinetic modeling.

Discontinuation of the previous antipsychotic should be made in accordance with the appropriate prescribing information. If INVEGA SUSTENNA 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 monthly maintenance dose is 75 mg; some patients may benefit from lower or higher doses within the recommended range of 25 to 150 mg based on individual patient tolerability and/or efficacy. Following the second initiation dose, monthly maintenance 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 section 5.2 Pharmacokinetic Properties), 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 section 5.2 Pharmacokinetic Properties). 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, adjusted within the range of 25 to 100 mg based on patient tolerability and/or efficacy.

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 **5.2 PHARMACOKINETIC PROPERTIES**).

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 4 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.

If the target date for the second INVEGA SUSTENNA injection (one week \pm 4 days) is missed, the recommended reinitiation depends on the length of time which has elapsed since the patient's first injection.

Missed second initiation dose (< 4 weeks from first injection)

If less than 4 weeks have elapsed since the first injection, then the patient should be administered the second injection of 100 mg in the deltoid muscle as soon as possible. A third INVEGA SUSTENNA injection of 75 mg in either the deltoid or gluteal muscles should be administered 5 weeks after the first injection (regardless of the timing of the second injection). The normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy should be followed thereafter.

Missed second initiation dose (4-7 weeks from first injection)

If 4 to 7 weeks have elapsed since the first injection of INVEGA SUSTENNA, resume dosing with two injections of 100 mg in the following manner: a deltoid injection as soon as possible followed by another deltoid injection one week later, then resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy.

Missed second initiation dose (> 7 weeks from first injection)

If more than 7 weeks have elapsed since the first injection of INVEGA SUSTENNA, initiate dosing as described for the initial recommended initiation of INVEGA SUSTENNA above - see 4.2 DOSE AND METHOD OF ADMINISTRATION – RECOMMENDED DOSING.

Missed Maintenance 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 stabilised dose should be administered as soon as possible, followed by injections at monthly intervals.

Missed Maintenance Dose (> 6 Weeks to 6 Months)

If more than 6 weeks have elapsed since the last injection of INVEGA SUSTENNA, the recommendation is as follows:

For patients stabilised with doses of 25 to 100 mg:

1. A deltoid injection as soon as possible at the same dose the patient was previously stabilised on.
2. Another deltoid injection (same dose) one week later (day 8).
3. Resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy.

For patients stabilised with 150 mg:

1. A deltoid injection as soon as possible at the 100 mg dose.
2. Another deltoid injection one week later (day 8) at the 100 mg dose.
3. Resumption of the normal monthly cycle of injections in either the deltoid or gluteal muscle of 25 mg to 150 mg based on individual patient tolerability and/or efficacy.

Missed Maintenance Dose (> 6 Months)

If more than 6 months have elapsed since the last injection of INVEGA SUSTENNA, initiate dosing as described above - see section 4.2 Dose and Method of Administration – Recommended Dosing.

Administration Instructions

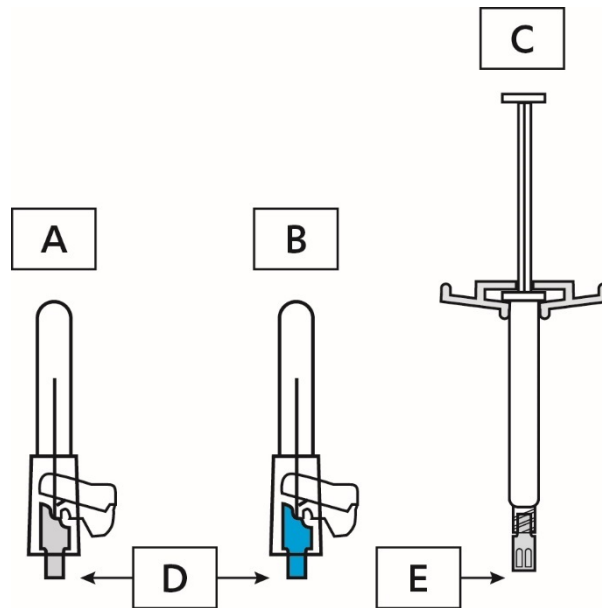
INVEGA SUSTENNA is intended for intramuscular use only. Inject slowly, deep into the muscle. Care should be taken to avoid inadvertent injection into a blood vessel. Each injection should be administered by a health care professional. Administration should be in a single injection. Do not administer 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 ≥ 90 kg (≥ 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

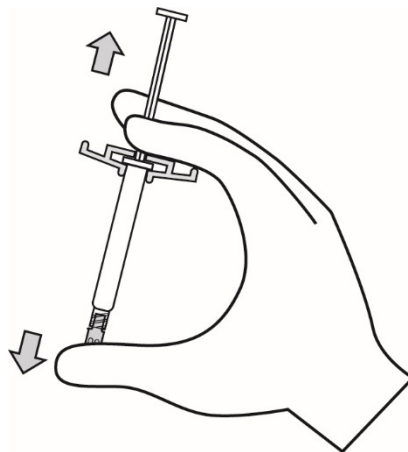
The kit contains a prefilled syringe with backstop and 2 safety needles (a 1½-inch 22-gauge needle and a 1-inch 23-gauge needle) for intramuscular injection.



**A-22Gx1½" Gray hub; B-23Gx1" Blue hub; C-Prefilled Syringe
D-Hub; E-Tip cap**

INVEGA SUSTENNA is for single use only.

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

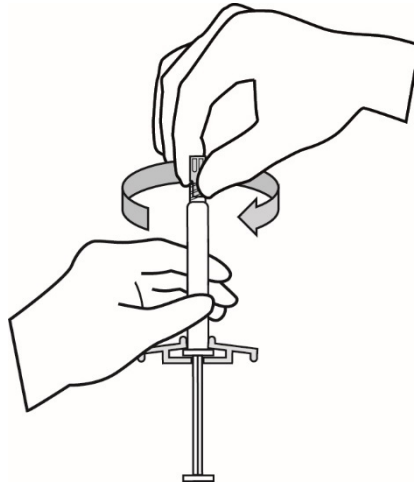


2. Select the appropriate needle.

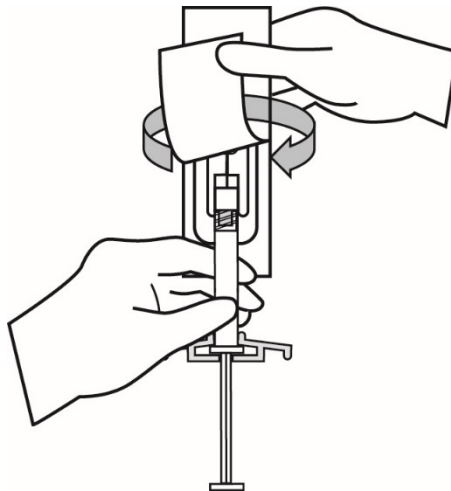
For DELTOID injection, if the patient weighs < 90 kg (< 200 lb), use the 1-inch **23**-gauge needle (needle with **blue** coloured hub); if the patient weighs ≥ 90 kg (≥ 200 lb), use the 1 ½-inch **22**-gauge needle (needle with **gray** coloured hub).

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

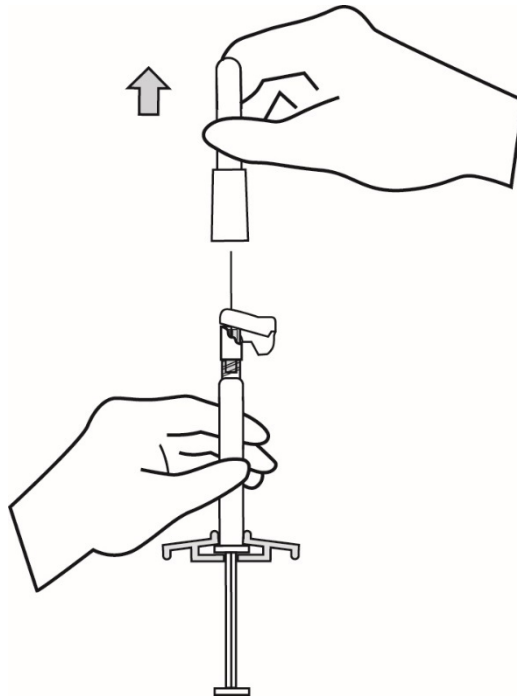
3. While holding the syringe upright, remove the rubber tip cap with an easy clockwise twisting motion.



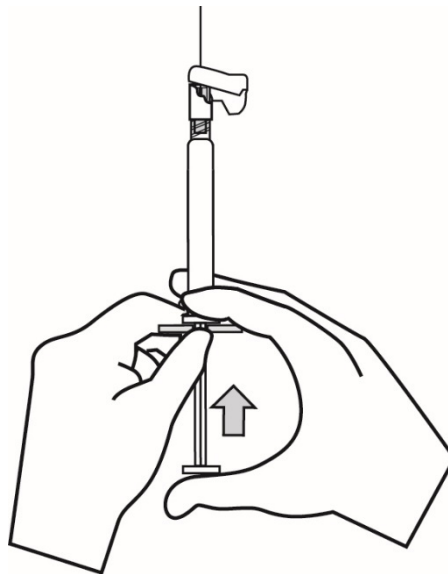
4. Peel the safety needle pouch half way open. Grasp the needle sheath using the plastic peel pouch. Attach the safety needle to the luer connection of the syringe with an easy clockwise twisting motion.



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.

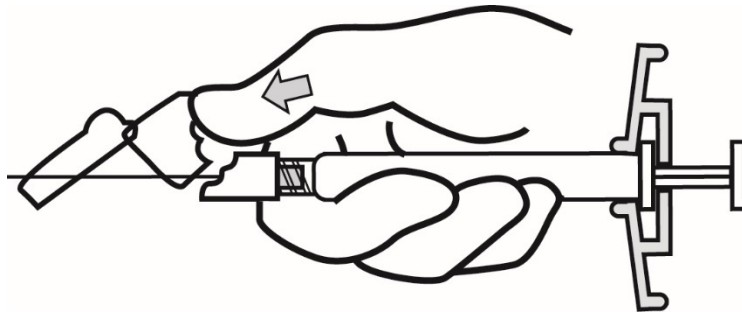


6. Bring the syringe with the attached needle in upright position to de-aerate. De-aerate the syringe by moving the plunger rod carefully forward.

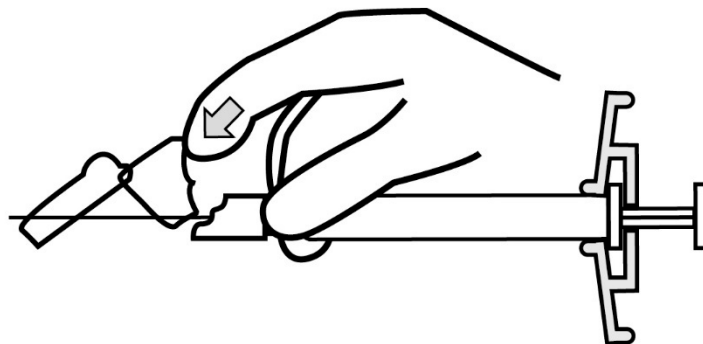


7. Inject the entire contents intramuscularly slowly, deep into the selected deltoid or gluteal muscle of the patient. Do not administer intravascularly or subcutaneously.
8. After the injection is complete, use either thumb or finger of one hand (8a, 8b) or a flat surface (8c) to activate the needle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

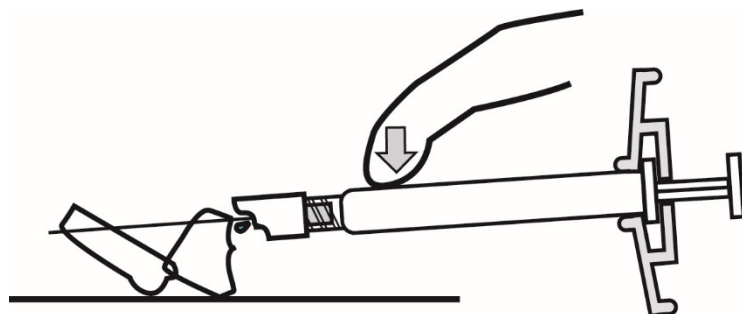
8a



8b



8c



4.3 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 formulation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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) hypokalaemia or hypomagnesaemia; (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), multicentre 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 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, 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, rhythmical movements, including those of the tongue and/or face, 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 should be prescribed in a manner that is most likely to minimise 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, drug discontinuation should be considered. However, some patients may require treatment with INVEGA SUSTENNA despite the presence of the syndrome.

Extrapyramidal symptoms

As with other antipsychotics, EPS including akathisia have been reported (see section 4.8 Adverse Effects (Undesirable Effects)). The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular attention should be paid to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

Extrapyramidal symptoms and psychostimulants

Caution is warranted in patients receiving both psychostimulants (e.g. methylphenidate) and paliperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of one or both treatments should be considered. (see section 4.5 Interactions with Other Medicines and Other Interactions).

Hypersensitivity reactions

Although tolerability with oral paliperidone or risperidone should be established prior to initiating treatment with INVEGA SUSTENNA, very rare cases of anaphylactic reactions have been reported during post-marketing experience in patients who have previously tolerated oral risperidone or oral paliperidone (see Sections 4.2 Dose and Method of Administration and 4.8 Adverse Effects (Undesirable Effects)).

If hypersensitivity reactions occur, discontinue use of INVEGA SUSTENNA; initiate general supportive measures as clinically appropriate and monitor the patient until signs and symptoms resolve. (See sections 4.3 Contraindications and 4.8 Adverse Effects (Undesirable Effects)).

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia, 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 hyperglycaemia or diabetes in trial subjects treated with INVEGA SUSTENNA. 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 hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Because INVEGA SUSTENNA was not marketed at the time these studies were performed, it is not known if INVEGA SUSTENNA 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 hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia 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 and other atypical antipsychotics. Clinical monitoring of weight is recommended. 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 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 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 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-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-treated subjects compared with 3% of placebo-treated subjects; the mean weight change from double-blind baseline was +0.5 kg for INVEGA SUSTENNA 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%.

Alcohol

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

Hyperprolactinaemia

Like other drugs that antagonise dopamine D₂ 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.

Hyperprolactinaemia, regardless of aetiology, 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. Galactorrhoea, amenorrhoea, gynaecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinaemia 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 section 5.3 Preclinical Safety Data). 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 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-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 should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischaemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolaemia, 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 post-marketing 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/mm³) should discontinue INVEGA SUSTENNA and have their WBC followed until recovery.

Venous Thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with INVEGA SUSTENNA and preventative measures undertaken.

Potential for Cognitive and Motor Impairment

Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA SUSTENNA (see section 4.8 Adverse Effects (Undesirable 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

Oesophageal 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. Priapism has been reported with oral paliperidone during post-marketing 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. 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 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 is intended for intramuscular injection, and care must be taken to avoid inadvertent injection into a blood vessel (see section 4.2 Dose and Method of Administration).

Intraoperative Floppy Iris Syndrome

Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, such as INVEGA SUSTENNA (see section 4.8 Adverse Effects (Undesirable Effects)).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

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 tumour.

Use in Patients with Concomitant Illness

Clinical experience with INVEGA SUSTENNA 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 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, caution should be observed in patients with known cardiovascular disease (see section 4.4 Special Warnings and Precautions for Use).

Monitoring: Laboratory Tests

No specific laboratory tests are recommended.

Use in 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.

Use in renal impairment

INVEGA SUSTENNA has not been systematically studied in patients with renal impairment (see section 5 Pharmacological Properties). A reduced dose is recommended in patients with mild renal impairment; INVEGA SUSTENNA is not recommended in patients with moderate or severe renal impairment (see section 4.2 Dose and Method of Administration).

Use in the elderly

Clinical studies of INVEGA SUSTENNA 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 section 5 Pharmacological Properties), 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 section 4.2 Dose and Method of 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 (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 were not marketed at the time these studies were performed and are not approved for the treatment of patients with dementia-related psychosis.

Paediatric Use

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

In a 7-week oral toxicity study in juvenile rats with paliperidone at doses of 0.16, 0.63, and 2.5 mg/kg/day, no effects on growth, sexual maturation or reproductive performance were observed. Doses up to 2.5 mg/kg/day did not affect neurobehavioral development, except for an impairment of learning and memory in females treated at 2.5 mg/kg/day, which was not observed after discontinuation of treatment. Respective exposures (plasma AUC) at these doses were 0.1, 0.4, and 1.3 times exposure in adolescents at the maximal recommended dose (12mg/day).

A 39-day oral toxicity study with risperidone (which is extensively converted to paliperidone) in juvenile rats noted increased pup mortality, a delay in physical development and, in a small proportion of animals, impairment of auditory startle, at exposures (plasma AUC) less than that at the maximum recommended paediatric risperidone dose (6 mg/day).

The clinical relevance of these findings for adolescents is uncertain, given the relative immaturity of the rat pups upon commencement of treatment.

A 40-week oral toxicity study with risperidone (which is extensively converted to paliperidone) in juvenile dogs noted delayed sexual maturation, probably secondary to hormonal changes. Long bone growth was slightly reduced at exposures (plasma AUC) of 3-fold and greater than those at the maximum dose in children and adolescents (6 mg/day); exposure at the no-effect dose was similar to human exposure.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Since paliperidone palmitate is hydrolysed to paliperidone (see section 5 Pharmacological Properties) results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

Concomitant use of INVEGA SUSTENNA with risperidone or with oral paliperidone

Paliperidone is the major active metabolite of risperidone. The co-administration of INVEGA SUSTENNA with oral risperidone or paliperidone is likely to result in an increase in the paliperidone concentration, within the bloodstream. Caution should be taken when INVEGA SUSTENNA is co-administered with risperidone or with oral paliperidone for extended periods of time.

Safety data involving concomitant use of INVEGA SUSTENNA with other antipsychotics are limited.

Concomitant use of INVEGA SUSTENNA with psychostimulants

The combined use of psychostimulants (e.g. methylphenidate) with paliperidone can lead to the emergence of extrapyramidal symptoms upon change of either or both treatments (see section 4.4 Special Warnings and Precautions for Use).

Potential for INVEGA SUSTENNA to Affect Other Drugs

Given the primary CNS effects of paliperidone (see section 4.8 Adverse Effects (Undesirable Effects)), INVEGA SUSTENNA should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonise 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 is administered with other therapeutic agents that have this potential (see section 4.4 Special Warnings and Precautions for Use).

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolised by cytochrome P450 isozymes. In vitro studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolised 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 metabolised 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.

Co-administration of oral paliperidone extended-release tablets at steady-state (12 mg once daily) with divalproex sodium extended-release tablets (500 mg to 2000 mg once daily) did not affect the steady-state pharmacokinetics of valproate.

Pharmacokinetic interaction between INVEGA SUSTENNA and lithium is unlikely.

Potential for Other Drugs to Affect INVEGA SUSTENNA

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 should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA SUSTENNA should be re-evaluated and decreased if necessary.

Paliperidone is metabolised to a limited extent by CYP2D6 (see section 5.2 PHARMACOKINETIC PROPERTIES). 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 metabolisers. 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, a clinically significant interaction would not be

expected between divalproex sodium and INVEGA SUSTENNA intramuscular injection. This interaction has not been studied with INVEGA SUSTENNA.

Pharmacokinetic interaction between lithium and INVEGA SUSTENNA is unlikely.

4.6 FERTILITY, PREGNANCY AND LACTATION

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/m²)). 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/m² 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/m² 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 C

The safety of INVEGA SUSTENNA during human pregnancy has not been established.

A retrospective observational cohort study based on a US claims database compared the risk of congenital malformations for live births among women with and without antipsychotic use during the first trimester of pregnancy. Paliperidone, the active metabolite of risperidone, was not specifically evaluated in this study. The risk of congenital malformations with risperidone, after adjusting for confounder variables available in the database, was elevated compared to no antipsychotic exposure (relative risk=1.26, 95% CI: 1.02-1.56). No biological mechanism has been identified to explain these findings and teratogenic effects have not been observed in non-clinical studies.

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/m² basis.

Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (including INVEGA SUSTENNA®) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited; in other cases, neonates have required additional medical treatment or monitoring.

INVEGA SUSTENNA® should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

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/m² 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/m² 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/m² 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/m² 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.

4.7 EFFECTS OF ABILITY TO DRIVE AND OPERATE MACHINES

As INVEGA SUSTENNA 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 therapy does not affect them adversely (see section 4.4 Special Warnings and Precautions for Use).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

The most common adverse reactions (reported by $\geq 5\%$ in any INVEGA SUSTENNA 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-treated subjects) (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE 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 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-treated subjects, 1293 received INVEGA SUSTENNA in four fixed-dose, double-blind, placebo-controlled trials (one 9-week and three 13-week studies), 849 received INVEGA SUSTENNA in the long-term recurrence prevention trial (of whom 205 continued to receive INVEGA SUSTENNA during the double-blind placebo-controlled phase of this study), and 1675 received INVEGA SUSTENNA 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 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 standardised 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 (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for INVEGA SUSTENNA 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-treated subjects with schizophrenia in the four fixed-dose, double-blind, placebo-controlled trials.

System/Organ Class Adverse Reaction	INVEGA SUSTENNA						
	Placebo ^a (N=510)	25 mg (N=130)	50 mg (N=302)	100 mg (N=312)	150/25 mg ^b (N=160)	150/100 mg ^b (N=165)	150/150 mg ^b (N=163)
Total percentage of subjects with adverse reaction	70	75	68	69	63	60	63
Gastrointestinal disorders							
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
General disorders and administration site conditions							
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
Infections and infestations							
Nasopharyngitis	2	0	2	2	4	2	2
Upper respiratory tract infection	2	2	2	2	1	2	4
Urinary tract infection	1	0	1	<1	1	1	2
Injury, poisoning and procedural complications							
Skin laceration	<1	2	<1	0	1	0	0
Investigations							
Alanine aminotransferase increased	2	0	2	1	1	1	1
Weight increased	1	4	4	1	1	1	2
Musculoskeletal and connective tissue disorders							
Back pain	2	2	1	3	1	1	1
Musculoskeletal stiffness	1	1	<1	<1	1	1	2
Myalgia	1	2	1	<1	1	0	2
Pain in extremity	1	0	2	2	2	3	0
Nervous system disorders							
Akathisia	3	2	2	3	1	5	6
Dizziness	1	6	2	4	1	4	2
Extrapyramidal disorder	1	5	2	3	1	0	0
Headache	12	11	11	15	11	7	6
Somnolence/sedation	3	5	7	4	1	5	5
Psychiatric disorders							
Agitation	7	10	5	9	8	5	4
Anxiety	7	8	5	3	5	6	6
Insomnia	15	15	15	13	12	10	13
Nightmare	<1	2	0	0	0	0	0
Suicidal ideation	2	0	1	2	2	2	1
Respiratory, thoracic and mediastinal disorders							
Cough	1	2	3	1	0	1	1
Vascular disorders							
Hypertension	1	2	1	1	1	1	0

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.

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

^b 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.

System/Organ Class Adverse Reaction	Placebo ^a (N=510)	25 mg (N=130)	50 mg (N=302)	INVEGA SUSTENNA			
				100 mg (N=312)	150/25 mg ^b (N=160)	150/100 mg ^b (N=165)	150/150 mg ^b (N=163)
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".							

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- 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, only akathisia, increased with dose. Hyperprolactinaemia also exhibited a dose relationship, but did not occur at $\geq 2\%$ incidence in INVEGA SUSTENNA-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 ≥ 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 2), and (5) incidence of spontaneous reports of EPS (Table 3).

Scale	Percentage of Subjects			
	Placebo (N=262)	25 mg (N=130)	50 mg (N=223)	100 mg (N=228)
Parkinsonism ^a	9	12	10	6
Akathisia ^b	5	5	6	5
Dyskinesia ^c	3	4	6	4
Use of Anticholinergic Medications ^d	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 ≥ 2 at endpoint
c: For Dyskinesia, percent of subjects with a score ≥ 3 on any of the first 7 items or a score ≥ 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 3. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term				
EPS Group	Percentage of Subjects			
	INVEGA SUSTENNA			
	Placebo (N=262)	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 ^a	5	6	6	4
Hyperkinesia ^b	2	2	2	4
Tremor	3	2	2	3
Dyskinesia ^c	1	2	3	1
Dystonia ^d	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, haematology, or urinalysis parameters. Similarly, there were no differences between INVEGA SUSTENNA and placebo in the incidence of discontinuations due to changes in haematology, 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 section 4.4 Special Warnings and Precautions for Use). 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 and placebo groups. Investigator ratings of injection pain were similar for the placebo and INVEGA SUSTENNA 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 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 and placebo groups.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Paliperidone and/or Risperidone

Paliperidone palmitate is hydrolysed to paliperidone. Paliperidone is the active metabolite of risperidone, therefore, the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. This subsection includes additional adverse reactions reported with paliperidone and/or risperidone in clinical trials.

The following adverse reactions were reported with paliperidone and/or risperidone by $\geq 2\%$ of INVEGA SUSTENNA-treated subjects in a pooled dataset of the 4 double-blind, placebo-controlled schizophrenia trials.

Nervous system disorders	parkinsonism (including akinesia, bradykinesia, cogwheel rigidity, drooling, extrapyramidal symptoms, glabellar reflex abnormal, muscle rigidity, muscle tightness, musculoskeletal stiffness, parkinsonian gait)
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Musculoskeletal and connective tissue disorders	musculoskeletal pain
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The following adverse reactions were reported with paliperidone and/or risperidone by $<2\%$ of INVEGA SUSTENNA-treated subjects in a pooled dataset of the 4 double-blind, placebo-controlled schizophrenia trials.

Infections and infestations	acarodermatitis, bronchitis, cellulitis, ear infection, eye infection, influenza, onychomycosis, pneumonia, respiratory tract infection, sinusitis, subcutaneous abscess, tonsillitis
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Blood and lymphatic system disorders	neutropenia, white blood cell count decreased
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Immune system disorders	Hypersensitivity
Metabolism and nutrition disorders	anorexia, blood cholesterol increased, blood triglycerides increased, decreased appetite, hyperglycaemia, increased appetite, polydipsia, weight decreased

Psychiatric disorders	depression, sleep disorder
Nervous system disorders	balance disorder, cerebrovascular accident, convulsion (including grand mal convulsion), disturbance in attention, dizziness postural, dysarthria, dyskinesia (including athetosis, chorea, choreoathetosis, movement disorder, muscle twitching, myoclonus), dystonia (including blepharospasm, cervical spasm, emprosthotonus, facial spasm, hypertonia, laryngospasm, muscle contractions involuntary, myotonia, oculogyration, opisthotonus,

	oropharyngeal spasm, pleurothotonus, risus sardonicus, tetany, tongue paralysis, tongue spasm, torticollis, trismus), hypoesthesia, paresthesia, psychomotor hyperactivity, syncope, tardive dyskinesia, tremor dry eye, eye rolling, lacrimation increased, ocular hyperaemia, vision blurred
Eye disorders	
Ear and labyrinth disorders	ear pain, vertigo
Cardiac disorders:	atrioventricular block, bradycardia, conduction disorder, electrocardiogram abnormal, electrocardiogram QT prolonged, palpitations, postural orthostatic tachycardia syndrome, sinus arrhythmia, tachycardia
Vascular disorders	orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	dyspnea, epistaxis, nasal congestion, pharyngolaryngeal pain, pulmonary congestion, respiratory tract congestion, wheezing
Gastrointestinal disorders:	dyspepsia, dysphagia, fecal incontinence, flatulence, gastroenteritis, swollen tongue
Hepatobiliary disorders	gamma-glutamyltransferase increased, hepatic enzyme increased, transaminases increased
Skin and subcutaneous tissue disorders	acne, dry skin, eczema, erythema, hyperkeratosis, pruritus, rash, urticaria
Musculoskeletal and connective tissue disorders	arthralgia, joint stiffness, joint swelling, muscle spasms, neck pain
Renal and urinary disorders	dysuria, pollakiuria, urinary incontinence
Reproductive system and breast disorders	amenorrhea, ejaculation disorder, erectile dysfunction, galactorrhea, gynecomastia, sexual dysfunction, vaginal discharge
General disorders and administration site conditions:	chest discomfort, chills, face edema, gait abnormal, induration, malaise, oedema including generalised oedema, oedema peripheral, pitting oedema), pyrexia, thirst
Injury, poisoning and procedural complications	fall
<i>Adverse reactions</i> reported with paliperidone and/or risperidone in other clinical trials but not reported by INVEGA SUSTENNA-treated subjects in a pooled dataset of the 4 double-blind, placebo-controlled schizophrenia trials are included in the following list.	
Infections and infestations	cystitis
Blood and lymphatic system disorders	anaemia, eosinophil count increased, haematocrit decreased
Immune system disorders:	anaphylactic reaction
Endocrine disorders	glucose urine present, hyperprolactinaemia
Metabolism and nutrition disorders	hyperinsulinaemia
Psychiatric disorders	anorgasmia, blunted affect, confusional state, libido decreased
Nervous system disorders:	cerebrovascular disorder, coordination abnormal, depressed level of consciousness, diabetic coma, head titubation, loss of consciousness, neuroleptic malignant syndrome, unresponsive to stimuli
Eye disorders	conjunctivitis, eye movement disorder, glaucoma, photophobia
Ear and labyrinth disorders	tinnitus
Vascular disorders	flushing, hypotension, ischaemia

Respiratory, thoracic and mediastinal disorders:	dysphonia, hyperventilation, pneumonia aspiration, rales
Gastrointestinal disorders	cheilitis, fecaloma, intestinal obstruction
Skin and subcutaneous tissue disorders:	drug eruption, seborrheic dermatitis, skin discolouration
Musculoskeletal and connective tissue disorders	blood creatine phosphokinase increased, muscular weakness, posture abnormal, rhabdomyolysis
Reproductive system and breast disorders	breast discharge, breast discomfort, breast engorgement, breast enlargement, menstrual disorder (including menstruation irregular, oligomenorrhea), menstruation delayed
General disorders and administration site conditions	body temperature decreased, body temperature increased, drug withdrawal syndrome

Post-Marketing Data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience with paliperidone and/or risperidone (Table 4).

Very common $\geq 1/10$

Common $\geq 1/100$ to $< 1/10$

Uncommon $\geq 1/1,000$ to $< 1/100$

Rare $\geq 1/10,000$ to $< 1/1,000$

Very rare $< 1/10,000$, including isolated reports

Unknown cannot be estimated from the available data

Table 4. Adverse Drug Reactions Identified During Post-Marketing Experience with Paliperidone and/or Risperidone by Frequency Category Estimated from Spontaneous Reporting Rates with Paliperidone	
Blood and lymphatic system disorders	
<i>Very rare</i>	Agranulocytosis, Thrombocytopenia
Endocrine disorders	
<i>Not known</i>	Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	
<i>Very rare</i>	Diabetes mellitus, Diabetic ketoacidosis, Hypoglycaemia
<i>Not known</i>	Water intoxication
Psychiatric disorders	
<i>Very rare</i>	Catatonia, Mania, Somnambulism
<i>Not Known</i>	Sleep-related eating disorder
Nervous system disorders	
<i>Very rare</i>	Dysgeusia
Eye disorders	
<i>Not known</i>	Floppy iris syndrome (intraoperative)
Cardiac disorders	
<i>Very rare</i>	Atrial fibrillation
Vascular disorder	
<i>Very rare</i>	Deep vein thrombosis, Pulmonary embolism
Respiratory, thoracic and mediastinal disorders	
<i>Very rare</i>	Sleep apnoea syndrome
Gastrointestinal disorders	
<i>Very rare</i>	Pancreatitis
<i>Very rare</i>	Ileus
Hepatobiliary disorders	
<i>Not known</i>	Jaundice
Skin and subcutaneous tissue disorders	
<i>Rare</i>	Angioedema
<i>Very rare</i>	Alopecia
<i>Not known</i>	Stevens-Johnson syndrome/Toxic epidermal necrolysis
Renal and urinary disorders	
<i>Very rare</i>	Urinary retention
Pregnancy, Puerperium and Perinatal conditions	
<i>Very rare</i>	Drug withdrawal syndrome neonatal
Reproductive system and breast disorders	
<i>Very rare</i>	Priapism
General disorders and administration site conditions	
<i>Very rare</i>	Hypothermia, Injection site abscess, Injection site cellulitis, Injection site haematoma
<i>Not known</i>	Injection site cyst, Injection site necrosis, Injection site ulcer

Very rarely, cases of anaphylactic reaction after injection with INVEGA SUSTENNA have been reported during post-marketing experience in patients who have previously tolerated oral risperidone or oral paliperidone.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <https://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

No cases of overdose were reported in premarketing studies with INVEGA SUSTENNA. Because INVEGA SUSTENNA 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 Overdose section of the risperidone Product Information.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

Management of Overdose

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 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Paliperidone palmitate is hydrolysed to paliperidone (see section 5 Pharmacological Properties). 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 (D2) and serotonin Type 2 (5HT2A) receptor antagonism.

Paliperidone is a centrally active dopamine Type 2 (D2) receptor antagonist and a serotonin Type 2 (5HT2A) receptor antagonist. Paliperidone is also active as an antagonist at α 1 and α 2 adrenergic receptors and H1 histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone has no affinity for cholinergic muscarinic or β 1- and β 2-adrenergic receptors. The

pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar in vitro.

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, randomised, 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, disorganised 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 behaviours. 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 behaviours is measured by the presence or absence of aggressive behaviours (e.g., rudeness, insulting others in public, breaking objects, verbal threats, physical assault) and the frequency in which these behaviours occur.

In a 13-week study (R092670 PSY-3007) (n=636) comparing three fixed doses of INVEGA SUSTENNA (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 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 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 behaviour. 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 (50 mg/4 weeks, 100 mg/4 weeks, and 150 mg/4 weeks) to placebo, only 100 mg/4 weeks of INVEGA SUSTENNA 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. 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 (25 mg/4 weeks, 50 mg/4 weeks, and 100 mg/4 weeks) to placebo, all three doses of INVEGA SUSTENNA were superior to placebo in improving the PANSS total score. In this study, none of the INVEGA SUSTENNA 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 (50 mg/4 weeks and 100 mg/4 weeks) to placebo, both doses of INVEGA SUSTENNA were superior to placebo in improving PANSS total score. Statistical superiority of both INVEGA SUSTENNA groups relative to placebo was achieved by Day 8 for the change in PANSS total score. 50 mg or 100 mg INVEGA SUSTENNA 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 in maintaining symptomatic control 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 849 non-elderly adult subjects who met DSM-IV criteria for schizophrenia. This study included a 9-week open-label acute treatment phase followed by a 24 week maintenance of response or stabilisation phase. Eligible subjects were then randomised to a double-blind placebo-controlled recurrence prevention phase with variable duration as this was determined by advent of a recurrent episode. A 52-week open-label extension period for those who had completed or suffered recurrence followed. In this study, doses of INVEGA SUSTENNA included 25, 50, 75, and 100 mg administered monthly; the 75 mg dose was allowed only in the 52-week open-label extension. Subjects initially received flexible doses (25-100 mg) of INVEGA SUSTENNA during a 9-week transition period. In order to enter the 24-week stabilisation phase, subjects were required to have a PANSS score of <75. Dosing adjustments were only allowed in the first 12 weeks of the stabilisation phase. During the variable length double-blind phase, patients were randomised to either the same dose of INVEGA SUSTENNA (median duration 171 days [range 1 day - 407 days]) they received during the stabilisation phase, administered every 4 weeks, or to placebo (median duration 105 days [range 8 days - 441 days]). A total of 410 stabilised patients were randomised to either INVEGA SUSTENNA or to placebo 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 hospitalisation, $\geq 25\%$ increase (if the baseline score was > 40) or a 10-point increase (if the baseline score was ≤ 40) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behaviour, suicidal/homicidal ideation, or a score of ≥ 5 (if the maximum baseline score was ≤ 3) or ≥ 6 (if the maximum baseline score was 4) on two consecutive assessments of the individual PANSS items P1 (Delusions), P2 (Conceptual disorganisation), P3 (Hallucinatory behaviour), 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 1.

The result of the analysis based on the final data, including all data up to the date of study termination, was consistent with that of the primary efficacy analysis based on the interim data.

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

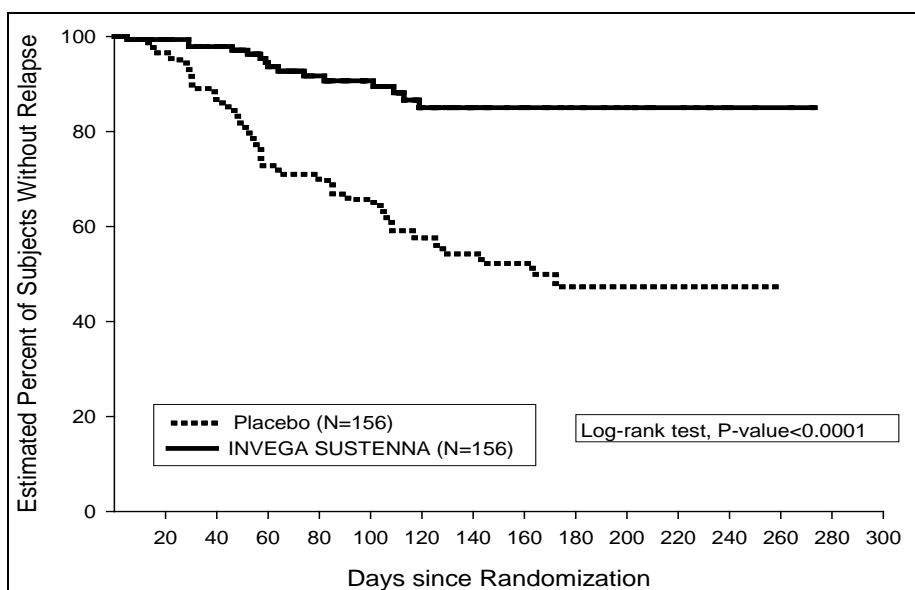


Figure 1: Kaplan-Meier Plot of Time to Relapse – Interim Analysis
INVEGA SUSTENNA
Intent-to-Treat Analysis Set

5.2 PHARMACOKINETIC PROPERTIES

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 results in sustained therapeutic concentrations. The AUC of paliperidone following INVEGA SUSTENNA 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 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 Excretion

In a study with oral immediate-release ^{14}C -paliperidone, one week following administration of a single oral dose of 1 mg immediate-release ^{14}C -paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolised 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 metabolisers and poor metabolisers of CYP2D6 substrates. In vitro studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolised 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 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 is designed to deliver paliperidone over a monthly period while modified-release oral paliperidone is administered on a daily basis. Figure 2 presents the median pharmacokinetic profiles for paliperidone for 5 weeks following INVEGA SUSTENNA 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 (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.

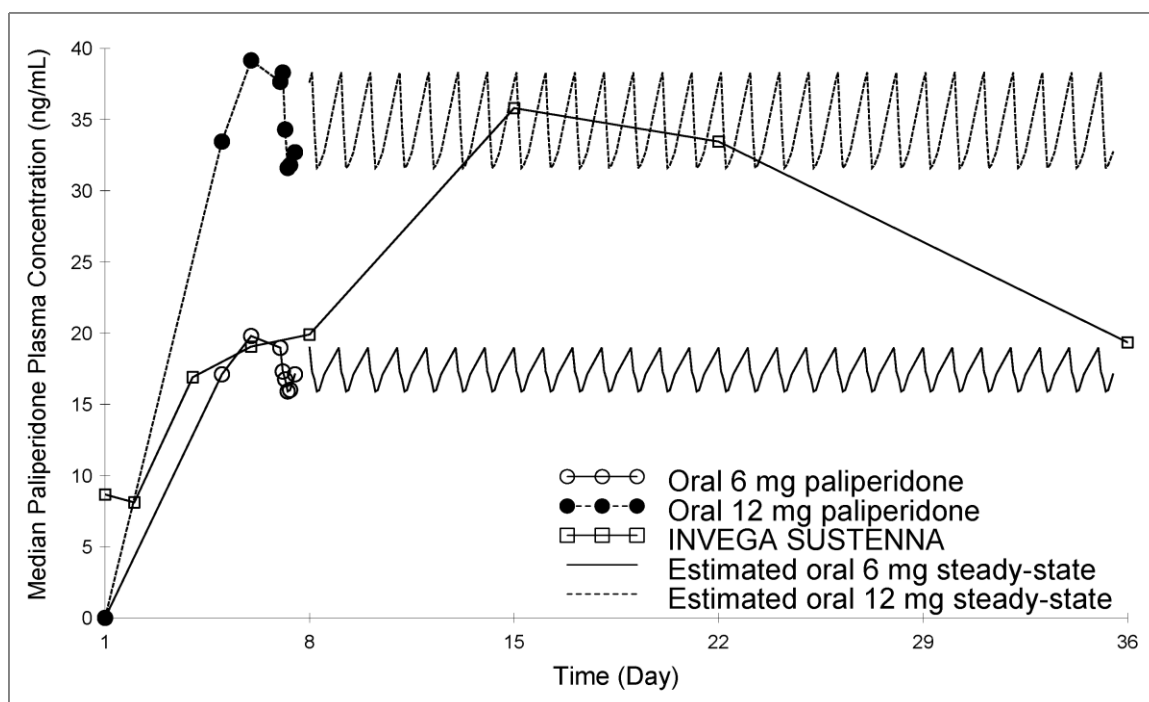


Figure 2. Median plasma concentration-time profiles following median pharmacokinetic profiles for paliperidone for 5 weeks following INVEGA SUSTENNA administration using the recommended initiation regimen (initiating with paliperidone palmitate equivalent to paliperidone 150 mg/100 mg in the deltoid 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 were within the exposure range observed with 6-12 mg modified-release oral paliperidone. The use of the INVEGA SUSTENNA 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 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 has not been systematically studied in patients with renal impairment. The dose of INVEGA SUSTENNA should be reduced in patients with mild renal impairment; INVEGA SUSTENNA is not recommended for use in patients with moderate or severe renal impairment (see Section 4.2 Dose and Method of Administration). Although INVEGA SUSTENNA 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; both administered in the deltoid muscle; thereafter, follow with monthly (every 4 weeks) injections of 50 mg in either the deltoid or gluteal muscle, adjusted within the range of 25 to 100 mg based on patient tolerability and/or efficacy (see Section 4.2 Dose and Method of 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 section 4.2 Dose and Method of 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 Renal Impairment above and section 4.2 Dose and Method of 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 utilising human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone.

5.3 PRECLINICAL SAFETY DATA

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).

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. 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/m² 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 D₂-receptor antagonism and hyperprolactinaemia. The relevance of these tumor findings in rodents in terms of human risk is unknown (see section 4.4 Special Warnings and Precautions for Use).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

polysorbate 20

macrogol 4000

citric acid monohydrate

sodium phosphate - dibasic anhydrous

sodium phosphate - monobasic monohydrate

sodium hydroxide

water for injection

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

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

INVEGA SUSTENNA is provided in a pre-filled syringe (cyclic-olefin-copolymer) with backstop, a plunger stopper and tip cap (bromobutyl rubber). The kit contains 2 safety needles (a 1½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle).

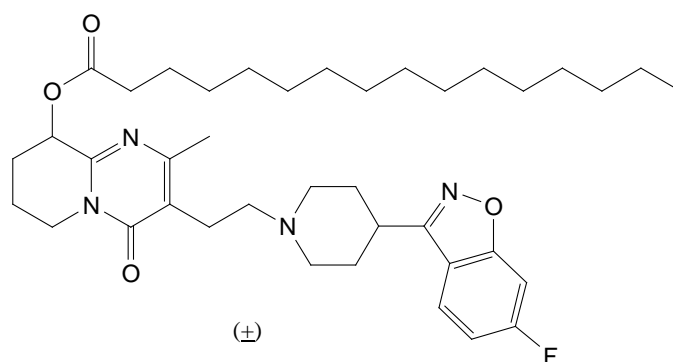
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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.

Chemical structure



$C_{39}H_{57}FN_4O_4$

MW=664.89

The chemical name of paliperidone palmitate 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 number

199739-10-1

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 - Prescription Only Medicine

8. SPONSOR

Janssen-Cilag Pty Ltd
1-5 Khartoum Road,
Macquarie Park,
NSW, 2113, AUSTRALIA
Telephone: 1800 226 334

NZ Office:
Auckland, NEW ZEALAND
Telephone: 0800 800 806

9. DATE OF FIRST APPROVAL

28 July 2010

10. DATE OF REVISION

29 July 2020

Summary table of changes

Section changed	Summary of new information
4.8	1. Addition of adverse reaction Stevens-Johnson syndrome/Toxic epidermal necrolysis