INVEGA HAFYERA®

Paliperidone palmitate

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

INVEGA HAFYERA paliperidone (as palmitate) 700 mg modified release suspension for injection

INVEGA HAFYERA paliperidone (as palmitate) 1000 mg modified release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

3. PHARMACEUTICAL FORM

INVEGA HAFYERA is available as a white to off-white sterile modified release suspension for intramuscular injection in dose strengths of 700 mg and 1000 mg paliperidone (as 1092 mg and 1560 mg paliperidone palmitate, respectively).

INVEGA HAFYERA paliperidone (as palmitate) 700 mg suspension for injection pre-filled syringe. Each 3.5 mL prefilled syringe contains 700 mg of paliperidone as 1092 mg paliperidone palmitate.

INVEGA HAFYERA paliperidone (as palmitate)1000 mg suspension for injection pre-filled syringe. Each 5.0 mL prefilled syringe contains 1000 mg of paliperidone as 1560 mg paliperidone palmitate.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

INVEGA HAFYERA, a 6-month injection, is indicated for the maintenance treatment of schizophrenia in adults aged 18 years and older who have been adequately treated with the 1-month paliperidone palmitate injectable product for at least four months or the 3-month paliperidone palmitate injectable product following at least one 3-month injection cycle.

4.2 DOSE AND METHOD OF ADMINISTRATION

INVEGA HAFYERA is to be used only after the 1-month paliperidone palmitate injectable product has been established as adequate treatment for at least four months at dosages of 100 mg or 150 mg (see Table 1) or the 3-month paliperidone palmitate injectable product at dosages of 350 mg or 525 mg (see Table 2) for at least one injection cycle.

In order to establish a consistent maintenance dose, it is recommended that the last two doses of the 1-month injection be the same dosage strength before starting INVEGA HAFYERA.

Dosage

INVEGA HAFYERA is for gluteal intramuscular use only. Do not administer by any other route.

INVEGA HAFYERA for patients adequately treated with 1-month paliperidone palmitate

Initiate INVEGA HAFYERA at the time when the next 1-month paliperidone palmitate dose is scheduled with a INVEGA HAFYERA dose based on the previous injection dose as shown in Table 1. INVEGA HAFYERA may be administered up to 7 days before or after the monthly time point of the next scheduled paliperidone palmitate dose.

Table 1: Conversion from 1-month paliperidone palmitate to 6-month paliperidone palmitate

If the last dose of 1-month paliperidone palmitate was:	Initiate 6-month paliperidone palmitate at the following dose:
100 mg	700 mg
150 mg	1000 mg

There are no equivalent doses of INVEGA HAFYERA for the 25, 50, and 75 mg doses of 1-month paliperidone palmitate injection, which were not studied.

INVEGA HAFYERA for patients adequately treated with 3-month paliperidone palmitate

Initiate INVEGA HAFYERA at the time when the next 3-month paliperidone palmitate dose is scheduled with a INVEGA HAFYERA dose based on the previous injection dose as shown in Table 2. INVEGA HAFYERA may be administered up to 14 days before or after the 3-monthly time point of the next scheduled paliperidone palmitate dose.

Table 2: Conversion from 3-month paliperidone palmitate to 6-month paliperidone palmitate

If the last dose of 3-month paliperidone palmitate was:	Initiate 6-month paliperidone palmitate at the following dose:
350 mg	700 mg
525 mg	1000 mg

There are no equivalent doses of INVEGA HAFYERA for the 175, and 263 mg 3-month paliperidone palmitate injectable product as these conversions were not studied.

If needed, dose adjustment of INVEGA HAFYERA can be made every 6 months between the dose levels of 700 mg and 1000 mg based on individual patient tolerability and/or efficacy. Due to the long-acting nature of 6-month paliperidone palmitate, the patient's response to an adjusted dose may not be apparent for several months (see section 5.2 Pharmacokinetic Properties). If the patient remains symptomatic, they should be managed according to clinical practice.

Switching from Other Antipsychotics

INVEGA HAFYERA is to be used only after the patient has been adequately treated with the 1-month paliperidone palmitate injectable product (100 mg or 150 mg) for at least 4 months or the 3-month paliperidone injectable product (350 mg or 525 mg) for one 3-month injection cycle (see sections 4.1 Therapeutic Indications and 4.2 Dose and Method of Administration).

If INVEGA HAFYERA 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.

Transitioning from INVEGA HAFYERA to the 3-Month Paliperidone Palmitate Injectable Product

Transitioning from INVEGA HAFYERA to the 3-month paliperidone palmitate injectable product should be started 6 months after the last INVEGA HAFYERA dose using the corresponding dose as shown in Table 3. The 3-month paliperidone palmitate injectable product should then continue, dosed at 3-monthly intervals.

Table 3: Transitioning from the last paliperidone palmitate 6-month injectable product (INVEGA HAFYERA) dose to the paliperidone palmitate 3-month injectable product dose

If the last INVEGA HAFYERA dose is:	Administer 3-Month Paliperidone Palmitate at the following dose:
700 mg	350 mg
1000 mg	525 mg

Transitioning from INVEGA HAFYERA to the 1-Month Paliperidone Palmitate Injectable Product

Transitioning from INVEGA HAFYERA to the 1-month paliperidone palmitate injectable product should be started 6 months after the last INVEGA HAFYERA dose, using the corresponding dose of 1-month paliperidone palmitate as shown in Table 4. The 1-month paliperidone palmitate injectable product should then continue dosed at monthly intervals.

Table 4: Transitioning from the last paliperidone palmitate 6-month injectable product (INVEGA HAFYERA) dose to the paliperidone palmitate 1-month injectable product dose

If the last INVEGA HAFYERA dose is:	Administer 1-Month Paliperidone Palmitate at the following dose:
700 mg	100 mg
1000 mg	150 mg

The initiation dosing as described in the prescribing information for the 1-month paliperidone palmitate injectable product is not required.

Transitioning from INVEGA HAFYERA to Oral Paliperidone Extended-Release Tablets

Transitioning from INVEGA HAFYERA to oral paliperidone extended-release tablets should be started 6 months after the last INVEGA HAFYERA dose and the daily dosing of the paliperidone extended-release tablets should be transitioned over the next several months as described in Table 5. Table 5 provides dose conversion regimens to allow patients previously stabilised on the dose levels of INVEGA HAFYERA to attain similar paliperidone exposure with once daily paliperidone extended-release tablets.

Table 5: Doses of paliperidone extended-release tablets for patients transitioning from INVEGA HAFYERA *

If the last dose of INVEGA HAFYERA is	Months after last INVEGA HAFYERA dose		
	6 months to 9 months	More than 9 months to 12 months	More than 12 months
	Daily dose of paliperidone prolonged release tablets		
700 mg	3 mg	6 mg	9 mg
1000 mg	6 mg	9 mg	12 mg

* All doses of once daily paliperidone prolonged release tablets should be individualised to the specific patient, taking into consideration variables such as reasons for transitioning, response to previous paliperidone treatment, severity of psychotic symptoms, and/or propensity for side effects

Dosage in Special Populations

Renal Impairment

INVEGA HAFYERA has not been systematically studied in patients with renal impairment (see section 5.2 Pharmacokinetic Properties).

For patients with mild renal impairment (creatinine clearance ≥ 50 to ≤ 80 mL/min), the dose should be adjusted and the patient stabilised using 1-month paliperidone palmitate injectable product; Transition to INVEGA HAFYERA at the time when the next 1-month or 3-month paliperidone palmitate dose was to be scheduled with a INVEGA HAFYERA dose based on the previous injection dose as shown in Table 1 and Table 2 respectively. The maximum recommended dose of INVEGA HAFYERA in patients with mild renal impairment is 700 mg.

INVEGA HAFYERA is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min).

Hepatic Impairment

INVEGA HAFYERA 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 section 5.2 Pharmacokinetic Properties).

Paediatric Use

Safety and effectiveness of INVEGA HAFYERA in patients < 18 years of age have not been studied. Use in these patients is not recommended.

Use in the Elderly

In general, recommended dosing of INVEGA HAFYERA 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.

Other populations

No dose adjustment for INVEGA HAFYERA is recommended based on gender, race, or smoking status. (For pregnant women and nursing mothers, see section 4.6 Fertility, Pregnancy and Lactation)

Missed Doses

Following the initial dose, INVEGA HAFYERA should be administered every 6 months. Missed doses of INVEGA HAFYERA should be avoided, although injections given up to 2 weeks before or 3 weeks after the scheduled 6-month time point are not considered a missed dose.

Dosing window

To avoid a missed dose, patients may be given the injection up to 2 weeks before or 3 weeks after the scheduled 6-month time point.

Missed dose over 6 months and 3 weeks, and up to, but less than 8 months since last injection

If more than 6 months and 3 weeks but less than 8 months have elapsed since the last injection of INVEGA HAFYERA do NOT administer the next dose of INVEGA HAFYERA. Instead, use the re-initiation regimen shown in Table 6.

Table 6: Re-initiation regimen after missing over 6 months and 3 weeks, up to but less than 8 months of INVEGA HAFYERA

Recommended re-initiation regimen after missing > 6 months and 3 weeks up to < 8 months of INVEGA HAFYERA		
If the last dose of INVEGA HAFYERA was	**Administer 1-monthly paliperidone palmitate injectable (into deltoid muscle)**	**Then administer INVEGA HAFYERA (into gluteal muscle)**
	Day 1	1 month after Day 1
700 mg	100 mg	700 mg
1000 mg	150 mg	1000 mg

Missed dose over 8 months up to and including 11 months since last injection

If 8 months up to and including 11 months have elapsed since the last injection of INVEGA HAFYERA, do NOT administer the next dose of INVEGA HAFYERA. Instead, use the re-initiation regimen shown in Table 7.

Table 7: Re-initiation regimen after missing over 8 months up to 11 months of INVEGA HAFYERA			
Recommended re-initiation regimen after missing ≥ 8 months to ≤ 11 months of INVEGA HAFYERA			
If the last dose of INVEGA HAFYERA was	**Administer 1-monthly paliperidone palmitate injectable (into deltoid muscle)**		**Then administer INVEGA HAFYERA (into gluteal muscle)**
	Day 1	**Day 8**	**1 month after Day 8**
700 mg	100 mg	100 mg	700 mg
1000 mg	100 mg	100 mg	1000 mg

Missed doses over 11 months since last injection

If more than 11 months have elapsed since the last injection of INVEGA HAFYERA, re-initiate treatment with 1-month paliperidone palmitate injection as described in the prescribing information for that product. INVEGA HAFYERA can then be resumed after the patient has been adequately treated with 1-month paliperidone palmitate injection for at least 4 months. To establish a consistent maintenance dose, it is recommended that the last two doses of 1-month paliperidone palmitate injection be the same dosage strength before re-starting INVEGA HAFYERA.

Administration Instructions

INVEGA HAFYERA is for gluteal intramuscular use only. Do not administer by any other route.

INVEGA HAFYERA should be administered once every 6 months.

Each injection must be administered only by a healthcare professional.

Parenteral drug products should be inspected visually for foreign matter and discoloration prior to administration.

Do not mix with any other product or diluent.

After shaking, INVEGA HAFYERA should appear uniform, thick and milky white.

This highly concentrated product requires specific steps to ensure complete resuspension:

- Holding the **syringe tip cap pointing up, shake** the syringe using a **very fast** up and down motion with a loose wrist **for at least 15 seconds**
- **Rest briefly,** then **shake** again in the same way, **very fast** up and down motion with a loose wrist **for a further 15 seconds**

Proceed immediately to inject INVEGA HAFYERA. If more than **five minutes** passes before the injection is administered, shake the syringe again, as above to resuspend the medication. (See Instructions for Use).

Avoid inadvertent injection into a blood vessel. Each injection must be administered only by a healthcare professional. Product is for single use in one patient only. Discard any residue.

Inject slowly, deep into the upper-outer quadrant of the gluteal muscle. Future injections should be alternated between the two gluteal muscles.

Regardless of the patient's weight, INVEGA HAFYERA must be administered using only the thin wall 20 G, 1½-inch needles that is provided in the INVEGA HAFYERA. To reduce the risk of needle blockage, do not use needles from the 1-month or 3-month paliperidone palmitate injectable product packs or other commercially-available needles.

Since paliperidone is the active metabolite of risperidone, caution should be exercised when INVEGA HAFYERA is co administered with risperidone or with oral paliperidone for extended periods of time. Safety data involving concomitant use of INVEGA HAFYERA with other antipsychotics are limited.

Incomplete Administration

INVEGA HAFYERA is a highly concentrated product that requires specific steps to ensure complete resuspension and prevent clogging of the needle during injection. Proper shaking can reduce the likelihood for an incomplete injection. Shipping and storing the carton in a horizontal orientation improves the ability to resuspend this highly concentrated product. Follow the details in the Instructions for Use to avoid an incomplete injection.

However, in the event of an incompletely administered dose, do not re-inject the dose remaining in the syringe and do not administer another dose of INVEGA HAFYERA. Closely monitor and treat the patient with oral paliperidone supplementation as clinically appropriate until the next scheduled 6-month injection of INVEGA HAFYERA. See the product information of the oral paliperidone product for the recommended dosage of that product.

4.3 CONTRAINDICATIONS

INVEGA HAFYERA is contraindicated in patients with a known hypersensitivity to paliperidone or to any of the components in the formulation. Since paliperidone is an active metabolite of risperidone, INVEGA HAFYERA is contraindicated in patients with a known hypersensitivity to risperidone.

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. Consideration should be given to the long-acting nature of INVEGA HAFYERA.

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.

If NMS has occurred with any paliperidone product, INVEGA HAFYERA should not be used.

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 HAFYERA 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 HAFYERA, drug discontinuation should be considered. Consideration should be given to the long-acting nature of INVEGA HAFYERA. However, some patients may require treatment with INVEGA HAFYERA 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 Forms of Interactions).

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.

If clinically significant QT prolongation has occurred with any paliperidone product, INVEGA HAFYERA should not be used.

Effect on QT/QTc interval and cardiac electrophysiology

The effects of paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicentre QT study with oral paliperidone in adults with schizophrenia and schizoaffective disorder and in four fixed-dose efficacy studies and one maintenance study of the 1-month paliperidone palmitate injectable product.

In the Thorough 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 (QT interval corrected for heart rate using the population specified linear derived method) 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 (Cmax ss = 113 ng/mL) was approximately 1.3-fold the exposure with the maximum recommended 1000 mg dose of INVEGA HAFYERA administered in the gluteal muscle (mean $C_{max\ md}$=89.3 ng/mL).. In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which Cmax 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 four fixed-dose efficacy studies of the 1-month paliperidone palmitate injectable product, no subject had 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.

In the INVEGA HAFYERA randomised double-blind active controlled study in subjects with schizophrenia, during the double-blind Phase, QTcLD exceeding 60 msec was observed in 2 subjects (0.4%) in the INVEGA HAFYERA treatment group and in 2 subjects (0.9%) in the INVEGA TRINZA (3-month paliperidone palmitate injectable product) treatment group. No subject had a QTcLD value of >480 msec at any point in the study.

Hypersensitivity reactions

Anaphylactic reactions in patients who have previously tolerated oral risperidone or oral paliperidone have been very rarely reported during post marketing experience with the 1-month paliperidone palmitate injectable product (see sections 4.2 Dose and Method of Administration and 4.8 Adverse Effects (Undesirable Effects)).

If hypersensitivity reactions occur, discontinue use of INVEGA HAFYERA; 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)).

Orthostatic hypotension and Syncope

Paliperidone may induce orthostatic hypotension and syncope in some patients based on its alpha-adrenergic blocking activity.

INVEGA HAFYERA should be used with caution in patients with known cardiovascular disease (e.g., heart failure, 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.

In the INVEGA HAFYERA, randomised double-blind active controlled study in subjects with schizophrenia, during the double-blind Phase, treatment-emergent orthostatic hypotension was observed in 6 subjects (1.3%) in the INVEGA HAFYERA treatment group and in 1 subject (0.5%) in the INVEGA TRINZA (3-month paliperidone palmitate injectable product) treatment group.

Seizures

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

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. INVEGA HAFYERA and other antipsychotic drugs should be used cautiously in patients at risk of aspiration pneumonia.

Suicide

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

Thrombotic Thrombocytopenic Purpura (TTP)

No cases of TTP were observed during clinical studies with oral paliperidone, the 1-month, 3-month or 6-month paliperidone palmitate injectable product. Although cases of TTP have been reported in association with risperidone administration, the relationship to risperidone therapy is unknown.

Hyperprolactinaemia

Like other drugs that antagonise dopamine D2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration (see section 4.8 Adverse Effects (Undesirable Effects)). 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 gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing 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.

In the randomised double-blind active controlled study, the mean (SD) change in serum prolactin levels from double-blind baseline during the double-blind phase in the INVEGA HAFYERA group was -2.19 (13.61) µg/L for males and -4.83 (34.39) µg/L for females and in the INVEGA TRINZA (3-month paliperidone palmitate injectable product) group was 1.56 (19.08) µg/L for males and 9.03 (40.94) µg/L for females.

Median prolactin levels remained relatively stable throughout the open-label and double-blind phases in male subjects, whereas in female subjects, median prolactin levels increased. During the double-blind phase, median prolactin levels continued to increase after dosing in both the INVEGA

HAFYERA and INVEGA TRINZA (3-month paliperidone palmitate injectable product) groups, returning to baseline level at Month 6 and at Month 12 (end of double-blind phase).

Prolactin levels relative to reference range from maintenance baseline were noted in a similar percentage of subjects in the INVEGA HAFYERA and INVEGA TRINZA (3-month paliperidone palmitate injectable product) groups in both males (approximately 35%) and females (approximately 30%). In the INVEGA HAFYERA group, 14 females (2.9%) and 4 males (0.8%) experienced potentially prolactin related adverse reactions, while 6 females (2.7%) and 1 male (0.4%) in the PP3M experienced potentially prolactin-related adverse reactions.

Falls

Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including paliperidone palmitate, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Leukopoenia, neutropoenia, and agranulocytosis

Events of leukopoenia, neutropoenia, and agranulocytosis have been reported with antipsychotic agents, including paliperidone. Agranulocytosis has been reported very rarely (< 1/10,000 patients) during post-marketing surveillance.

Possible risk factors for leukopoenia/neutropoenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopoenia/neutropoenia. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopoenia/neutropoenia should be monitored during the first few months of therapy and discontinuation of INVEGA HAFYERA 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 neutropoenia 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 neutropoenia (absolute neutrophil count < 1000/mm^3) should discontinue INVEGA HAFYERA and have their WBC followed until recovery. Consideration should be given to the long-acting nature of INVEGA HAFYERA . If clinically significant drug-induced leukopoenia/neutropoenia has occurred with any paliperidone product, INVEGA HAFYERA should not be used.

Potential for Cognitive and Motor Impairment

Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA HAFYERA (see section 4.8 Adverse Effects (Undesirable Effects)). Antipsychotics, including INVEGA HAFYERA, 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.

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 HAFYERA and preventive measures undertaken.

Parkinson's disease and Dementia with Lewy Bodies

Physicians should weigh the risks versus the benefits when prescribing antipsychotic drugs, including INVEGA HAFYERA, to patients with Parkinson's disease or Dementia with Lewy Bodies (DLB), who may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Priapism

A case (0.2%) of priapism was reported in the clinical trial with INVEGA HAFYERA. Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with paliperidone during post-marketing surveillance (see section 4.8 Adverse Effects (Undesirable Effects)). Severe priapism may require surgical intervention.

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 HAFYERA 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.

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.

Administration

Care must be taken to avoid inadvertent injection of INVEGA HAFYERA into a blood vessel.

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 HAFYERA (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.

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 HAFYERA. 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 HAFYERA was not marketed at the time these studies were performed, it is not known if INVEGA HAFYERA 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.

Data from the randomised double-blind active controlled study with INVEGA HAFYERA in patients with schizophrenia are presented in Table 8.

Table 8 Change in Fasting Glucose from the randomised double-blind active controlled study with INVEGA HAFYERA in patients with schizophrenia

Total no. of patients[a]	PP3M[1] N=195	INVEGA HAFYERA N = 423
Normal to high	3%	4%
Impaired glucose tolerance to high	4%	5%
Normal/impaired glucose tolerance to high	7%	9%
< 6.9 mmol/L to ≥ 7.8 mmol/L	4%	5%
< 6.9 mmol/L to ≥ 11.0 mmol/L	0	1%
< 6.9 mmol/L to ≥ 16.7 mmol/L	0	<1%

[1] PP3M – 3-month paliperidone palmitate injection
[a] The number of subjects with paired fasting data (baseline and any post baseline assessment).

The American Diabetes Association (ADA) specified limits are as follows:
Normal: <5.6 mmol/L
Impaired: ≥5.6 mmol/L to <6.9 mmol/L
High: ≥7.0 mmol/L

Dyslipidaemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Shifts in lipid parameters from the randomised double-blind active controlled study with INVEGA HAFYERA in patients with schizophrenia are presented in Table 9.

Table 9. Shifts in Fasting Lipids in the Double-Blind Phase from the randomized active controlled study with INVEGA HAFYERA in patients with schizophrenia

	PP3M[1] N=194	**INVEGA HAFYERA N=423**
Fasting Cholesterol (mg/dL) <200 mg/dL to >=240 mg/dL	2 (1%)	3 (0.7%)
Fasting HDL Cholesterol (mg/dL) >=40 mg/dL to <40 mg/dL	28 (14%)	55 (13%)
Fasting LDL Cholesterol (mg/dL) <100 mg/dL to >=160 mg/dL	1 (0.5%)	2 (0.5%)
Fasting Triglycerides (mg/dL) <150 mg/dL to >=200 mg/dL	22 (11%)	22 (5%)

[1]PP3M – 3-month paliperidone palmitate injectable suspension.

For each fasting parameter, subjects with both Baseline (DB) record and any post baseline (DB) record during Double-Blind Phase are included in the denominator.

Cholesterol: Using the conversion factor (1 mg/dL=0.02586 mmol/L), the specified limits are as follows:

200 mg/dL = 5.172 mmol/L; 240 mg/dL = 6.206 mmol/L

HDL: Using the conversion factor (1 mg/dL=0.02586 mmol/L), the specified limits are as follows:

40 mg/dL = 1.034 mmol/L;

LDL: Using the conversion factor (1 mg/dL=0.02586 mmol/L), the specified limits are as follows:

100 mg/dL = 2.586 mmol/L; 160 mg/dL = 4.138 mmol/L

Triglycerides: Using the conversion factor (1 mg/dL=0.01129 mmol/L), the specified limits are as follows:

150 mg/dL = 1.694 mmol/L ; 200 mg/dL = 2.258 mmol/L

Body weight change

Weight gain has been observed with INVEGA HAFYERA and other atypical antipsychotics. Clinical monitoring of weight is recommended.

In the randomised active controlled clinical study of INVEGA HAFYERA the overall mean weight change from double-blind baseline to double-blind end point was +0.10 kg for the INVEGA HAFYERA and +0.96 kg for the INVEGA TRINZA (3-month paliperidone palmitate injectable product) group. In subjects in the 18-25 years group mean (SD) weight change of -0.65 (4.955) kg was observed for INVEGA HAFYERA group; and +4.33 (7.112) kg in the INVEGA TRINZA group. For overweight subjects (BMI 25 to <30) mean weight change of -0.53 kg in the INVEGA HAFYERA group and +1.15 kg in the INVEGA TRINZA group was observed.

Alcohol

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

Use in hepatic impairment

See sections 4.2 Dose and Method of Administration – Dosage in Special Populations and 5.2 Pharmacokinetic Properties – Special populations.

INVEGA HAFYERA 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

See sections 4.2 Dose and Method of Administration – Dosage in Special Populations and 5.2 Pharmacokinetic Properties – Special populations. INVEGA HAFYERA 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 HAFYERA is not recommended in patients with moderate or severe renal impairment (see section 4.2 Dose and Method of Administration).

Use in elderly

See sections 4.2 Dose and Method of Administration – Dosage in Special Populations and 5.2 Pharmacokinetic Properties – Special populations.

The clinical study of INVEGA HAFYERA 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 substantially excreted by the kidney and clearance is decreased in patients with renal impairment. Because elderly patients are more likely to have decreased renal function, INVEGA HAFYERA is not recommended to be used in elderly patients with moderate or severe renal impairment.

<u>Use in elderly patients with dementia</u>

INVEGA HAFYERA has not been studied in elderly patients with dementia.

Overall mortality

Elderly patients with dementia, treated with atypical antipsychotic drugs, had an increased risk of mortality compared to placebo. INVEGA HAFYERA (paliperidone palmitate) is not approved for the treatment of dementia-related psychosis.

Cerebrovascular Adverse Events

In placebo-controlled trials in elderly patients with dementia treated with some atypical antipsychotic drugs, including risperidone, aripiprazole, and olanzapine, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities, compared to placebo. Oral paliperidone and INVEGA

HAFYERA 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 HAFYERA in patients less than 18 years of age have not been established. Use of INVEGA HAFYERA is not recommended in paediatric patients because of the potential longer duration of an adverse event. In clinical trials of oral paliperidone, there were notably higher incidences of dystonia, hyperkinesia, tremor, and parkinsonism in the adolescent population as compared to the adult studies.

In a 7-week oral toxicity study in juvenile rats with oral 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 neurobehavioural 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 (12 mg/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 of 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 of laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Caution is advised when prescribing INVEGA HAFYERA with drugs known to prolong the QT interval.

Since paliperidone palmitate is hydrolysed to paliperidone (see Section 5.2 Pharmacokinetic Properties), results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

Concomitant use of INVEGA HAFYERA with risperidone or with oral paliperidone

Since paliperidone is the major active metabolite of risperidone, the co-administration of INVEGA HAFYERA with oral risperidone or paliperidone is likely to result in an increase in the paliperidone concentration, within the bloodstream. Caution should be exercised when INVEGA HAFYERA is co-administered with risperidone or with oral paliperidone for extended periods of time. Safety data involving concomitant use of INVEGA HAFYERA with other antipsychotics are limited.

Concomitant use of INVEGA HAFYERA 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 HAFYERA to Affect Other Drugs:

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolised by cytochrome P-450 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.

Given the primary CNS effects of paliperidone (see section 4.8 Adverse Effects (Undesirable Effects)), INVEGA HAFYERA 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 (see section 4.4 Special Warnings and Precautions for Use), an additive effect may be observed when INVEGA HAFYERA is administered with other therapeutic agents that have this potential.

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 HAFYERA and lithium is unlikely.

Potential for Other Drugs to Affect INVEGA HAFYERA:

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.

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 oral paliperidone extended-release once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state Cmax 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 HAFYERA should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA HAFYERA should be re-evaluated and decreased if necessary. Consideration should be given to the long-acting nature of INVEGA HAFYERA.

Paliperidone, a cation under physiological pH, is primarily excreted unchanged by the kidneys, approximately half via filtration and half via active secretion. Concomitant administration of trimethoprim, a drug known to inhibit active renal cation drug transport, did not influence the pharmacokinetics of paliperidone.

Co-administration of a single dose of an oral paliperidone extended-release tablet 12 mg with divalproex sodium extended-release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the Cmax and AUC of paliperidone. Although this interaction has not been studied with INVEGA HAFYERA, a clinically significant interaction would not be expected between divalproex sodium extended-release tablets and INVEGA HAFYERA intramuscular injection. This interaction has not been studied with INVEGA HAFYERA.

Pharmacokinetic interaction between lithium and INVEGA HAFYERA is unlikely.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy – Category C

The safety of intramuscularly-injected paliperidone palmitate or orally-dosed paliperidone 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/m^2 basis.

Neonates exposed to antipsychotic drugs (including paliperidone) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may vary in severity following delivery. These symptoms in the neonates may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Since paliperidone has been detected in plasma up to 18 months after a single-dose administration of INVEGA HAFYERA, consideration should be given to the long-acting nature of INVEGA HAFYERA as maternal exposure to INVEGA HAFYERA before or during pregnancy may lead to adverse reactions in the newborn child. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recover within hours or days without specific treatment; others may require prolonged hospitalisation.

INVEGA HAFYERA should only be used during pregnancy if the benefits outweigh the risks. The effect of INVEGA HAFYERA on labour and delivery in humans is unknown.

Breastfeeding

In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Therefore, women receiving INVEGA HAFYERA should not breast-feed infants. Since paliperidone has been detected in plasma up to 18 months after a single-dose administration of INVEGA HAFYERA, consideration should be given to the long-acting nature of INVEGA HAFYERA as nursing infants may be at risk even from INVEGA HAFYERA administration long before nursing.

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 a mg/m^2 basis; the no-effect dose was less than the clinical dose. In risperidone studies in rats, oral administration of risperidone during late gestation and lactation was associated with increased pup deaths during early lactation at doses 0.2 to 5 times the maximum human dose on a mg/m^2 basis (a no-effect dose was not determined) and with reduced pup weight gain at doses five-fold or greater than the maximal recommended human dose on a mg/m^2 basis. There were also increases in stillborn rat pups at an oral risperidone dose 2.5 to 5 times the maximum human dose on a mg/m^2 basis. It is not known whether these effects of risperidone and paliperidone resulted from a direct effect on the foetuses and pups and/or an effect on the dams.

Fertility

Based on the pharmacologic action of paliperidone (D_2 receptor antagonism), treatment with INVEGA HAFYERA may result in an increase in serum prolactin levels, which may lead to a

reversible reduction in fertility in females of reproductive potential (see section 4.4 Special Warnings and Precautions for use – Hyperprolactinaemia).

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

In rat fertility studies with risperidone, which is extensively converted to paliperidone in rats and humans, mating (but not fertility) was impaired at doses 0.2 to 5 times the maximum human dose on a mg/m^2 basis, by an effect on females. In repeat dose toxicity studies in beagle dogs, risperidone at doses of 1 to 17 times the maximum human dose on a mg/m^2 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.

4.7 EFFECTS OF ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

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 paliperidone palmitate based on the comprehensive assessment of the available adverse event information. A causal relationship with paliperidone palmitate 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.

Clinical trial data

The data presented in the Table 10 are derived from the non-inferiority clinical study of INVEGA HAFYERA. 702 patients stabilised on either 1-month or 3-month paliperidone palmitate were randomised in a 2:1 ratio to receive INVEGA HAFYERA (478 patients) or 3-month paliperidone palmitate (224 patients) over a 12-month duration.

The majority of adverse events were mild to moderate in severity.

Table 10: Treatment-emergent Adverse Events in at Least 2% of Subjects in Either Treatment Group by MedDRA System Organ Class and Preferred Term During the Double-blind Phase;DB Safety (Study R092670PSY3015)

	PP3M (N=224)	PP6M (N=478)
Subjects with 1 or more TEAEs	131 (58.5%)	297 (62.1%)
System organ class Preferred term		
Infections and infestations	44 (19.6%)	107 (22.4%)

Table 10: Treatment-emergent Adverse Events in at Least 2% of Subjects in Either Treatment Group by MedDRA System Organ Class and Preferred Term During the Double-blind Phase;DB Safety (Study R092670PSY3015)

	PP3M (N=224)	PP6M (N=478)
Upper respiratory tract infection	9 (4.0%)	24 (5.0%)
Nasopharyngitis	13 (5.8%)	22 (4.6%)
Influenza	4 (1.8%)	13 (2.7%)
Urinary tract infection	2 (0.9%)	13 (2.7%)
Nervous system disorders	36 (16.1%)	87 (18.2%)
Headache	12 (5.4%)	32 (6.7%)
Akathisia	8 (3.6%)	17 (3.6%)
Investigations	38 (17.0%)	78 (16.3%)
Weight increased	17 (7.6%)	40 (8.4%)
Weight decreased	7 (3.1%)	8 (1.7%)
General disorders and administration site conditions	19 (8.5%)	69 (14.4%)
Injection site pain	9 (4.0%)	37 (7.7%)
Psychiatric disorders	20 (8.9%)	59 (12.3%)
Anxiety	1 (0.4%)	15 (3.1%)
Insomnia	5 (2.2%)	15 (3.1%)
Schizophrenia	3 (1.3%)	11 (2.3%)
Suicidal ideation	6 (2.7%)	4 (0.8%)

TEAE = treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 22.1.

[TSFAE02B_AUS.RTF]

Events of particular interest to the class

Extrapyramidal symptoms (EPS)

In the clinical trial of INVEGA HAFYERA, akathisia, dyskinesia, dystonia, parkinsonism, and tremor were reported in 3.6%, 1.5%, 0.6%, 5.0%, and 0.2% of subjects, respectively.

Evaluation of extrapyramidal symptoms (EPS) included a pooled analysis of the following terms: parkinsonism (includes extrapyramidal disorder, extrapyramidal symptoms, on and off phenomenon, Parkinson's disease, parkinsonian crisis, salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, glabellar reflex abnormal, and parkinsonian rest tremor), akathisia (includes akathisia, restlessness, hyperkinesia, and restless leg syndrome), dyskinesia (dyskinesia, chorea, movement disorder, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia (includes dystonia, cervical spasm, emprosthotonus, oculogyric crisis, oromandibular dystonia, risus sardonicus, tetany, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus), and tremor (tremor, action, tremor).

Changes in body weight

In the randomised double-blind active controlled clinical trial of INVEGA HAFYERA the number of subjects with abnormal weight percent change from double-blind baseline at double-blind end point is presented in the below Table. The overall mean weight change from double-blind baseline to double-blind end point were 0.10 kg for the INVEGA HAFYERA group and 0.96 kg for the 3-monthly paliperidone palmitate group. In subjects in the 18-25 years group mean weight change of -0.65 (4.955) kg was observed for the INVEGA HAFYERA group and 4.33 (7.112) kg in the 3-monthly paliperidone palmitate group. For overweight subjects (BMI 25 to < 30) mean weight change of -0.53 kg in the INVEGA HAFYERA group and 1.15 kg in the 3-monthly paliperidone palmitate group.

Table 11: Number of patients with abnormal weight percent change from baseline (double-blind) at end Point		
Weight percent change	PP3M[1] (N=219)	INVEGA HAFYERA (N=473)
Decrease ≥ 7%	15 (6.8%)	43 (9.1%)
Increase ≥ 7%	29 (13.2%)	50 (10.6%)
[1]PP3M – 3-month paliperidone palmitate injection		

Hyperprolactinaemia

In the clinical study in the double-blind Phase in the INVEGA HAFYERA group, the mean (SD) change from baseline (DB) over time during the double-blind Phase was -2.19 (13.61) µg/L for males and -4.83 (34.39) µg/L for females. In the 3-monthly paliperidone palmitate group the mean (SD) change from baseline (DB) over time during the double-blind phase was 1.56(19.08) µg/L for males and 9.03 (40.94) µg/L for females. In the double-blind phase, 3 females (4.3%) in the 3-monthly paliperidone palmitate group and 5 females (3.3%) in the 6-monthly paliperidone palmitate group experienced amenorrhoea.

Pain Assessment and Local Injection Site Reactions

Investigator ratings of injection site. Induration, redness and swelling were observed in 13% in the INVEGA HAFYERA group and 9% in the PP3M group during the double-blind Phase. Investigator evaluation of tenderness was higher for subjects in the INVEGA HAFYERA group versus the PP3M group (31% vs. 19%) during the double-blind Phase. Active INVEGA HAFYERA medication was given at double-blind baseline and Month 6, while placebo medication was given at the other injection times.

Subject ratings of injection site pain. The average score for the subject's evaluation of injection pain on a scale of 0 to 100 was approximately 16 at the open-label Phase end point and approximately 5 in both groups at the double-blind Phase end point.

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. Table 12 lists adverse reactions that were reported with paliperidone and/or risperidone by frequency category estimated from subjects who received at least one injection of INVEGA HAFYERA in Study PSY3015.

The following terms and frequencies are applied: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

Table 12: Adverse Reactions Reported with Paliperidone and/or Risperidone, Reported in Subjects who Received at least One injection of PP6M in Study PSY3015 (Not already Listed in Table 10 or the Postmarketing Data section)

	Adverse Drug Reaction Frequency		
System Organ Class	Common	Uncommon	Not Known
Infections and infestations		Pneumonia, Bronchitis, Respiratory tract infection, Sinusitis, Cystitis, Ear infection, Tonsillitis, Onychomycosis	Eye infection, Cellulitis, Acarodermatitis, Subcutaneous abscess

Adverse Drug Reaction Frequency

System Organ Class	Common	Uncommon	Not Known
Blood and lymphatic system disorders	Anaemia		Neutropenia, White blood cell count decreased, Eosinophil count increased
Immune system disorders			Anaphylactic reaction, Hypersensitivity
Endocrine disorders		Hyperprolactinaemia	Glucose urine present
Metabolism and nutrition disorders	Diabetes mellitus, Blood triglycerides increased	Hyperglycaemia, Increased appetite, Decreased appetite, Blood cholesterol increased	Hyperinsulinaemia, Polydipsia, Anorexia
Psychiatric disorders		Agitation, Depression	Sleep disorder, Confusional state, Blunted affect, Libido decreased, Anorgasmia, Nervousness, Nightmare
Nervous system disorders	Parkinsonism, Sedation/somnolence, Dyskinesia, Headache	Tardive dyskinesia, Dystonia, Dizziness postural, Dizziness, Head titubation, Tremor	Neuroleptic malignant syndrome, Cerebral ischaemia, Unresponsive to stimuli, Loss of consciousness, Depressed level of consciousness, Diabetic coma, Convulsion, Syncope, Psychomotor hyperactivity, Balance disorder, Coordination abnormal, Disturbance in attention, Dysarthria, Hypoaesthesia, Paraesthesia
Eye disorders		Vision blurred, Conjunctivitis	Glaucoma, Eye movement disorder, Eye rolling, Photophobia, Dry eye, Lacrimation increased, Ocular hyperaemia
Ear and labyrinth disorders		Vertigo, Ear pain	Tinnitus
Cardiac disorders	Tachycardia	Atrioventricular block, Conduction disorder, Electrocardiogram QT prolonged, Bradycardia, Palpitations	Postural orthostatic tachycardia syndrome, Sinus arrhythmia, Electrocardiogram abnormal
Vascular disorders	Hypertension		Hypotension, Ischaemia, Orthostatic hypotension, Flushing, Pulmonary embolism
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnoea, Pharyngolaryngeal pain, Epistaxis, Nasal congestion	Hyperventilation, Pneumonia aspiration, Pulmonary congestion, Respiratory tract congestion, Rales, Wheezing, Dysphonia
Gastrointestinal disorders	Abdominal pain, Vomiting, Nausea, Constipation, Gastroenteritis, Diarrhoea, Toothache	Intestinal obstruction, Abdominal discomfort, Dysphagia, Dyspepsia, Dry mouth	Swollen tongue, Faecal incontinence, Faecaloma, Cheilitis, Flatulence
Hepatobiliary disorders	Transaminases increased	Gamma-glutamyltransferase increased, Hepatic enzyme increased	

Adverse Drug Reaction Frequency

System Organ Class	Common	Uncommon	Not Known
Skin and subcutaneous tissue disorders		Urticaria, Pruritus, Rash, Erythema, Seborrhoeic dermatitis	Drug eruption, Hyperkeratosis, Eczema, Dry skin, Skin discolouration, Acne, Dandruff
Musculoskeletal and connective tissue disorders	Blood creatine phosphokinase increased, Musculoskeletal pain, Back pain, Arthralgia	Muscle spasms, Joint stiffness, Joint swelling, Muscular weakness	Rhabdomyolysis, Posture abnormal, Neck pain
Renal and urinary disorders		Urinary incontinence, Pollakiuria	Dysuria
Reproductive system and breast disorders	Amenorrhoea, Menstrual disorder	Erectile dysfunction, Galactorrhoea, Breast pain, Breast enlargement	Ejaculation disorder, Gynaecomastia, Sexual dysfunction, Breast discomfort, Breast engorgement, Vaginal discharge
General disorders and administration site conditions	Pyrexia, Fatigue	Oedema, Body temperature increased, Chest pain, Asthenia, Malaise	Face oedema, Body temperature decreased, Chills, Gait abnormal, Thirst, Chest discomfort, Drug withdrawal syndrome, Induration
Injury, poisoning and procedural complications		Fall	

Note:

- The incidence category is based on all subjects who received at least one dose of PP6M (N=478)
- No adverse reactions fell within the category of *'rare'*
- *'Not known'* adverse reactions include adverse reactions reported with paliperidone and/or risperidone in other clinical trials but not reported by INVEGA HAFYERA-treated subjects during PSY3015.

Post-Marketing data

In addition to the adverse reactions reported during clinical studies and listed in Table 12, the following adverse reactions have been reported during post-marketing experience with paliperidone and/or risperidone (Table 13). In each table, the frequencies are provided according to the following convention:

Very common ≥ 1/10

Common ≥ 1/100 and < 1/10

Uncommon ≥ 1/ 1000 and < 1/100

Rare ≥ 1/10000 and < 1/1000

Very rare < 1/10000, including isolated reports.

Unknown cannot be estimated from the available data

In Table 13, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 13. Adverse 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	
Very rare	Agranulocytosis, Thrombocytopaenia
Endocrine disorders	
Not known	Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	
Very rare	Diabetic ketoacidosis, Hypoglycaemia
Not known	Water intoxication
Psychiatric disorders	
Very rare	Catatonia, Mania, Somnambulism
Not Known	Sleep-related eating disorder
Nervous system disorders	
Very rare	Dysgeusia
Eye disorders	
Not known	Floppy iris syndrome (intraoperative)
Cardiac disorders	
Very rare	Atrial fibrillation
Vascular disorder	
Very rare	Venous thrombosis, Pulmonary embolism
Respiratory, thoracic and mediastinal disorders	
Very rare	Sleep apnoea syndrome
Gastrointestinal disorders	
Very rare	Pancreatitis
Very rare	Ileus
Hepatobiliary disorders	
Not known	Jaundice
Skin and subcutaneous tissue disorders	
Rare	Angioedema
Very rare	Alopecia
Not known	Stevens-Johnson syndrome/Toxic epidermal necrolysis
Renal and urinary disorders	
Very rare	Urinary retention
Pregnancy, puerperium and perinatal conditions	
Very rare	Drug withdrawal syndrome neonatal
Reproductive system and breast disorders	
Very rare	Priapism
General disorders and administration site conditions	
Very rare	Hypothermia, Injection site abscess, Injection site cellulitis, Injection site hematoma
Not known	Injection site cyst, Injection site necrosis, Injection site ulcer

Very rarely, cases of anaphylactic reaction after administration of the 1-month paliperidone palmitate injectable product 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 authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Because INVEGA HAFYERA is to be administered by healthcare professionals, the potential for overdose by patients is low.

Symptoms and signs

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.

The possibility of multiple drug involvement should be considered.

Treatment

Consideration should be given to the extended-release nature of INVEGA HAFYERA and the long apparent half-life of paliperidone when assessing treatment needs and recovery. There is no specific antidote to paliperidone. General supportive measures should be employed. Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring for possible arrhythmias.

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluid and/or sympathomimetic agents.

In case of severe extrapyramidal symptoms, anticholinergic agents should be administered. Close supervision and monitoring should continue until the patient recovers.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX13.

Mechanism of Action

Paliperidone palmitate, the active ingredient in INVEGA HAFYERA, is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives (atypical neuroleptic antipsychotic). INVEGA HAFYERA contains a racemic mixture of (+)- and (-)-paliperidone.

Paliperidone palmitate is hydrolysed to paliperidone (see Section 5.2 Pharmacokinetic Properties). Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidoneis unclear. However the drug's therapeutic effect in schizophrenia could be mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

Paliperidone is a centrally active dopamine Type 2 (D_2) receptor antagonist and a serotonin Type 2 ($5HT_{2A}$) receptor antagonist. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H_1 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 efficacy and safety

The efficacy of INVEGA HAFYERA for the treatment of schizophrenia in patients who had previously been stably treated with either 1-month paliperidone palmitate injectable for at least 4 months or 3-month paliperidone palmitate injectable for at least one 3-month injection cycle was evaluated in a Phase 3, randomised, double-blind, active-controlled, interventional, parallel-group, multicenter, non-inferiority study in adult patients. The study evaluated time to relapse and determined that the efficacy of INVEGA HAFYERA was noninferior to the efficacy of 3-month paliperidone palmitate in adults with a DSM-5 diagnosis of schizophrenia.

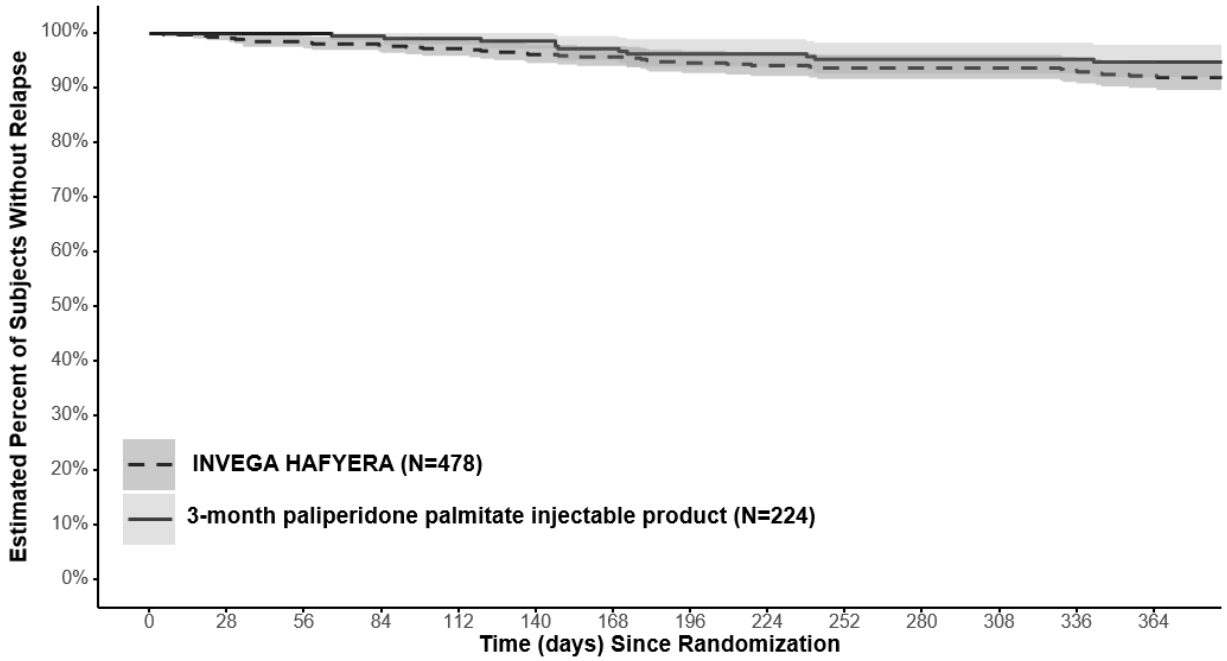
Patients could enter the study if previously treated with 1-month paliperidone palmitate injectable product (at dosages of 100 or 150 mg), 3-month paliperidone palmitate injectable product (at dosages of 350 or 525 mg), injectable risperidone (at dosages of 50 mg), or any oral antipsychotic with a reason to change (e.g. efficacy, safety, tolerability, or a preference for a long-acting injectable medication) and with a PANSS total score of <70 points. The PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); total PANSS scores range from 30-210.

After establishing tolerability with PP1M (at dosages of 100 or 150 mg) or PP3M (at dosages of 350 or 525 mg) and clinical stability, defined by having a PANSS total score of <70 points for the previous 2 assessments prior to the double-blind phase, patients were randomised in a 2:1 ratio to receive INVEGA HAFYERA (478 patients) or PP3M (224 patients).

The primary efficacy variable was time to first relapse in the double-blind phase. The primary efficacy analysis was based on the difference in Kaplan-Meier 12 month estimates of survival (i.e. percentage of subjects remaining relapse-free) between INVEGA HAFYERA and 3-month paliperidone palmitate injectable product. Relapse was pre-defined as emergence of one or more of the following: psychiatric hospitalization, ≥ 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 behavior, suicidal/homicidal ideation: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 specific PANSS items.

A relapse event was experienced by 7.5% and 4.9% of patients in the INVEGA HAFYERA and PP3M treatment groups, respectively, with the Kaplan-Meier estimated difference (INVEGA HAFYERA – PP3M) of 2.9% (95% CI: -1.1 to 6.8). The upper bound of the 95% CI (6.8%) was less than 10%, the prespecified non-inferiority margin. The study demonstrated non-inferiority of INVEGA HAFYERA to PP3M. A Kalpan-Meier plot of time to relapse by treatment group is shown in Figure 1.

Figure 1: Kaplan-Meier Plot and 95% pointwise Confidence Bands of Patients Without Relapse During the Double blind Phase; DB ITT (Study R09267PSY3015)



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

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics for INVEGA HAFYERA presented below are based on gluteal administration only.

Absorption and Distribution

Due to its extremely low water solubility, the 6-month formulation of paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolysed to paliperidone and absorbed into the systemic circulation.

The release of the drug starts as early as day 1 and is predicted to last longer than 18 months.

Following a single injection of INVEGA HAFYERA at doses of 700 and 1000 mg, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations predicted on day 33 and 35, respectively. The release profile and dosing regimen of INVEGA HAFYERA results in sustained therapeutic concentrations over 6 months. The total and peak dose normalised exposures of paliperidone following INVEGA HAFYERA administration were comparable between 700 mg and 1000 mg dose levels. The median steady-state peak:trough ratio for an INVEGA HAFYERA dose is 3.1 and 3.0 following gluteal administration of 700 and 1000 mg respectively. Following administration of INVEGA HAFYERA, the apparent volume of distribution of paliperidone is 1960 L.

The plasma protein binding of racemic paliperidone is 74%.

Biotransformation and Elimination

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 faeces. 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 discernible 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 a single INVEGA HAFYERA of either 700 or 1000 mg was 148 and 159 days respectively. the concentration of paliperidone remaining in the circulation 18 months after dosing of 1000 mg 6 month paliperidone palmitate injectable product stopped is estimated to be 18% of the average steady-state levels.

Long-acting 6-month paliperidone palmitate injection versus other paliperidone formulations

INVEGA HAFYERA is designed to deliver paliperidone over a 6-month period, compared to the 1-month or 3-month products which are administered every month or every three months respectively. INVEGA HAFYERA doses of 700 and 1000 mg result in a range of paliperidone exposures that are comparable to those obtained with corresponding doses of 1-month paliperidone palmitate injections (100 mg and 150 mg) or corresponding doses of 3-month paliperidone palmitate injections (350 mg and 525 mg, respectively) or to corresponding once daily doses of paliperidone extended release tablets.

Intersubject variability in paliperidone PK parameters for INVEGA HAFYERA was estimated by non-compartmental analysis in the randomised double-blind active controlled study. The variability in $AUC_{6months}$ after up to two administrations of 700 and 1000 mg doses of INVEGA HAFYERA was moderate and ranged from 43 to 48%. The variability in C_{max} was higher and ranged from 56 to 103% across the two injected dose levels and each of the two administrations of INVEGA HAFYERA. For comparison, the inter-subject variability in AUC_{3month} and C_{max} observed after 3-month paliperidone palmitate injection administrations, ranged from 41-56% and 48-82%, respectively. Because of the difference in pharmacokinetic profiles among the four paliperidone products, caution should be exercised when making a direct comparison of their pharmacokinetic properties.

Special Populations

Renal Impairment

INVEGA HAFYERA has not been systematically studied in patients with renal impairment. The disposition of a single oral dose of a paliperidone 3 mg extended-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 to < 80 mL/min), 64% in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (CrCl = 10 to < 30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC_{inf}) of 1.5, 2.6, and 4.8-fold, respectively, compared to healthy subjects. Based on a limited number of observations with INVEGA TRINZA in subjects with mild renal impairment and pharmacokinetic simulations, the initiation and maintenance dose of 1-month paliperidone palmitate injection should be reduced in patients with mild renal impairment.

INVEGA HAFYERA is not recommended for patients with moderate or severe renal impairment (see section 4.2 Dose and Method of Administration**)**.

Hepatic Impairment

Paliperidone is not extensively metabolised in the liver. Although INVEGA HAFYERA has not been studied in patients with hepatic impairment, 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 (65 years of age and older)

After oral administration of paliperidone in elderly subjects, the Cmax and AUC increased 1.2 fold compared to young subjects. This may be attributable to age-related decreases in creatinine clearance (see section 4.2 Dose and Method of Administration).

Race

Pharmacokinetic analysis showed no evidence of clinically relevant difference in pharmacokinetics between races.

Gender

Population pharmacokinetics analysis showed no evidence of gender related pharmacokinetics differences.

Smoking Status

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. Effect of smoking on the pharmacokinetics of paliperidone was not studied with INVEGA HAFYERA.

Body Mass Index (BMI)/Body Weight

Lower C_{max} was observed in overweight and obese subjects. At apparent steady state with INVEGA HAFYERA, the trough concentrations were similar among normal, overweight, and obese subjects.

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

No carcinogenicity studies have been conducted with the 6-month paliperidone palmitate extended-release injection.

The carcinogenic potential of the 1-month intramuscular paliperidone palmitate injection 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, which is 0.5, 1.6 and 3.3 times, respectively, the MRHD of 1000 mg of INVEGA HAFYERA based on mg/m^2 body surface area. A no-effect dose was not established. Male rats showed an increase in total mammary gland tumours at 30 and 60 mg/kg/month. A carcinogenicity study in mice has not been conducted with paliperidone palmitate.

Carcinogenicity studies of risperidone, which is extensively converted to paliperidone in rats, mice and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats, equivalent to 0.3, 1.3 and 5 times (mice) and 0.6, 2.5 and 10 times (rats) the maximum human dose on a mg/m^2 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 tumour 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

The inactive ingredients are citric acid monohydrate, macrogol 4000, polysorbate 20, monobasic sodium phosphate monohydrate, sodium hydroxide, water for injections.

6.2 INCOMPATIBILITIES

INVEGA HAFYERA should not be mixed with any other product or diluent and is intended for intramuscular administration directly from the syringe in which it is packaged.

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25^{o}C.

Store in a horizontal position. See arrows on product carton for proper orientation.

6.5 NATURE AND CONTENTS OF CONTAINER

INVEGA HAFYERA is provided in a prefilled syringe (cyclic-olefin-copolymer) prefilled with either 700 mg (3.5 mL), or 1000 mg (5.0 mL) paliperidone (as 1092 mg, or 1560 mg paliperidone palmitate respectively) suspension with a tip cap (bromobutyl rubber), plunger rod, backstop and a thin walled 20G, 1 ½ inch safety needle.

INVEGA HAFYERA is available in cartons containing a single pre-filled syringe.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Instructions for Use

Administer every 6 months

For Gluteal Intramuscular injection only.

Storing the carton in a horizontal orientation improves the ability to resuspend this highly concentrated product.

Preparation

INVEGA HAFYERA requires longer and faster shaking than the 1-month and 3-month paliperidone palmitate injectable products.

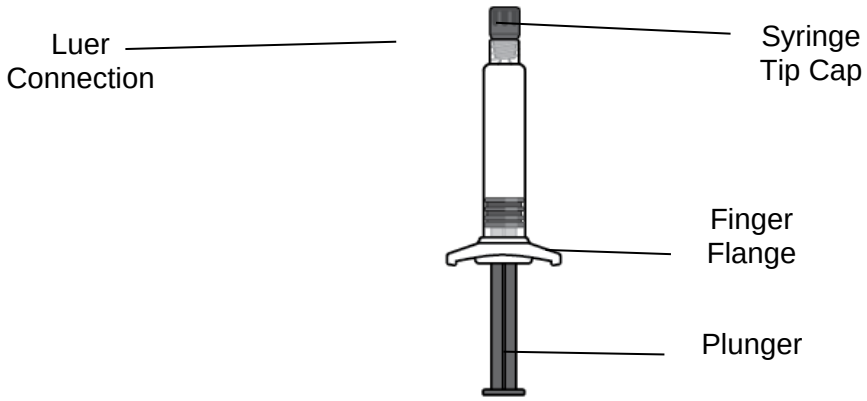
Shake syringe with the syringe tip cap pointing up VERY FAST for at least 15 seconds, rest briefly, then shake again for 15 seconds

INVEGA HAFYERA should be administered by a healthcare professional. Product is for single use in one patient only. Discard any residue.

INVEGA HAFYERA is intended for gluteal intramuscular use only. Inject slowly, deep into the muscle taking care to avoid injection into a blood vessel.

Dose pack contents

Prefilled syringe

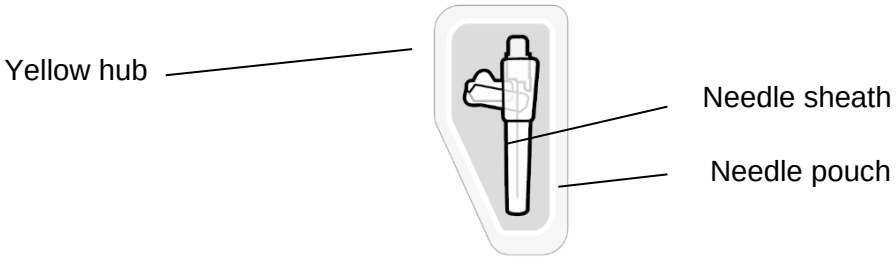


Thin Wall Safety Needle

Thin wall safety needle is designed to be used with INVEGA HAFYERA. Therefore, it is important to only use the needle provided in the INVEGA HAFYERA suspension kit.

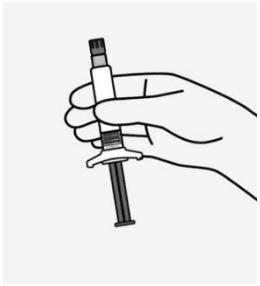
20G x 1½”

Only use the needle included in this kit



1. Prepare for the injection: this highly concentrated product requires specific steps to resuspend

Hold syringe with the tip cap pointing up



Shake syringe VERY FAST for at least 15 seconds, rest briefly, then shake again for 15 seconds

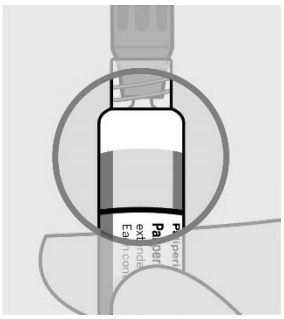
To ensure complete resuspension shake syringe with:

- **Short VERY FAST up and down motion**
- **Loose wrist**

If more than <u>5 minutes</u> pass before injection, shake the syringe VERY FAST with the tip cap pointing up again for at least 30 seconds to resuspend the medication.

Proceed to the next step immediately after shaking.

Check suspension for solid product



Mixed well

- Uniform, thick and milky white
- It is normal to see air bubbles

Not mixed well

STOP

- Solid product on the sides and top of syringe
- Uneven mix
- Thin liquid

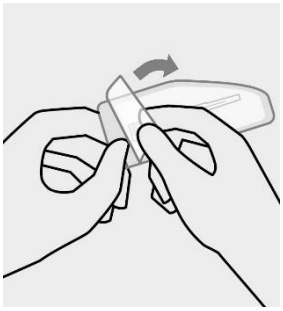
Product may clog.

Shake syringe with the syringe tip cap pointing up VERY FAST for at least 15 seconds, rest, then shake again for 15 seconds.

Open needle pouch

Peel off the pouch cover.

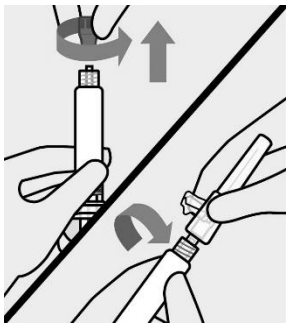
Place pouch with the needle inside on a clean surface.



Remove syringe tip cap and attach needle

Hold the syringe with the tip cap pointing up. Twist and pull the cap off.

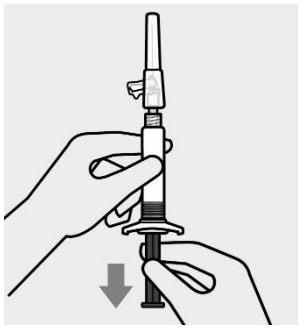
Attach the safety needle to the syringe using a gentle twisting motion to avoid needle hub cracks or damage. Always check for signs of damage or leakage prior to administration.



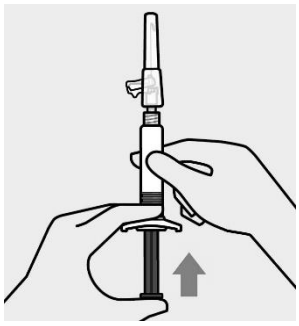
Only use the needle included in this kit

Pull back plunger
Hold the syringe upright.

Gently pull back the plunger to clear the syringe tip of any solid product. This will make pressing the plunger easier during the injection.

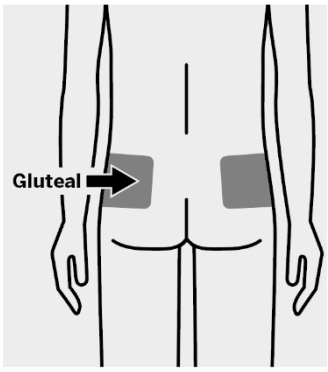


Remove air bubbles
Press the plunger carefully until a drop of liquid comes out of the needle tip.

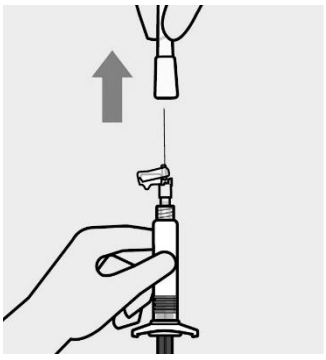


2. Slowly inject entire content and confirm

Select and clean a gluteal injection site
Do not administer by any other route.
Wipe the injection site with an alcohol swab and allow it to dry.
Do not touch, fan or blow the injection site after you have cleaned it.



Remove needle sheath
Pull the needle sheath away from the needle in a straight motion.
Do not twist the sheath, as this may loosen the needle from the syringe.



Slowly inject and confirm

Use slow, firm consistent pressure to press the plunger **completely**. This should take approximately 30 seconds.

Continue to press the plunger if you feel resistance. This is normal.

While the needle is in the muscle, confirm that the entire content of the syringe has been injected.

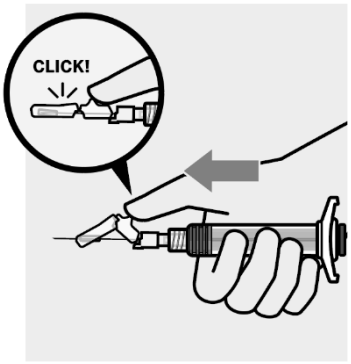
Remove needle from the muscle.

3. After the injection

Secure needle

After the injection is complete, use your thumb or a flat surface to secure the needle in the safety device.

The needle is secure when you hear a “click” sound.



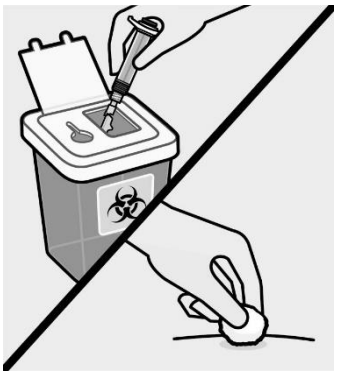
Dispose of properly and check injection site

Dispose of the syringe in an approved sharps container.

There may be a small amount of blood or liquid at the injection site. Hold pressure over the skin with a cotton ball or gauze pad until any bleeding stops.

Do not rub the injection site.

If needed, cover injection site with a bandage.



7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd
Auckland, NEW ZEALAND
Telephone: 0800 800 806
Fax: (09) 588 1398
Email: medinfo@janau.jnj.com

9. DATE OF FIRST APPROVAL

7 September 2023