PRODUCT NAME

INVEGA HAFYERA® 700 mg (as 1092 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

INVEGA HAFYERA® 1000 mg (as 1560 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

International Non-proprietary Name
Paliperidone palmitate

DOSAGE FORMS AND STRENGTHS

INVEGA HAFYERA® contains 700, or 1000 mg paliperidone (as 1092, or 1560 mg of paliperidone palmitate, respectively).

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

Prolonged-release suspension in prefilled syringes. The suspension is white to off-white.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

INVEGA HAFYERA®, a 6-month injection, is indicated for the treatment of schizophrenia in adult patients 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.

Dosage and Administration

INVEGA HAFYERA® is to be used only after adequate treatment has been established with either the 1-month paliperidone palmitate injectable product 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® for patients adequately treated with 1-month paliperidone palmitate

Initiate INVEGA HAFYERA® at the time when the next 1-month paliperidone palmitate dose was to be 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 was to be 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.

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.

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 *Pharmacokinetic Properties*). If the patient remains symptomatic, they should be managed according to clinical practice.

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, up to but less than 8 months since last injection

If more than 6 months and 3 weeks up to 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 3.

Table 3: 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 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 4.

Table 4: Re-initiation regimen after missing over 8 months up to and including 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[a] 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®.

Switching from other antipsychotic agents

INVEGA HAFYERA® is to be used only after the patient has been adequately treated with the 1-month paliperidone palmitate injectable product for at least 4 months or the 3-month paliperidone injectable product for one 3-month injection cycle (see *Indications* and *Dosage and 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 5. The 3-month paliperidone palmitate injectable product should then continue, dosed at 3-monthly intervals.

Table 5: 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 6. The 1-month paliperidone palmitate injectable product should then continue dosed at monthly intervals.

Table 6: 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 7. Table 7 provides dose conversion regimens to allow patients previously stabilized on the dose levels of INVEGA HAFYERA® to attain similar paliperidone exposure with once daily paliperidone extended-release tablets.

Table 7: 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 individualized 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

Special populations

Pediatrics

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

Elderly (65 years of age and older)

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 below for dosing recommendations in patients with renal impairment.

Renal impairment

INVEGA HAFYERA® has not been systematically studied in patients with renal impairment (see *Pharmacokinetic Properties*). For patients with mild renal impairment (creatinine clearance ≥ 50 to $\leq$ 80 mL/min), the dose should be adjusted and the patient stabilized 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 *Pharmacokinetic Properties*)

Other populations

No dose adjustment for INVEGA HAFYERA® is recommended based on gender, race, or smoking status. (For pregnant women and nursing mothers, see *Pregnancy, Breast-feeding and Fertility.*)

Administration

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.

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 and Handling and Disposal*).

INVEGA HAFYERA® is for gluteal intramuscular use only. Do not administer by any other route. Avoid inadvertent injection into a blood vessel. Each injection must be administered only by a healthcare professional. Administer the dose in a single injection; do not administer the dose in divided injections. 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® pack. Do not use needles from the 1-month or 3-month paliperidone palmitate injectable product packs or other commercially-available needles to reduce the risk of blockage.

Since paliperidone is the active metabolite of risperidone, caution should be exercised when INVEGA HAFYERA® is coadministered with risperidone or with oral paliperidone for extended periods of time. Safety data involving concomitant use of INVEGA HAFYERA® with other antipsychotics is 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 and Handling and Disposal* 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 supplementation as clinically appropriate until the next scheduled 6-month injection of INVEGA HAFYERA®.

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.

Warnings and Precautions

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotic drugs, including paliperidone. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs or symptoms indicative of NMS, all antipsychotic drugs, including INVEGA HAFYERA®, should be discontinued. Consideration should be given to the long-acting nature of INVEGA HAFYERA®.

Tardive dyskinesia/extrapyramidal symptoms

Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterized by rhythmical, involuntary movements, predominantly of the tongue and/or face. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotic drugs, including INVEGA HAFYERA®, should be considered. Consideration should be given to the long-acting nature of INVEGA HAFYERA®.

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 *Interactions*).

QT interval

As with other antipsychotics, caution should be exercised when INVEGA HAFYERA® is prescribed in patients with a history of cardiac arrhythmias, in patients with congenital long QT syndrome, and in concomitant use with drugs known to prolong the QT interval (see *Pharmacodynamic Properties: Effect on QT/QTc interval and cardiac electrophysiology*).

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 *Dosage and Administration* and *Adverse Reactions*).
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 *Contraindications* and *Adverse Reactions*)

Hyperglycemia and diabetes mellitus

Hyperglycemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment with antipsychotic drugs. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. Any patient treated with atypical antipsychotics, including INVEGA HAFYERA® should be monitored for symptoms of hyperglycemia and diabetes mellitus. (See also *Adverse Reactions*)

Body weight change

Weight gain has been observed with atypical antipsychotic use. Significant weight change has been reported with INVEGA HAFYERA®. Clinical monitoring of weight is recommended. (See also *Adverse Reactions ,Changes in body weight*)

Orthostatic hypotension

Paliperidone may induce orthostatic hypotension 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 ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications).

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.

Elderly patients with dementia

INVEGA HAFYERA® has not been studied in elderly patients with dementia. INVEGA HAFYERA® is not recommended to treat elderly patients with dementia due to increased risk of overall mortality and cerebrovascular adverse reactions.

Overall mortality

In a meta-analysis of 17 controlled clinical trials, elderly patients with dementia treated with other atypical antipsychotic drugs, including risperidone, aripiprazole, olanzapine, and quetiapine, had an increased risk of mortality compared to placebo. Among those treated with risperidone, the mortality was 4% compared with 3.1% for placebo.

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.

Leukopenia, neutropenia, and agranulocytosis

Events of leukopenia, neutropenia, and agranulocytosis have been reported with antipsychotic agents, including paliperidone. Agranulocytosis has been reported very rarely (< 1/10000 patients) during postmarketing surveillance.

Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia 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 neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 X 10^9/L) should discontinue INVEGA HAFYERA® and have their WBC followed until recovery.

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

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) since both groups 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

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with paliperidone during postmarketing surveillance (see *Adverse Reactions*).

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 overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

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 *Adverse Reactions*).

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.

Interactions

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

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

Potential for INVEGA HAFYERA® to affect other drugs

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P-450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

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

Given the primary CNS effects of paliperidone (see *Adverse Reactions*), INVEGA HAFYERA® should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

Because of its potential for inducing orthostatic hypotension (see *Warnings and Precautions: Orthostatic hypotension*), 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, CYP2C19, and CYP3A5. This suggests 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, there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. *In vitro* studies have shown that paliperidone is a P-gp substrate.

Paliperidone is metabolized to a limited extent by CYP2D6 (see *Pharmacokinetic Properties: Metabolism and Excretion*). In an interaction study in healthy subjects in which oral paliperidone was administered concomitantly with paroxetine, a potent CYP2D6 inhibitor, no clinically relevant effects on the pharmacokinetics of paliperidone were observed.

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 likely as a result of induction of renal P-gp by carbamazepine. 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, likely the result of an increased oral absorption. Since no significant effect on the systemic clearance was observed, 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.

Concomitant use of INVEGA HAFYERA® with risperidone or with oral paliperidone

Since paliperidone is the active metabolite of risperidone, caution should be exercised when INVEGA HAFYERA® is coadministered with risperidone or with oral paliperidone for extended periods of time. Safety data involving concomitant use of INVEGA HAFYERA® with other antipsychotics is 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 *Warnings and Precautions*).

Pregnancy, Breast-feeding and Fertility

Women of childbearing potential

Plasma exposure to paliperidone after a single dose of INVEGA HAFYERA® is expected to remain for up to 4 years (see Pharmacokinetic Properties). This should be taken into account when initiating treatment in women of childbearing potential, considering a possible future pregnancy or breast-feeding. INVEGA HAFYERA® should only be used in women planning to become pregnant if clearly necessary.

Pregnancy

The safety of intramuscularly-injected paliperidone palmitate or orally-dosed paliperidone for use 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. Based on the findings of this single observational study, a causal relationship between *in utero* exposure to risperidone and congenital malformations has not been established.

No teratogenic effect was noted in any animal study. Laboratory animals treated with a high dose of oral paliperidone showed a slight increase in fetal deaths. Pregnancy parameters were not affected in rats given the intramuscular injection of the 1-month paliperidone palmitate injectable product. The high doses were toxic to the mothers. The offspring was not affected at oral exposures 20- to 22-fold the maximum human dose of oral paliperidone or at intramuscular exposures 6-fold the maximum human dose of the 1-month paliperidone palmitate injectable product.

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 neonates may be at risk from INVEGA HAFYERA® administration before pregnancy or during first and second trimesters as well.

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

Breast-feeding

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.

Fertility

There were no relevant effects observed in the non-clinical studies.

Effects on Ability to Drive and Use Machines

INVEGA HAFYERA® may interfere with activities requiring mental alertness and may have visual effects (see *Adverse Reactions*). Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

Adverse Reactions

Throughout this section, adverse reactions are presented. 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 Table 8 are derived from the clinical study of INVEGA HAFYERA®, in which 702 patients stabilized on either 1-month or 3-month paliperidone palmitate were randomized 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 reactions were mild to moderate in severity.

Table 8: Incidences of adverse reactions for INVEGA HAFYERA®-treated patients for the randomized double-blind active controlled trial in patients with schizophrenia

	----------Open Label ----------	---------- Double Blind ----------	
	PP1M/PP3M[a]	**PP3M[a]**	**INVEGA HAFYERA®**
	(N=838)	**(N=224)**	**(N=478)**
System Organ Class Adverse Reaction[b]	**n(%)**	**n(%)**	**n(%)**
Blood and lymphatic system disorders			
Anemia	0	2 (0.9)	5 (1.0)
Cardiac disorders			
Bradycardia	0	2 (0.9)	1 (0.2)
Tachycardia	3 (0.4)	1 (0.4)	7 (1.5)
Ear and labyrinth disorders			
Vertigo	1 (0.1)	1 (0.4)	4 (0.8)
Gastrointestinal disorders			
Constipation	2 (0.2)	0	5 (1.0)
Diarrhea	6 (0.7)	2 (0.9)	11 (2.3)
Nausea	5 (0.6)	2 (0.9)	5 (1.0)
Vomiting	4 (0.5)	0	5 (1.0)
General disorders and administration site conditions			
Fatigue	8 (1.0)	1 (0.4)	9 (1.9)
Injection site reaction	82 (9.8)	10 (4.5)	51 (10.7)
Hepatobiliary disorders			
Transaminases increased	1 (0.1)	3 (1.3)	8 (1.7)
Infections and infestations			
Cystitis	1 (0.1)	1 (0.4)	3 (0.6)
Respiratory tract infection	0	0	3 (0.6)
Tonsillitis	1 (0.1)	0	4 (0.8)

Upper respiratory tract infection	47 (5.6)	28 (12.5)	55 (11.5)
Urinary tract infection	4 (0.5)	2 (0.9)	13 (2.7)
Metabolism and nutrition disorders			
Blood triglycerides increased	0	2 (0.9)	6 (1.3)
Decreased appetite	3 (0.4)	0	2 (0.4)
Diabetes mellitus	1 (0.1)	2 (0.9)	9 (1.9)
Hyperglycemia	0	3 (1.3)	4 (0.8)
Increased appetite	4 (0.5)	1 (0.4)	1 (0.2)
Weight decreased	4 (0.5)	7 (3.1)	8 (1.7)
Weight increased	8 (1.0)	18 (8.0)	43 (9.0)
Musculoskeletal and connective tissue disorders			
Back pain	5 (0.6)	2 (0.9)	12 (2.5)
Musculoskeletal pain	13 (1.6)	3 (1.3)	13 (2.7)
Nervous system disorders			
Akathisia	25 (3.0)	8 (3.6)	17 (3.6)
Dyskinesia	11 (1.3)	2 (0.9)	7 (1.5)
Dystonia	3 (0.4)	2 (0.9)	3 (0.6)
Headache	16 (1.9)	12 (5.4)	32 (6.7)
Parkinsonism	28 (3.3)	8 (3.6)	24 (5.0)
Sedation/somnolence	14 (1.7)	3 (1.3)	8 (1.7)
Tardive dyskinesia	0	0	1 (0.2)
Tremor	2 (0.2)	1 (0.4)	1 (0.2)
Psychiatric disorders			
Anxiety	25 (3.0)	1 (0.4)	15 (3.1)
Depression	5 (0.6)	4 (1.8)	4 (0.8)
Insomnia	30 (3.6)	5 (2.2)	15 (3.1)
Reproductive system and breast disorders			
Amenorrhea	6 (0.7)	3 (1.3)	5 (1.0)
Breast pain	0	0	1 (0.2)
Galactorrhea	2 (0.2)	1 (0.4)	2 (0.4)
Menstrual disorder	9 (1.1)	5 (2.2)	9 (1.9)
Skin and subcutaneous tissue disorders			
Rash	1 (0.1)	1 (0.4)	2 (0.4)
Vascular disorders			
Hypertension	1 (0.1)	4 (1.8)	5 (1.0)

[a] PP1M/PP3M – 1-month paliperidone palmitate extended-release injectable suspension/3-month paliperidone palmitate extended-release injectable suspension

[b] The following terms were combined:

Anemia includes Anemia, Hematocrit decreased, Hemoglobin decreased, Microcytic anemia, Normochromic normocytic anemia, Red blood cell count decreased

Bradycardia includes Bradycardia, Sinus bradycardia

Tachycardia includes Heart rate increased, Sinus tachycardia, Tachycardia

Diarrhea includes Diarrhea, Diarrhea infectious

Fatigue includes Fatigue, Lethargy, Listless, Sluggishness

Injection site reaction includes Administration site pain, Administration site reaction, Buttock pain, Injection site discomfort, Injection site erythema, Injection site extravasation, Injection site hemorrhage, Injection site induration, Injection site inflammation, Injection site irritation, Injection site mass, Injection site nodule, Injection site edema, Injection site pain, Injection site pruritus, Injection site rash

Transaminases increased includes Alanine aminotransferase increased, Aspartate aminotransferase increased,

Transaminases increased
Respiratory tract infection includes Respiratory tract infection, Respiratory tract infection viral
Tonsillitis includes Pharyngotonsillitis, Tonsillitis
Upper respiratory tract infection includes Nasopharyngitis, Pharyngitis, Rhinitis, Upper respiratory tract infection, Viral pharyngitis, Viral upper respiratory tract infection
Blood triglycerides increased includes Blood triglycerides increased, Hypertriglyceridemia
Diabetes mellitus includes Diabetes mellitus, Diabetes mellitus inadequate control, Diabetes mellitus non-insulin-dependent, Insulin-requiring diabetes mellitus, Insulin-requiring type 2 diabetes mellitus, Insulin-requiring type 2 diabetes mellitus, Type 1 diabetes mellitus, Type 2 diabetes mellitus
Hyperglycemia includes Blood glucose increased, Hyperglycemia
Weight increased includes Abnormal weight gain, Body mass index increased, Obesity, Waist circumference increased, Weight increased
Back pain includes Back pain, Neck pain, Spinal pain
Musculoskeletal pain includes Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Pain in extremity
Akathisia includes Akathisia, Hyperkinesia, Restless legs syndrome, Restlessness
Dystonia includes Blepharospasm, Cervical spasm, Dystonia, Emprosthotonus, Facial spasm, Hypertonia, Laryngospasm, Muscle contractions involuntary, Muscle contracture, Myotonia, Oculogyration, Oculogyric crisis, Opisthotonos, Oromandibular dystonia, Oropharyngeal spasm, Pleurothotonus, Risus sardonicus, Tetany, Tongue paralysis, Tongue spasm, Torticollis, Trismus
Parkinsonism includes Akinesia, Bradykinesia, Cogwheel rigidity, Drooling, Extrapyramidal disorder, Extrapyramidal symptoms, Glabellar reflex abnormal, Hypokinesia, Masked facies, Muscle rigidity, Muscle tightness, Musculoskeletal stiffness, Nuchal rigidity, On and off phenomenon, Parkinson's disease, Parkinsonian crisis, Parkinsonian gait, Parkinsonian rest tremor, Parkinsonism, Salivary hypersecretion
Sedation/somnolence includes Hypersomnia, Sedation, Somnolence
Tremor includes Action tremor, Tremor
Depression includes Depressed mood, Depression, Depressive symptom
Galactorrhea includes Breast discharge, Galactorrhea
Menstrual disorder includes Hypomenorrhea, Menstrual disorder, Menstruation delayed, Menstruation irregular, Oligomenorrhea
Rash includes Rash, Rash erythematous, Rash generalized, Rash maculo-papular, Rash papular, Rash vesicular
Hypertension includes Blood pressure increased, Essential hypertension, Hypertension

Other clinical trial data

Paliperidone palmitate is hydrolyzed 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.

Additional adverse reactions reported in the clinical trial of INVEGA HAFYERA®, not included in Table 8, are shown in Table 9a.

Table 9a: Additional adverse reactions for risperidone/paliperidone that were reported in INVEGA HAFYERA®-treated patients in the randomized double-blind active controlled trial in patients with schizophrenia

System/Organ Class Adverse Reaction[b]
Cardiac disorders Atrioventricular block, Conduction disorder, Electrocardiogram QT prolonged, Palpitations
Ear and labyrinth disorders Ear pain
Endocrine disorders Hyperprolactinemia
Eye disorders Conjunctivitis, Vision blurred
Gastrointestinal disorders Abdominal discomfort, Abdominal pain, Dry mouth, Dyspepsia, Dysphagia, Gastroenteritis, Intestinal Obstruction, Toothache[a]
Infections and infestations Bronchitis, Ear infection, Influenza, Onychomycosis, Pneumonia, Sinusitis
Injury, poisoning and procedural complications Fall
Metabolism and nutrition disorders Blood cholesterol increased
Musculoskeletal and connective tissue disorder Arthralgia, Blood creatine phosphokinase increased, Joint stiffness, Join swelling, Muscle spasms, Muscular weakness
Nervous system disorders Dizziness, Dizziness postural, Head titubation
Psychiatric disorders Agitation
Renal and urinary disorders Pollakiuria, Urinary incontinence
Reproductive system and breast disorders Breast enlargement, Erectile dysfunction
Respiratory, thoracic and mediastinal disorders Cough, Dyspnea, Epistaxis, Nasal congestion, Pharyngolaryngeal pain

General disorders and administration site conditions

Asthenia, Body temperature increased, Chest pain, Malaise, Edema, Pyrexia

Hepatobiliary disorders

Gamma-Glutamyltransferase increased, Hepatic enzyme increased

Skin and subcutaneous tissue disorder

Erythema, Pruritis, Sebborheic dermatitis, Urticaria

[a] Reported by ≥2% of subjects treated with 1-month or 3-month paliperidone palmitate injectable products

[b] The following terms were combined:

Atrioventricular block includes Atrioventricular block, Atrioventricular block first degree

Conduction disorder includes Bundle branch block, Bundle branch block left, Bundle branch block right, Conduction disorder

Electrocardiogram QT prolonged includes Electrocardiogram QT corrected interval prolonged, Electrocardiogram QT corrected interval abnormal, Electrocardiogram QT prolonged, Long QT syndrome, Long QT syndrome congenital

Hyperprolactinemia includes, Blood prolactin increased, Hyperprolactinemia

Conjunctivitis includes Conjunctivitis, Eye discharge

Vision blurred includes Vision blurred, Visual acuity reduced

Abdominal discomfort includes Abdominal discomfort, Stomach discomfort

Abdominal pain includes Abdominal pain, Abdominal pain upper

Dry mouth includes Aptyalism, Dry mouth

Gastroenteritis includes Gastritis, Gastroenteritis

Intestinal obstruction includes Intestinal obstruction, Small intestinal obstruction

Bronchitis includes Bronchitis, Tracheobronchitis

Ear infection includes Ear infection, Otitis media, Otitis media chronic

Influenza includes Influenza, Influenza like illness

Pneumonia includes Bronchopneumonia, Lower respiratory tract infection, Pneumonia

Sinusitis includes Sinus congestion, Sinusitis

Urinary incontinence includes Enuresis, Urinary incontinence

Cough includes Cough, Productive cough

Nasal congestion includes Nasal congestion, Nasal edema, Rhinorrhea

Pharyngolaryngeal pain includes Oropharyngeal pain, Pharyngolaryngeal pain

Pruritus includes Pruritis, Pruritis generalized

Additional adverse reactions reported in other clinical trials of paliperidone and risperidone are shown in Table 9b.

Table 9b: Additional adverse reactions for risperidone/paliperidone that were not reported in INVEGA HAFYERA®-treated patients in the randomized double-blind active controlled trial in patients with schizophrenia

System/Organ Class Adverse Reaction[b]
Blood and lymphatic system disorders Eosinophil count increased, Neutropenia, White blood cell count decreased
Cardiac disorders Electrocardiogram abnormal, Postural orthostatic tachycardia syndrome, Sinus arrythmia
Ear and labyrinth disorders Tinnitus
Endocrine disorders Glucose urine present
Eye disorders Dry eye, Eye movement disorder, Eye rolling, Glaucoma, Lacrimation increased, Ocular hyperemia, Photophobia
Gastrointestinal disorders Cheilitis, Fecal incontinence, Fecaloma, Flatulence, Swollen tongue
Metabolism and nutrition disorders Anorexia, Hyperinsulinemia, Polydipsia
Musculoskeletal and connective tissue disorder Posture abnormal, Rhabdomyolysis
Nervous system disorders Balance disorder, Cerebral ischemia, Convulsion. Coordination abnormal, Depressed level of consciousness, Diabetic coma, Disturbance in attention, Dysarthria, Hypoesthesia, Loss of consciousness, Neuroleptic malignant syndrome, Paresthesia, Psychomotor hyperactivity, Syncope, Unresponsive to stimuli
Psychiatric disorders Anorgasmia, Blunted affect, Confusional state, Libido decreased, Nervousness, Nightmare, Sleep disorder
Renal and urinary disorders Dysuria
Reproductive system and breast disorders Breast discomfort, Breast engorgement, Ejaculation disorder, Gynecomastia, Sexual dysfunction, Vaginal discharge
Respiratory, thoracic and mediastinal disorders Dysphonia, Hyperventilation, Pneumonia aspiration, Pulmonary congestion, Rales, Respiratory tract congestion, Wheezing

Skin and subcutaneous tissue disorders
Acne, Dandruff, Drug eruption, Dry skin, Eczema, Hyperkeratosis, Skin discoloration

Vascular disorders
Flushing, Hypotension, Ischemia, Orthostatic hypotension

General disorders and administration site conditions
Body temperature decreased, Chest discomfort, Chills, Drug withdrawal syndrome, Face Edema, Gait abnormal, Induration, Thirst

Immune system disorders
Anaphylactic reaction, Hypersensitivity

Infections and infestations
Acarodermatitis, Cellulitis, Eye infection, Subcutaneous abscess

[b] The following terms were combined:
Neutropenia includes: Granulocytopenia, Neutropenia
Postural orthostatic tachycardia syndrome includes: Orthostatic heart rate response increased, Postural orthostatic tachycardia syndrome
Hyperinsulinemia includes: Blood insulin increased, Hyperinsulinemia
Cerebral Ischemia includes: Cerebral Ischemia, Cerebrovascular accident, Cerebrovascular disorder, Transient ischemic attack
Convulsion includes: Convulsion, Grand mal convulsion
Dysarthria includes: Dysarthria, Speech disorder
Breast discomfort includes: Breast discomfort, Breast swelling, Breast tenderness
Ejaculation disorder includes: Ejaculation delayed, Ejaculation disorder, Ejaculation failure, Retrograde ejaculation
Eczema includes: Dyshidrotic eczema, Eczema, Eczema asteatotic
Hypotension includes: Blood pressure decreased, Hypotension
Face edema includes: Circumoral edema, Eye swelling, Eyelid edema, Face edema, Lip swelling, Edema mouth, Periorbital edema
Gait abnormal includes: Gait abnormal, Gait disturbance
Hypersensitivity includes: Drug hypersensitivity, Hypersensitivity

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, opisthotonos, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus), and tremor (tremor, action, tremor).

Changes in body weight

In the randomized 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 10: 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

Hyperprolactinemia

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 amenorrhea.

Injection site reactions

In the clinical trial of INVEGA HAFYERA®, 10.7% of subjects reported injection site related adverse reaction (4.5% in subjects treated with the comparator 3-monthly paliperidone palmitate injectable). None of these events were serious or led to discontinuation. Based on the investigators' clinical ratings, induration, redness, and swelling were absent or mild in ≥ 95% of the assessments. Subject-rated injection site pain based on a visual analogue scale was low and decreased in intensity over time.

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience with paliperidone and/or risperidone (Table 11). 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
Not known	Cannot be estimated from the available data.

In Table 11, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 11: Adverse reactions identified during postmarketing experience with paliperidone and/or risperidone by frequency category estimated from spontaneous reporting rates with paliperidone

Blood and lymphatic system disorders	
Very rare	Agranulocytosis, Thrombocytopenia
Endocrine disorders	
Not known	Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	
Very rare	Diabetic ketoacidosis, Hypoglycemia
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 apnea 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 postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone.

Overdose

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

Symptoms and signs

In general, expected signs and symptoms are those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, QT prolongation, and extrapyramidal symptoms. Torsade de pointes and ventricular fibrillation have been reported in the setting of overdose with oral paliperidone. In the case of acute overdosage, the possibility of multiple drug involvement should be considered.

Treatment

Consideration should be given to the extended-release *[prolonged-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.

PHARMACOLOGICAL PROPERTIES

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 hydrolyzed to paliperidone (see *Non-clinical Information*). Paliperidone is a centrally active dopamine D_2 antagonist with predominant serotonergic 5-HT_{2A} antagonistic activity. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H_1 histaminergic receptors. 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.

The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown. It has been proposed that the therapeutic activity of paliperidone in schizophrenia is

mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_{2A}$ may explain some of the other effects of paliperidone.

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), multicenter Thorough 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 ($C_{max\ ss}$ = 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 $C_{max\ ss}$ = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.

In the 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 maintenance 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® randomized 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 3-month paliperidone palmitate injection treatment group. No subject had a QTcLD value of > 480 msec at any point in the study.

Clinical studies

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, randomized, 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 (at dosages of 100 or 150 mg), 3-month paliperidone palmitate extended-release injectable suspension (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.

This study consisted of the following four treatment periods:

- Screening Phase of up to 28 days duration. A total of 1036 patients entered this phase of the study. Stabilized patients who entered the study who were already being treated with either 1-month paliperidone palmitate extended-release injectable suspension (at dosages of 100 or 150 mg) or 3-month paliperidone palmitate injectable (at dosages of 350 or 525 mg) for at least one 3 month injection cycle proceeded directly to the maintenance phase.

- Transition Phase, duration from 1 to 4 months applicable to those patients who entered the Screening Phase without being stabilized on 1-month or 3-month paliperidone palmitate extended-release injectable suspension. Patients who entered the study on an oral antipsychotic, injectable risperidone or previously initiated but not stabilized 1-month paliperidone palmitate extended-release injectable suspension (stability defined as at least 3 months of injections with the last two doses being the same strength), entered the transition phase and were treated with 1 to 5 injections of 1-month paliperidone palmitate extended-release injectable suspension over a period of 1 to 4 months, depending on the patient's previous treatment as well as individual efficacy and tolerability results. Patients who completed the transition phase, which included receiving 100 or 150 mg of 1-month paliperidone palmitate extended-release injectable suspension, proceeded to the maintenance phase.

- Maintenance Phase, 767 patients entered this open-label phase of the study. During the maintenance phase, patients received 1 dose of 1-month paliperidone palmitate extended-release injectable suspension at 100 or 150 mg dosage or 3-month paliperidone palmitate extended-release injectable suspension at 350 or 525 mg dosage and remained in this phase for 1 or 3 months, accordingly. The maintenance phase dose was matched

by straightforward progression (1-month paliperidone palmitate injectable to 1-month paliperidone palmitate injectable, or 3-month paliperidone palmitate injectable to 3-month paliperidone palmitate injectable) or by established conversion (1-month paliperidone palmitate injectable to 3-month paliperidone palmitate injectable) from the same dose that they had been receiving during the screening phase or at the end of the transition phase, as applicable.

Patients who completed the open-label maintenance phase and met the prospectively-defined criteria for clinical stability/symptom control which included PANSS total score of <70 points for the previous 2 assessments, proceeded to the double-blind phase.

- Double-blind Phase 12-month duration. A total of 702 stabilized patients were randomized in a 2:1 ratio to receive INVEGA HAFYERA® (478 patients) or 3-month paliperidone palmitate injectable (224 patients). Patients received either 2 injection cycles of INVEGA HAFYERA® (4 injections in total; INVEGA HAFYERA® with alternating placebo) or 4 injection cycles of 3-month paliperidone palmitate injectable:

INVEGA HAFYERA® treatment group:

- The open-label 100 mg 1-month paliperidone palmitate injectable and 3-month paliperidone palmitate injectable 350 mg doses were converted to double blind INVEGA HAFYERA® 700 mg doses.
- The open-label 150 mg 1-month paliperidone palmitate injectable and 525 mg 3-month paliperidone palmitate injectable doses were converted to double blind INVEGA HAFYERA® 1000 mg doses.

3-month paliperidone palmitate injectable treatment group:

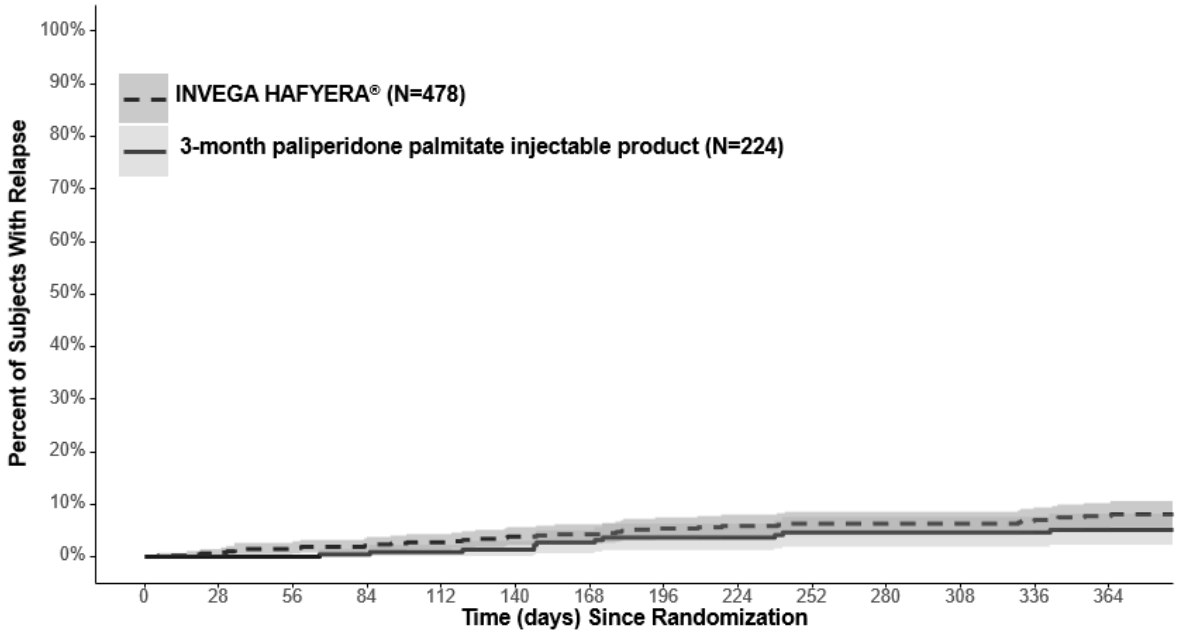
- The open-label 1-month paliperidone palmitate injectable doses (100 or 150 mg) were converted to double-blind 3-month paliperidone palmitate injectable suspension doses (350 or 525 mg).
- The open-label 3-month paliperidone palmitate injectable doses (350 or 525 mg) were continued at the same double-blind dose level.
- Dose adjustment was not permitted during the double-blind phase. Patients remained in this phase until they experienced a relapse event, met discontinuation/withdrawal criteria, or until predefined study conclusion criteria were reached.

The primary efficacy variable was time to first relapse in the double-blind phase. 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. 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 extended-release injectable suspension. The upper bound of the 95% CI (6.8%) of this difference was less than 10%, the prespecified non-inferiority margin. A Kaplan-Meier plot of time to relapse by treatment group is shown in Figure 1.

7.5% of patients in the INVEGA HAFYERA® treatment group and 4.9% of patients in the 3-month Paliperidone palmitate extended-release injectable suspension treatment group experienced a relapse event.

Figure 1: Kaplan-Meier plot of cumulative proportion of patients with relapse over time including 95% pointwise confidence bands



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

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 hydrolyzed 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. The release of INVEGA HAFYERA® is expected to last longer. Paliperidone plasma concentrations have only been studied up to 6 months after administration of INVEGA HAFYERA®. Based on population pharmacokinetic simulations paliperidone concentrations are expected to remain in plasma for up to approximately 4 years following a single 1000 mg dose of INVEGA HAFYERA®. The concentration of paliperidone remaining in the circulation approximately 4 years after a single dose of 1000 mg INVEGA HAFYERA® is expected to be low (< 1% of the average steady state levels).

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- normalized 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 a 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%.

Metabolism and Excretion

In a study with oral immediate-release ^{14}C-paliperidone, one week following administration of a single oral dose of 1 mg immediate-release ^{14}C-paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolized in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces. Four metabolic pathways have been identified *in vivo*, none of which accounted for more than 10% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates.

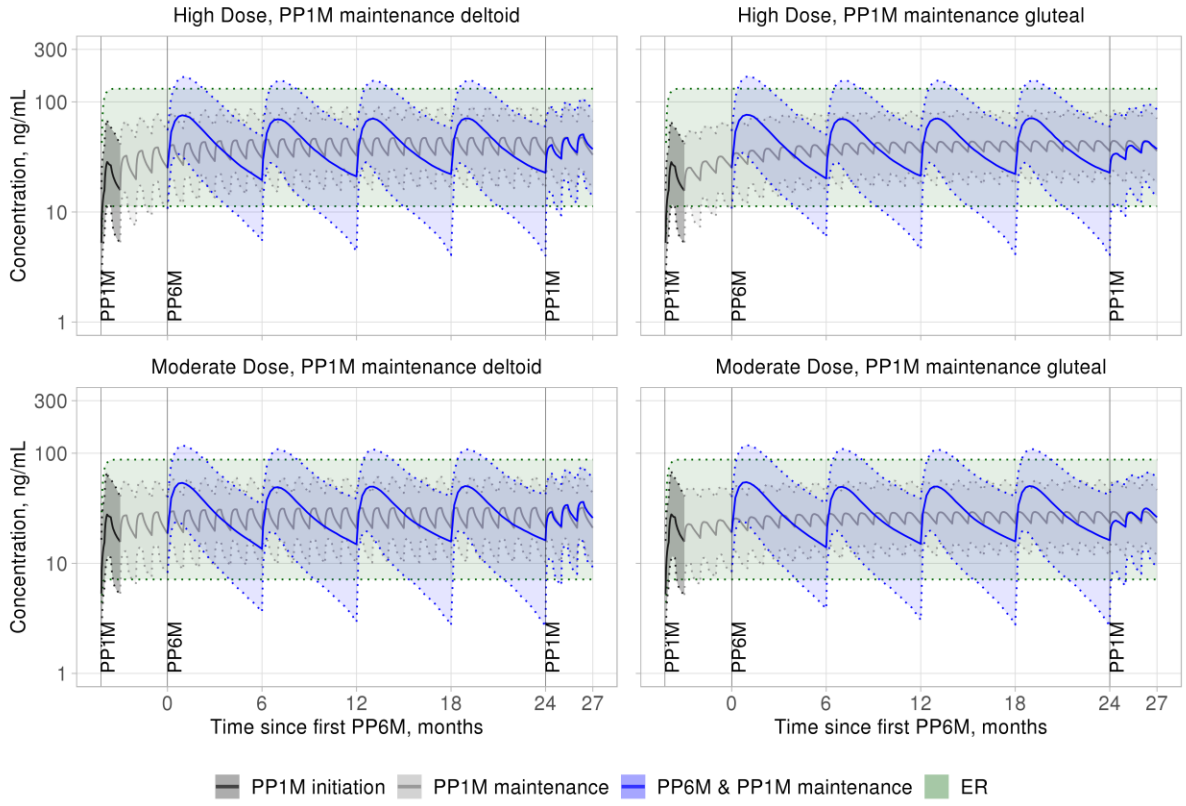
The median apparent half-life of paliperidone following a single INVEGA HAFYERA® of either 700 or 1000 mg was 148 and 159 days respectively. The concentration of paliperidone remaining in the circulation 18 months after dosing of 1000 mg 6-month paliperidone palmitate extended-release injectable suspension 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.

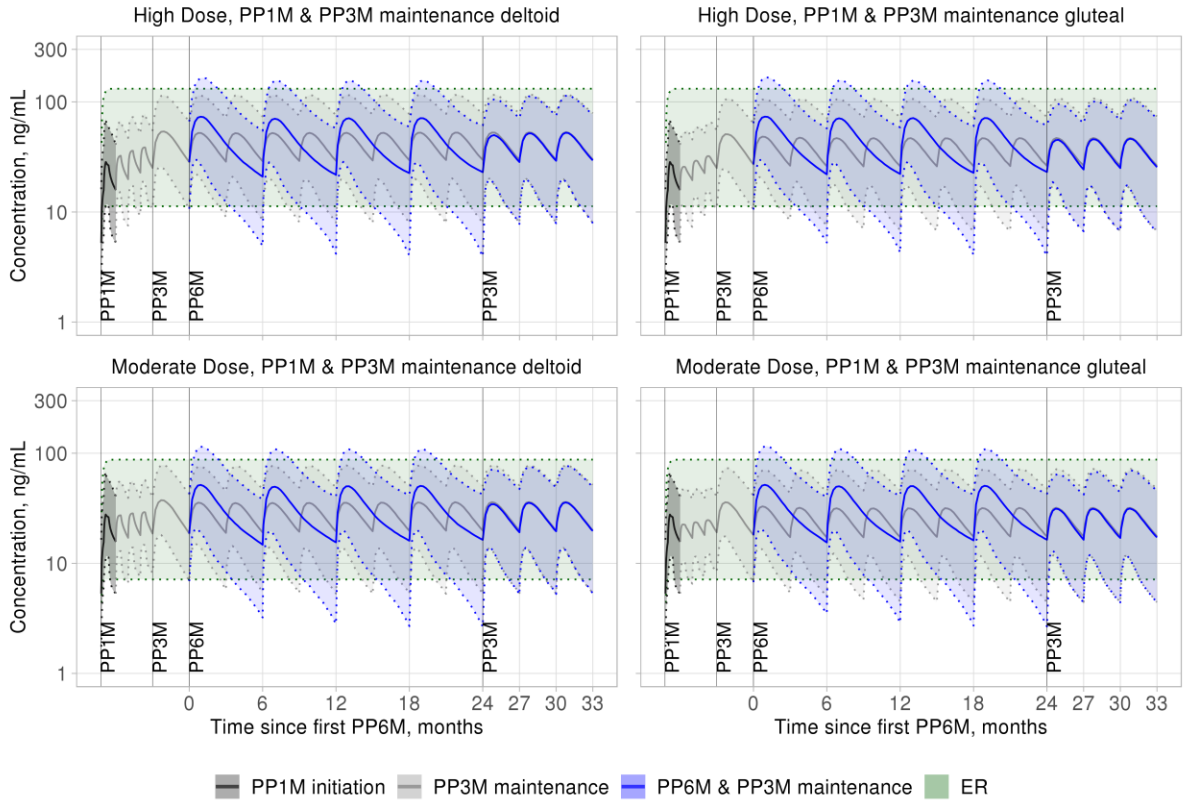
Intersubject variability in paliperidone PK parameters for INVEGA HAFYERA® was estimated by non-compartmental analysis in the randomized double-blind active controlled study. The variability in $AUC_{6months}$ after up to two administrations of 700 and 1000 mg doses of INVEGA HAFYERA® was moderate and 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.

Figure 2: Simulated paliperidone plasma concentrations versus time for INVEGA HAFYERA® (PP6M) 700 and 1000 mg eq. dose groups compared to monthly dosing of 1-month paliperidone palmitate injection (PP1M) 100 and 150 mg eq. The simulation paliperidone concentration range (90% prediction interval) following treatment with 8 mg and 12 mg oral paliperidone extended-release tablets is represented by the green shaded area.



PP1M: 1-month paliperidone palmitate injection
PP6M: 6-month paliperidone palmitate injection
ER: paliperidone extended-release tablets

Figure 3: Simulated paliperidone plasma concentrations versus time for INVEGA HAFYERA® (PP6M) 700 and 1000 mg eq. dose groups compared to 3-monthly dosing of 3-month paliperidone palmitate injection (PP3M) 350 and 525 mg eq. The simulation paliperidone concentration range (90% prediction interval) following treatment with 8 mg and 12 mg oral paliperidone extended-release tablets is represented by the green shaded area.



PP1M: 1-month paliperidone palmitate injection
PP3M: 3-month paliperidone palmitate injection
PP6M: 6-month paliperidone palmitate injection
ER: paliperidone extended-release tablets

Special populations

Elderly (65 years of age and older)

After oral administration of paliperidone in elderly subjects, the C_{max} and AUC increased 1.2-fold compared to young subjects. This may be attributable to age-related decreases in creatinine clearance (see *Dosage and Administration*).

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 prolonged 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.

Hepatic impairment

Paliperidone is not extensively metabolized in the liver. Although INVEGA HAFYERA® was not studied in patients with hepatic impairment, no dose adjustment is required in patients with mild or moderate hepatic impairment. In a 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. Paliperidone has not been studied in patients with severe hepatic impairment.

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

Based on *in vitro* studies utilizing human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone. Effect of smoking on the pharmacokinetics of paliperidone was not studied with INVEGA HAFYERA®. A population pharmacokinetic analysis based on data with oral paliperidone prolonged release tablets showed a slightly lower exposure to paliperidone in smokers compared with non-smokers. The difference is not likely to be of clinical relevance.

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.

NON-CLINICAL INFORMATION

Toxicology

As with other drugs that antagonize dopamine D_2 receptors, intramuscularly-injected paliperidone palmitate, as well as orally-dosed paliperidone, elevated serum prolactin levels in repeat-dose toxicity studies.

In a study in which juvenile rats were treated with oral paliperidone from days 24 to 73 of age, a reversible impairment of performance in a test of learning and memory was seen, in females only, with a no-effect dose of 0.63 mg/kg/day, which produced plasma levels (AUC) of paliperidone similar to those in adolescents dosed at 12 mg/day. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest dose tested (2.5 mg/kg/day), which produced plasma levels of paliperidone 2-3 times those in adolescents.

Juvenile dogs were treated for 40 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone which were similar to those in children and adolescents receiving the MRHD of risperidone. In addition, a delay in sexual maturation was seen at all doses in both males and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period.

Carcinogenicity

The carcinogenic potential of intramuscularly injected 1-month paliperidone palmitate extended-release injectable suspension was assessed in rats. There was an increase in mammary gland adenocarcinomas in female rats at 16, 47, and 94 mg/kg/month, which is 0.1, 0.3 and 0.6 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 mammary gland adenomas, fibroadenomas, and carcinomas at 0.3 and 0.6 times the MRHD based on mg/m^2 body surface area. A carcinogenicity study in mice has not been conducted with paliperidone palmitate.

Carcinogenicity studies with 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. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no-effect dose for these tumors was less than or equal to the maximum recommended human dose of risperidone based on mg/m^2 body surface area. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2 antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents to human risk is unclear.

Mutagenicity

No evidence of mutagenic potential for paliperidone was found in the Ames reverse mutation test, the mouse lymphoma assay, or the rat micronucleus test. Paliperidone palmitate showed no genotoxic properties in the Ames reverse mutation test or the mouse lymphoma assay.

Fertility

Although oral paliperidone treatment resulted in prolactin- and CNS-mediated effects, the fertility of male and female rats was not affected. At a maternally toxic dose, female rats showed a slightly lower number of live embryos.

PHARMACEUTICAL INFORMATION

List of Excipients

Inactive ingredients in INVEGA HAFYERA® are citric acid monohydrate, polyethylene glycol 4000, polysorbate 20, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injection.

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.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

Keep out of the sight and reach of children.

Ship and store in a horizontal position. See arrows on product carton for proper orientation.

Do not store above 30ºC.

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) suspension with a tip cap, plunger rod, backstop and a thin walled 20G, 1 ½-inch safety needle.

Instructions for Use and Handling and Disposal

Administer every 6 months **INVEGA HAFYERA® (paliperidone palmitate)**

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

For Gluteal Intramuscular injection only.

Shipping and storing the carton in a horizontal orientation improves the ability to resuspend this highly concentrated product.

Preparation

INVEGA HAFYERA® (6-month paliperidone palmitate extended release injectable suspension) requires longer and faster shaking than 1-month paliperidone palmitate extended-release injectable suspension.

INVEGA HAFYERA® should be administered by a healthcare professional as a single injection. Do not divide dose into multiple injections.

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

Dosing

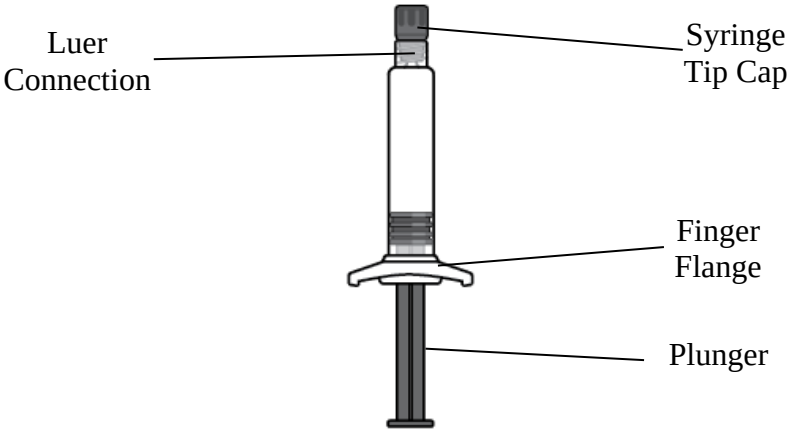
INVEGA HAFYERA® should be administered **once every 6 months.**

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.

Dose pack contents

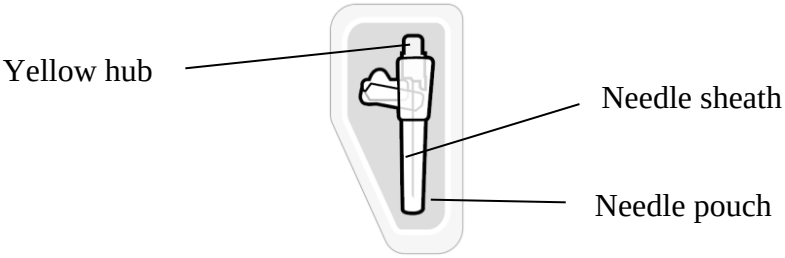
Prefilled syringe



Thin Wall Safety Needle

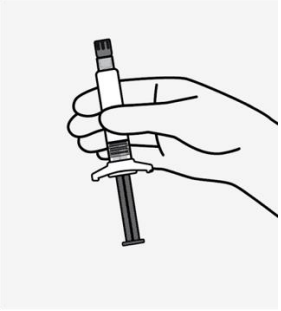
20G x 1½”

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

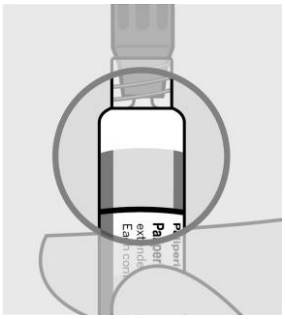
To ensure complete resuspension shake syringe with:

- **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 sides and top of syringe
- Uneven mix
- Thin liquid

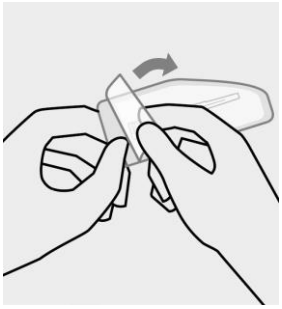
Product may clog.

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.

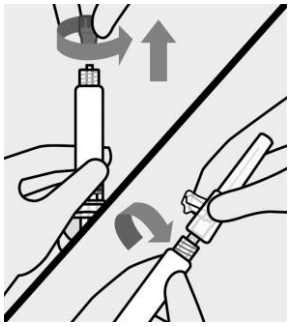


Remove syringe tip cap and attach needle

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



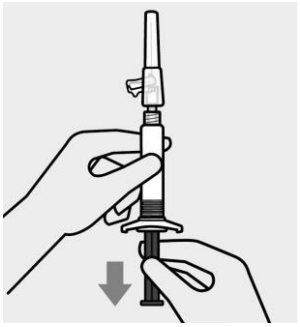
Only use the needle included in this kit

administration.

Pull back plunger

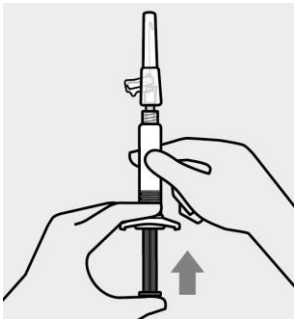
Hold the syringe upright.

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.



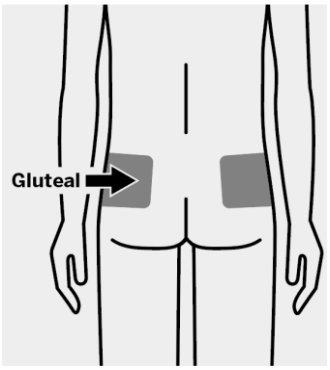
2. Slowly inject entire content and confirm

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.

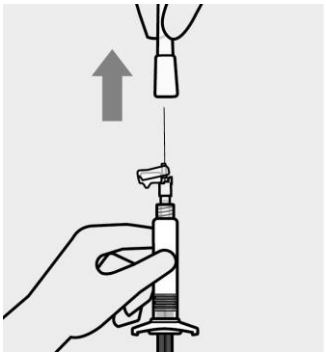
Do not touch, fan or blow the injection site after you have cleaned it.



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.

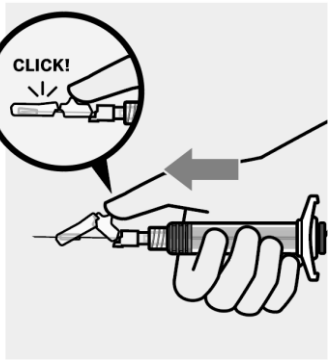
Remove needle from the muscle.

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.



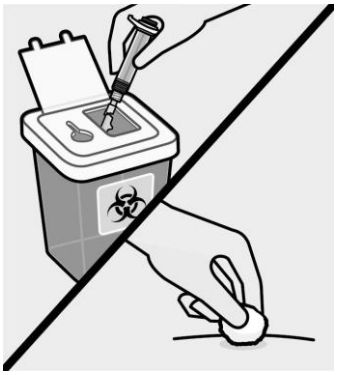
Dispose of properly and check injection site

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.



PRODUCT REGISTRANT

Johnson & Johnson International (Singapore) Pte. Ltd.
2 Science Park Drive, #07-13,
Ascent, Singapore Science Park 1,
Singapore 118222

BATCH RELEASER

Janssen Pharmaceutica NV
Turnhoutseweg 30,
B-2340 Beerse,
Belgium

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