NAME OF THE MEDICINAL PRODUCT

Trade Name

INVEGA® Sustenna™ (25 mg paliperidone as 39 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

INVEGA® Sustenna™ (50 mg paliperidone as 78 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

INVEGA® Sustenna™ (75 mg paliperidone as 117 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

INVEGA® Sustenna™ (100 mg paliperidone as 156 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

INVEGA® Sustenna™ (150 mg paliperidone as 234 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

International Non-Proprietary Name

Paliperidone palmitate

QUALITATIVE AND QUANTITATIVE COMPOSITION

INVEGA® Sustenna™ contains 25, 50, 75, 100, or 150 mg paliperidone (as 39, 78, 117, 156, or 234 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.

For excipients, see List of Excipients.

PHARMACEUTICAL FORM

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

CLINICAL PARTICULARS

Therapeutic Indications

INVEGA® Sustenna™ is indicated for the treatment of schizophrenia and for the prevention of recurrence of symptoms of schizophrenia.

Posology and Method of Administration

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

Recommended initiation of INVEGA® Sustenna™ is with a dose of 150 mg on treatment day 1 and 100 mg one week later, both administered in the deltoid muscle. The recommended monthly maintenance dose is 75 mg; some patients may benefit from lower or higher doses within the recommended range of 25 to 150 mg based on individual patient tolerability and/or efficacy. Following the second dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

Adjustment of the maintenance dose may be made monthly. When making dose adjustments, the prolonged-release characteristics of INVEGA® Sustenna™ should be considered (see Pharmacokinetic Properties), as the full effect of the dose adjustment may not be evident for several months.

Missed Doses

Avoiding Missed Doses. It is recommended that the second initiation dose of INVEGA® Sustenna™ be given one week after the first dose. To avoid a missed dose,

patients may be given the second dose 2 days before or after the one-week timepoint. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly timepoint.

If the target date for the second INVEGA® Sustenna™ injection (one week ± 2 days) is missed, the recommended reinitiation depends on the length of time which has elapsed since the patient's first injection.

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

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

Missed second initiation dose (> 7 weeks from first injection). If more than 7 weeks have elapsed since the first injection of INVEGA® Sustenna™, initiate dosing as described for the initial recommended initiation of INVEGA® Sustenna™ above.

Missed Maintenance Dose (1 Month to 6 Weeks). After initiation, the recommended injection cycle of INVEGA® Sustenna™ is monthly. If less than 6 weeks have elapsed since the last injection, then the previously stabilized dose should be administered as soon as possible, followed by injections at monthly intervals.

Missed Maintenance Dose (> 6 Weeks to 6 Months). If more than 6 weeks have elapsed since the last injection of INVEGA® Sustenna™, the recommendation is as follows:

For patients stabilised with doses of 25 to 100 mg:

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

For patients stabilised with 150 mg:

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

Missed Maintenance Dose (> 6 Months). If more than 6 months have elapsed since the last injection of INVEGA® Sustenna™, initiate dosing as described for the initial recommended initiation of INVEGA Sustenna™ above.

Administration Information

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

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

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

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

Patients with Hepatic Impairment

INVEGA® Sustenna™ has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment. (See Pharmacokinetic Properties)

Patients with Renal Impairment

INVEGA® Sustenna™ has not been systematically studied in patients with renal impairment (see Pharmacokinetic Properties). For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 mL/min), recommended initiation of INVEGA® Sustenna™ is with a dose of 100 mg on treatment day 1 and 75 mg one week later, both administered in the deltoid muscle. Thereafter, follow with monthly injections of 50 mg in either the deltoid or gluteal muscle adjusted within the range of 25 to 100 mg based on patient tolerability and/or efficacy.

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

Elderly

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

Adolescents and Children

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

Other Special Populations

No dose adjustment for INVEGA® Sustenna™ is recommended based on gender, race, or smoking status. (For pregnant women and nursing mothers, see Pregnancy and Lactation)

Switching From Other Antipsychotic Agents

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to INVEGA® Sustenna™, or concerning concomitant administration with other antipsychotics. For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA® Sustenna™ (see Posology and Method of Administration)

Previous oral antipsychotics can be discontinued at the time of initiation of treatment with INVEGA® Sustenna™. INVEGA® Sustenna™ should be initiated as described at the beginning of Posology and Method of Administration section above.

When switching patients currently at steady-state on a long-acting injectable antipsychotic, initiate INVEGA® Sustenna™ therapy in place of the next scheduled injection. INVEGA® Sustenna™ should then be continued at monthly intervals. The one week initiation dosing regimen as described at the beginning of Posology and Method of Administration section above is not required.

Patients previously stabilised on different doses of RISPERDAL CONSTA prolonged-release suspension for intramuscular injection can attain similar active moiety steady-state exposure during maintenance treatment with INVEGA® Sustenna™ monthly doses according to the following:

Doses of RISPERDAL CONSTA and INVEGA® Sustenna™ needed to attain similar active moiety exposure at steady-state

Previous RISPERDAL® CONSTA® Dose	INVEGA® Sustenna™ Injection
25 mg every 2 weeks	50 mg monthly
37.5 mg every 2 weeks	75 mg monthly
50 mg every 2 weeks	100 mg monthly

Discontinuation of the previous antipsychotic should be made in accordance with the appropriate prescribing information. If INVEGA® Sustenna™ is discontinued, its prolonged-release characteristics must be considered. As recommended with other antipsychotic medications, the need for continuing existing extrapyramidal symptoms (EPS) medication should be re evaluated periodically.

Contraindications

INVEGA® Sustenna™ 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® Sustenna™ is contraindicated in patients with a known hypersensitivity to risperidone.

Special Warnings and Special Precautions for Use

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® Sustenna™, should be discontinued.

Tardive Dyskinesia

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® Sustenna™, should be considered.

QT Interval

As with other antipsychotics, caution should be exercised when INVEGA® Sustenna™ 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.

Hyperglycemia and Diabetes Mellitus

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

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.*Orthostatic Hypotension*

Paliperidone may induce orthostatic hypotension in some patients based on its alpha-blocking activity. INVEGA® Sustenna™ 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® Sustenna™ 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® Sustenna™ has not been studied in elderly patients with dementia.

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 leucopenia, neutropenia, and agranulocytosis have been reported with antipsychotic agents, including INVEGA® Sustenna™. 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® Sustenna™ should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 X 10^9/L) should discontinue INVEGA® Sustenna™ and have their WBC followed until recovery.

Venous Thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with INVEGA® Sustenna™ and 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® Sustenna™, 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 Undesirable Effects).

Body Temperature Regulation

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

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® Sustenna™ into a blood vessel.

Interactions with Other Medicinal Products and Other Forms of Interaction

Caution is advised when prescribing INVEGA® Sustenna™ 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® Sustenna™ 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 Undesirable Effects), INVEGA® Sustenna™ 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 Special Warnings and Special Precautions for Use: *Orthostatic Hypotension*), an additive effect may be observed when INVEGA® Sustenna™ 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® Sustenna™ and lithium is unlikely.

Potential for Other Drugs to Affect INVEGA® Sustenna ™

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 CLINICAL PHARMACOLOGY: Pharmacokinetics: Metabolism and Elimination). In an interaction study in healthy subjects in which oral palieridone 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® Sustenna™ should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA® Sustenna™ should be re-evaluated and decreased if necessary.

Paliperidone, 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® Sustenna™ intramuscular injection. This interaction has not been studied with INVEGA® Sustenna™.

Pharmacokinetic interaction between lithium and INVEGA® Sustenna™ is unlikely.

Concomitant Use of INVEGA® Sustenna ™with Risperidone

Concomitant Use of INVEGA® Sustenna™ with risperidone has not been studied. Since paliperidone is an active metabolite of risperidone, consideration should be given to the additive paliperidone exposure if risperidone is coadministered with INVEGA® Sustenna™.

Pregnancy and Lactation

Pregnancy

The safety of intramuscularly-injected paliperidone palmitate or orally-dose paliperidone for use during human pregnancy 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 paliperidone palmitate. The high doses were toxic to the mothers. The offspring was not affected at oral exposures 20- to 22-fold the maximum human exposure, or intramuscular exposures 6-fold the maximum human exposure. 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.

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

Lactation

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

Effects on Ability to Drive and Use Machines

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

Undesirable Effects

The data described in this section are derived from clinical trial database consisting of a total of 3817 subjects with schizophrenia who received at least one dose of INVEGA® Sustenna™ in the recommended dose range of 25 to 150 mg and a total of 510 subjects with schizophrenia who received placebo. Among the 3817 INVEGA®

Sustenna™-treated subjects, 1293 received INVEGA® Sustenna™ in four fixed-dose, double-blind, placebo-controlled trials (one 9-week and three 13-week studies), 849 received INVEGA® Sustenna™ in the long-term recurrence prevention trial (of whom 205 continued to receive INVEGA® Sustenna™ during the double-blind placebo-controlled phase of this study), and 1675 received INVEGA® Sustenna™ in five non-placebo controlled trials (a noninferiority active-comparator trials, one long-term open-label pharmacokinetic and safety study and an injection site [deltoid-gluteal] cross-over trial). One of the 13-week studies included a 150 mg INVEGA® Sustenna™ inititation dose followed by treatment with either 25 mg, 100 mg, or 150 mg every 4 weeks.

The majority of ADRs were mild to moderate in severity.

Double-Blind Placebo-Controlled Data

Adverse drug reactions (ADRs) reported by ≥ 2% of INVEGA® Sustenna™-treated subjects with schizophrenia in the four fixed-dose, double-blind, placebo-controlled trials are shown in Table 1.

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

		INVEGA® Sustenna™					
System/Organ Class	**Placebo**[a]	**25 mg**	**50 mg**	**100 mg**	**150/25 mg**[b]	**150/100 mg**[b]	**150/150 mg**[b]
Adverse Reaction	**(N=510)**	**(N=130)**	**(N=302)**	**(N=312)**	**(N=160)**	**(N=165)**	**(N=163)**
Total percentage of subjects with adverse reaction	46	54	50	52	44	43	47
Infections and infestations							
Upper respiratory tract infection	2	2	2	2	1	2	4
Psychiatric disorders							
Agitation	7	10	5	9	8	5	4
Insomnia	15	15	15	13	12	10	13
Nightmare	<1	2	0	0	0	0	0
Nervous system disorders							
Akathisia	3	2	2	3	1	5	6
Dizziness	1	6	2	4	1	4	2
Extrapyramidal disorder	1	5	2	3	1	0	0
Headache	12	11	11	15	11	7	6
Somnolence/sedation	3	5	7	4	1	5	5
Vascular disorders							
Hypertension	1	2	1	1	1	1	0
Gastrointestinal disorders							
Abdominal pain upper	1	0	1	2	1	1	1
Constipation	5	3	5	5	2	4	1
Diarrhoea	2	0	3	2	1	2	2
Dry mouth	1	3	1	0	1	1	1
Nausea	3	4	4	3	2	2	2
Toothache	1	1	1	3	1	2	3
Vomiting	4	5	4	2	3	2	2
Musculoskeletal and connective tissue disorders							
Pain in extremity	1	0	2	2	2	3	0
General disorders and administration site conditions							

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

		INVEGA® Sustenna™					
System/Organ Class	**Placebo**[a]	**25 mg**	**50 mg**	**100 mg**	**150/25 mg**[b]	**150/100 mg**[b]	**150/150 mg**[b]
Adverse Reaction	**(N=510)**	**(N=130)**	**(N=302)**	**(N=312)**	**(N=160)**	**(N=165)**	**(N=163)**
Asthenia	0	2	1	<1	0	1	1
Fatigue	1	1	2	2	1	2	1
Injection site pain[c]	2	0	3	5	9	7	8
Investigations							
Weight increased	1	4	4	1	1	1	2

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

[b] Initial deltoid injection of 150 mg followed by either 25 mg, 100 mg, or 150 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (25 mg, 50 mg, and 100 mg) are from studies involving only gluteal injection. (See Pharmacodynamic Properties)

[c] Injection site pain includes injection site pain, pruritus, nodule, and induration.

In the long-term recurrence prevention trial, adverse reaction types, frequencies, and severities during the open-label phases of this study were generally comparable to those observed in the four 13-week and the 9-week placebo-controlled fixed-dose studies shown in Table 1. Adverse reactions reported during the double-blind phase of this study were generally similar in type and severity to those observed in the open-label phases.

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 ADRs reported with paliperidone and/or risperidone in clinical trials.

ADRs reported with paliperidone and/or risperidone by ≥ 2% of INVEGA® Sustenna™-treated subjects in a pooled dataset of the 4 double-blind, placebo-controlled schizophrenia trials are shown in Table 2a.

Table 2a. ADRs Reported with Paliperidone and/or Risperidone by ≥2% of INVEGA® Sustenna™-treated Subjects in a Pooled Dataset of the 4 Double-blind, Placebo-controlled Schizophrenia Trials. The Terms within each System Organ Class are Sorted Alphabetically.

System/Organ Class
Adverse Reaction
Psychiatric disorders
Anxiety
Nervous system disorders
Akathisia*, Parkinsonism*
Gastrointestinal disorders
Abdominal discomfort
Musculoskeletal and connective tissue disorders
Musculoskeletal pain
General disorders and administration site conditions

System/Organ Class Adverse Reaction
Injection site reaction

* **Akathisia includes**: hyperkinesia, restless legs syndrome, restlessness; **Parkinsonism includes**: akinesia, bradykinesia, cogwheel rigidity, drooling, extrapyramidal symptoms, glabellar reflex abnormal, muscle rigidity, muscle tightness, musculoskeletal stiffness.

ADRs reported with paliperidone and/or risperidone by <2% of INVEGA® Sustenna™-treated subjects in a pooled dataset of the 4 double-blind, placebo-controlled schizophrenia trials are shown in Table 2b.

Table 2b. ADRs Reported with Paliperidone and/or Risperidone by <2% of INVEGA® Sustenna™-treated Subjects in a Pooled Dataset of the 4 Double-blind, Placebo-controlled Schizophrenia Trials. The Terms within each System Organ Class are Sorted Alphabetically.

System/Organ Class Adverse Reaction
Infections and infestations
Acarodermatitis, Bronchitis, Cellulitis, Ear infection, Eye infection, Influenza, Onychomycosis, Pneumonia, Respiratory tract infection, Sinusitis, Subcutaneous abscess, Tonsillitis, Urinary tract infection
Blood and lymphatic system disorders
Neutropenia, White blood cell count decreased
Immune system disorders
Hypersensitivity
Metabolism and nutritional disorders
Anorexia, Blood cholesterol increased, Blood triglycerides increased, Decreased appetite, Hyperglycaemia, Increased appetite, Polydipsia, Weight decreased
Psychiatric disorders
Depression, Sleep disorder
Nervous system disorders
Balance disorder, Cerebrovascular accident, Convulsion*, Disturbance in attention, Dizziness postural, Dysarthria, Dyskinesia*, Dystonia*, Hypoaesthesia, Paraesthesia, Psychomotor hyperactivity, Syncope, Tardive dyskinesia, Tremor
Eye disorders
Dry eye, Eye rolling, Lacrimation increased, Ocular hyperaemia,Vision blurred
Ear and labyrinth disorders
Ear pain, Vertigo
Cardiac disorders
Atrioventricular block, Bradycardia, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Palpitations, Postural orthostatic tachycardia syndrome, Sinus arrhythmia, Tachycardia
Vascular disorders
Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders

System/Organ Class Adverse Reaction
Cough, Dyspnoea, Epistaxis, Nasal congestion, Pharyngolaryngeal pain, Pulmonary congestion, Respiratory tract congestion, Wheezing
Gastrointestinal disorders Dyspepsia, Dysphagia, Faecal incontinence, Flatulence, Gastroenteritis, Swollen tongue
Hepatobiliary disorders Gamma-glutamyltransferase increased, Hepatic enzyme increased, Transaminases increased
Skin and subcutaneous tissue disorder Acne, Dry skin, Eczema, Erythema, Hyperkeratosis, Pruritus, Rash, Urticaria
Musculoskeletal and connective tissue disorders Arthralgia, Back pain, Joint stiffness, Joint swelling, Muscle spasms, Neck pain
Renal and urinary disorders Dysuria, Pollakiuria, Urinary incontinence
Reproductive system and breast disorders Amenorrhoea, Ejaculation disorder, Erectile dysfunction, Galactorrhoea, Gynaecomastia, Sexual dysfunction, Vaginal discharge
General disorders and administration site conditions Chest discomfort, Chills, Face oedema, Gait abnormal, Induration, Malaise, Oedema*, Pyrexia, Thirst
Injury, poisoning and procedural complications Fall

* **Convulsion includes:** grand mal convulsion; **Dyskinesia includes:** athetosis, chorea, choreoathetosis, movement disorder, muscle twitching, myoclonus; **Dystonia includes:** blepharospasm, cervical spasm, emprosthotonus, facial spasm, hypertonia, laryngospasm, muscle contractions involuntary, myotonia, oculogyration, opisthotonus, oropharyngeal spasm, pleurothotonus, risus sardonicus, tetany, tongue paralysis, tongue spasm, torticollis, trismus; **Oedema includes:** generalised oedema, oedema peripheral, pitting oedema.

ADRs reported with paliperidone and/or risperidone in other clinical trials but not reported by INVEGA® Sustenna™-treated subjects in a pooled dataset of the 4 double-blind, placebo-controlled schizophrenia trials are shown in Table 2c.

Table 2c. ADRs Reported with Paliperidone and/or Risperidone in Other Clinical Trials but not Reported by INVEGA® Sustenna™- treated Subjects in a Pooled Dataset of the 4 Double-blind, Placebo-controlled Schizophrenia Trials. The Terms within each System Organ Class are Sorted Alphabetically.

System/Organ Class
Adverse Reaction
Infections and infestations Cystitis
Blood and lymphatic system disorders Anaemia, Eosinophil count increased, Haematocrit decreased
Immune system disorders Anaphylactic reaction
Endocrine disorders Glucose urine present, Hyperprolactinaemia
Metabolism and nutritional disorders Hyperinsulinaemia
Psychiatric disorders Anorgasmia, Blunted affect, Confusional state, Libido decreased
Nervous system disorders Cerebrovascular disorder, Coordination abnormal, Depressed level of consciousness, Diabetic coma, Head titubation, Loss of consciousness, Neuroleptic malignant syndrome, Unresponsive to stimuli
Eye disorders Conjunctivitis, Eye movement disorder, Glaucoma, Photophobia
Ear and labyrinth disorders Tinnitus
Vascular disorders Flushing, Hypotension, Ischaemia
Respiratory, thoracic and mediastinal disorders Dysphonia, Hyperventilation, Pneumonia aspiration, Rales
Gastrointestinal disorders Cheilitis, Faecaloma, Intestinal obstruction
Skin and subcutaneous tissue disorders Drug eruption, Seborrhoeic dermatitis, Skin discolouration
Musculoskeletal and connective tissue disorders Blood creatine phosphokinase increased, Muscular weakness, Posture abnormal, Rhabdomyolysis
Reproductive system and breast disorders Breast discharge, Breast discomfort, Breast engorgement, Breast enlargement, Menstrual disorder*, Menstruation delayed
General disorders and administration site conditions Body temperature decreased, Body temperature increased, Drug withdrawal syndrome

***Menstrual disorder includes:** menstruation irregular, oligomenorrhoea.

Events of Particular Interest to the Class

Extrapyramidal Symptoms (EPS). Pooled data from the two 13-week, fixed-dose, double-blind, placebo-controlled schizophrenia trials (see Pharmacodynamic Properties: Clinical Efficacy) showed no differences in treatment-emergent EPS between placebo and INVEGA® Sustenna™ Evaluation of EPS included a pooled analysis of the following EPS groups: dyskinesia, dystonia, hyperkinesia, Parkinsonism, and tremor. The results from the 13-week study involving the 150 mg initiation dosing, the 9-week, fixed-dose, double-blind, placebo-controlled trial, and across all phases of the long-term recurrence prevention trial exhibited comparable findings.

Weight Gain. The proportions of subjects meeting a weight gain criterion of ≥ 7% of body weight in the 13-week study involving 150 mg initiation dosing, weight increases from baseline of ≥ 7% were more common among subjects in the INVEGA® Sustenna™ groups than in the placebo group. The proportion of subjects with an abnormal weight increase ≥ 7% showed a dose-related trend, with a 5% incidence rate in the placebo group compared with rates of 6%, 8%, and 13% in the INVEGA® Sustenna™ 25 mg, 100 mg, and 150 mg groups, respectively.

In the two 13-week, fixed-dose, double-blind, placebo-controlled trials (pooled data), the proportions of subjects meeting a weight gain criterion of ≥ 7% of body weight were 6%, 9%, and 10% in the INVEGA® Sustenna™ 25, 50, and 100 mg groups, respectively, compared with 2% in the placebo group. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, 8% and 6% in the INVEGA® Sustenna™ 50 and 100 mg groups, respectively, met this criterion compared with 4% in the placebo group.

During the 33-week open-label transition/maintenance period of the long-term recurrence prevention trial, 12% of INVEGA® Sustenna™-treated subjects met this criterion (weight gain of ≥ 7% from double-blind phase to endpoint); the mean (SD) weight change from open-label baseline was +0.7 (4.79) kg. In the variable length double-blind phase, this criterion was met by 6% of INVEGA® Sustenna™-treated subjects (median duration 171 days [range 1-407 days]) compared with 3% of placebo-treated subjects (median duration 105 days [range 8-441 days]); the mean (SD) weight change from double-blind baseline was +0.5 (3.83) kg for INVEGA® Sustenna™ compared with -1.0 kg (3.08) for placebo. Similar results were observed in the open-label extension phase of this study.

Laboratory Tests: Serum Prolactin. Based on pooled data from the two 13-week, fixed-dose double-blind, placebo-controlled trials (see Pharmacodynamic Properties: Clinical Efficacy), median increases in serum prolactin were observed in subjects of both genders who received INVEGA® Sustenna™. The results from the 13-week study involving 150 mg initiation dosing, the 9-week, fixed-dose, double-blind, placebo-controlled trial, and the double-blind phase of the recurrence prevention trial exhibited comparable findings.

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with paliperidone and/or risperidone are included in Table 3. In this table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10

Uncommon	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000, including isolated reports

In Table 3, ADRs are presented by frequency category based on spontaneous reporting rates.

Table 3. Adverse Drug 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	Diabetes mellitus, Diabetic ketoacidosis, Hypoglycaemia
Not known	Water intoxication
Psychiatric disorders	
Very rare	Mania
Nervous system disorders	
Very rare	Dysgeusia
Cardiac disorders	
Very rare	Atrial fibrillation
Vascular disorder	
Very rare	Deep vein thrombosis, Pulmonary embolism
Respiratory, thoracic and mediastinal disorders	
Very rare	Sleep apnoea syndrome
Gastrointestinal disorders	
Very rare	Pancreatitis
Hepatobiliary disorders	
Not known	Jaundice
Skin and subcutaneous tissue disorders	
Rare	Angioedema
Very rare	Alopecia
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 haematoma
Not known	Injection site cyst, Injection site necrosis, Injection site ulcer

Overdose

Because INVEGA® Sustenna™ is to be administered by health care professionals, the potential for overdosage by patients is low.

Symptoms

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 prolonged-release nature of INVEGA® Sustenna™ 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

Paliperidone palmitate, the active ingredient in INVEGA® Sustenna™-, is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives (atypical neuroleptic antipsychotic, ATC Code: N05AX13). INVEGA® Sustenna™- contains a racemic mixture of (+)- and (-)-paliperidone.

Mechanism of Action

Paliperidone palmitate is hydrolyzed to paliperidone (see Preclinical Safety Data). 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. However, it has been proposed that the drug's therapeutic activity 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.

Electrophysiology

The effects of oral paliperidone on the QT interval were evaluated in two randomized, double-blind, multicenter, phase 1 studies in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

In the first phase 1 study (n = 141), subjects were randomized to receive either 7 days of immediate-release oral paliperidone once daily (titrated from 4 to 8 mg) or a single dose of moxifloxacin (400 mg). The 8 mg once daily dose of immediate-release oral paliperidone (n = 50, $C_{max\ ss}$ = 113 ng/mL) achieved a mean steady-state maximum plasma concentration greater than 2-fold the exposure observed with the maximum recommended 150 mg dose of INVEGA Sustenna™ administered in the deltoid muscle (predicted median $C_{max\ ss}$ = 50 ng/mL). In the model-adjusted day-averaged linear-derived QT correction (QTcLD), there was a mean increase of 5.5 msec (90% CI: 3.66; 7.25) in the INVEGA® Sustenna™ treatment group (n = 50).

In the second phase 1 study (n = 109), subjects were randomized to receive either placebo, the maximum recommended dose of oral extended-release paliperidone (12

mg once daily), subsequently titrated to a dose above the recommended range (18 mg once daily), or an active control from the same pharmacologic class of drugs (400 mg quetiapine twice daily). The primary comparison in this 10-day noninferiority study was between extended-release paliperidone 12 mg and quetiapine. The least squares mean change from baseline in QTcLD at each individual's observed t_{max} was estimated to be 5.1 ms lower for 12 mg extended-release paliperidone (mean C_{max} 34 ng/mL) compared with 400 mg quetiapine twice daily (mean C_{max} 1183 ng/mL) (90% CI: -9.2; -0.9), meeting the prespecified noninferiority criterion of 10 ms. The mean change from baseline in QTcLD at each individual's observed t_{max} was estimated to be 2.3 ms lower for 18 mg extended-release paliperidone (mean C_{max} 53 ng/mL) compared with 400 mg quetiapine twice daily (mean C_{max} 1183 ng/mL) (90% CI: -6.8; 2.3).

The mean change from baseline in QTcLD at each individual's observed t_{max} was estimated to be 1.5 ms higher (90% CI: -3.3; 6.2) for 12 mg extended-release paliperidone and 8.0 ms higher (90% CI: 3.1; 12.9) for 400 mg quetiapine twice daily compared with the mean change from baseline in QTcLD at median observed t_{max} (of the active drug in the comparison) in the concurrent placebo arm. The mean change from baseline in QTcLD at each individual's observed t_{max} was estimated to be 4.9 ms higher (90% CI: -0.5; 10.3) for extended-release paliperidone 18 mg and 7.5 ms higher (90% CI: 2.5; 12.5) for quetiapine 400 mg twice daily compared with the mean change from baseline in QTcLD at median observed t_{max} (of the active drug in the comparison) in the concurrent placebo arm.

None of the subjects had a change from baseline exceeding 60 msec or a QTcLD exceeding 500 msec at any time during either of these studies.

In the three fixed-dose efficacy studies of oral extended-release paliperidone, extensive electrocardiography (ECG) measurements were taken at 15 time points on specified days (including the times of expected C_{max}) using a standardized methodology. Mean QTcLD increase did not exceed 5 msec in any treatment group at any time point, based on pooled data from 836 subjects treated with extended-release paliperidone, 357 subjects treated with olanzapine, and 350 subjects treated with placebo. One subject each in the extended-release paliperidone 12 mg and olanzapine groups had a change exceeding 60 msec at one time-point during these studies (increases of 62 and 110 msec, respectively).

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

Clinical Efficacy

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

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

In a 13-week study (n=636) comparing three fixed doses of INVEGA® Sustenna™ (initial deltoid injection of 150 mg followed by 3 gluteal or deltoid doses of either 25 mg/4 weeks, 100 mg/4 weeks or 150 mg/4 weeks) to placebo, all three doses of INVEGA® Sustenna™ were superior to placebo in improving the PANSS total score. In this study, both the 100 mg/4 weeks and 150 mg /4 weeks, but not the 25 mg/4 weeks, treatment groups demonstrated statistical superiority to placebo for the PSP score. These results support efficacy across the entire duration of treatment and improvement in PANSS and was observed as early as day 4 with significant separation from placebo in the 25 mg and 150 mg INVEGA® Sustenna™groups by day 8.

In another 13-week study (n=349) comparing three fixed doses of INVEGA® Sustenna™ (50 mg/4 weeks, 100 mg/4 weeks, and 150 mg/4 weeks) to placebo, only 100 mg/4 weeks of INVEGA® Sustenna™ was superior to placebo in improving the PANSS total score. In this study, both the 50 mg/4 weeks and the 100 mg/4 weeks doses were superior to placebo in improving the PSP score. Although a 150 mg dose was included in this study, there were insufficient numbers of subjects receiving this dose to allow definitive conclusions concerning the efficacy of this dose.

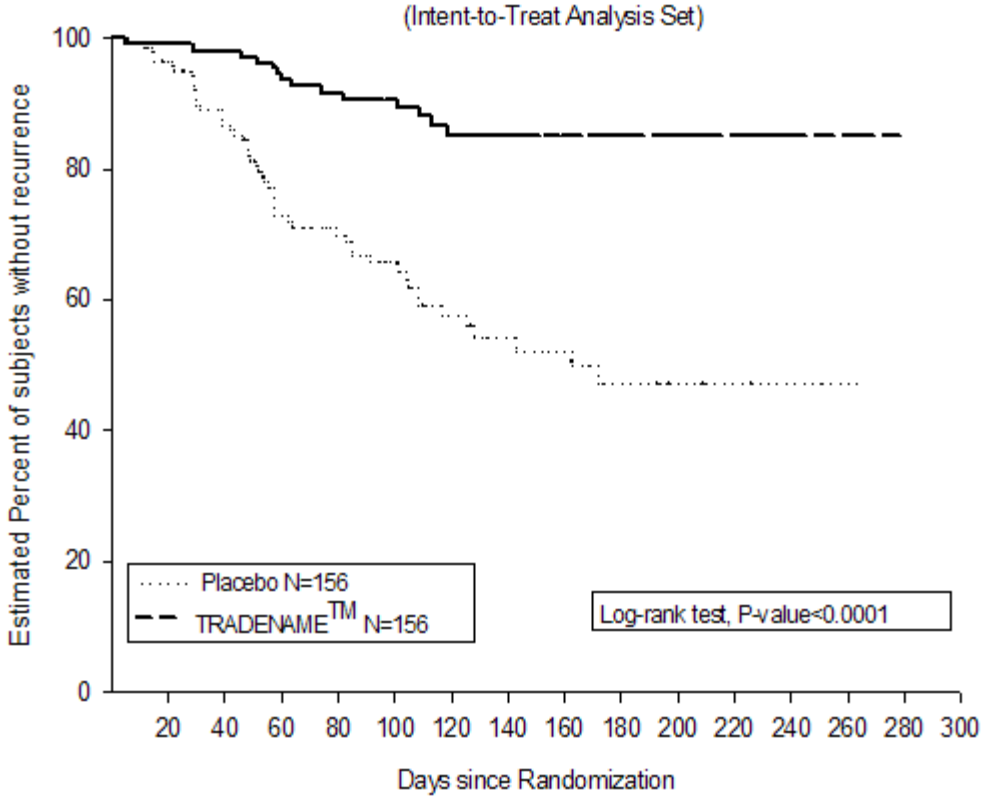
In a third 13-week study (n=513) comparing three fixed doses of INVEGA® Sustenna™ (25 mg/4 weeks, 50 mg/4 weeks, and 100 mg/4 weeks) to placebo, all three doses of INVEGA® Sustenna™ were superior to placebo in improving the PANSS total score. In this study, none of the paliperidone dose groups achieved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

In the 9-week study (n=197) comparing two fixed doses of INVEGA® Sustenna™ 50 mg/4 weeks and 100 mg/4 weeks) to placebo, both doses of INVEGA® Sustenna™ were superior to placebo in improving PANSS total score.

The efficacy of INVEGA® Sustenna™ in maintaining symptomatic control and delaying relapse of schizophrenia was established in a longer-term double-blind, placebo-controlled, flexible-dose study involving 849 non-elderly adult subjects who met DSM-IV criteria for schizophrenia. This study included a 33-week open-label acute treatment and stabilization phase, a randomized, placebo-controlled phase to observe for relapse and a 52-week open-label extension period. In this study, doses of INVEGA® Sustenna™ included 25, 50, 75, and 100 mg administered monthly; the 75 mg dose was allowed only in the 52-week open-label extension. Subjects initially

received flexible doses (25-100 mg) of INVEGA® Sustenna™ during a 9-week transition period. In order to enter the 24-week maintenance period, subjects were required to have a PANSS score of ≤ 75. Dosing adjustments were only allowed in the first 12 weeks of the maintenance period.. During the variable length double-blind phase, patients were randomized to either the same dose of INVEGA® Sustenna™ (median duration 171 days [range 1 day - 407 days]) they received during the stabilization phase, administered every 4 weeks, or to placebo (median duration 105 days [range 8 days - 441 days]). A total of 410 stabilized patients were randomized to either INVEGA® Sustenna™ or to placebo until they experienced a relapse of schizophrenia symptoms. Relapse was pre-defined as time to first 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, or a score of ≥ 5 (if the maximum baseline score was ≤ 3) or ≥ 6 (if the maximum baseline score was 4) on two consecutive assessments of the individual PANSS items P1 (Delusions), P2 (Conceptual disorganization), P3 (Hallucinatory behavior), P6 (Suspiciousness/persecution), P7 (Hostility), or G8 (Uncooperativeness). The primary efficacy variable was time to relapse. A pre-planned interim analysis (after 68 recurrence events occurred), showed a significantly longer time to relapse in patients treated with INVEGA® Sustenna™ compared to placebo (Figure 1), and the study was stopped early because maintenance of efficacy was demonstrated.

Figure1. Kaplan-Meier Plot of Time to Recurrence - Interim Analysis
(Intent-to-Treat Analysis Set)



The result of the analysis based on the final data, including all data up to the date of study termination, was consistent with that of the primary efficacy analysis based on the interim data.
An examination of population subgroups did not reveal any clinically significant differences in responsiveness on the basis of gender, age, or race.

Pharmacokinetic Properties

Absorption and Distribution

Due to its extremely low water solubility, paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. Following a single intramuscular dose, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median tmax of 13 days. The release of the drug starts as early as day 1 and lasts for as long as 126 days.
Following intramuscular injection of single doses (25-150 mg) in the deltoid muscle, on average, a 28% higher Cmax was observed compared with injection in the gluteal muscle. The two initial deltoid intramuscular injections of 150 mg on day 1 and 100 mg on day 8 help attain therapeutic concentrations rapidly. The release profile and dosing regimen of INVEGA® Sustenna™ results in sustained therapeutic concentrations. The total exposure of paliperidone following INVEGA® Sustenna™ administration was dose-proportional over a 25-150 mg dose range, and less than dose-proportional for Cmax for doses exceeding 50 mg. The mean steady-state peak:trough ratio for a INVEGA® Sustenna™ dose of 100 mg was 1.8 following gluteal administration and 2.2 following deltoid administration. The median apparent half-life of paliperidone following INVEGA® Sustenna™ administration over the dose range of 25-150 mg ranged from 25-49 days.
Following administration of paliperidone palmitate the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6-1.8.
Based on a population analysis, the apparent volume of distribution of paliperidone is 391 L. The plasma protein binding of racemic paliperidone is 74%.

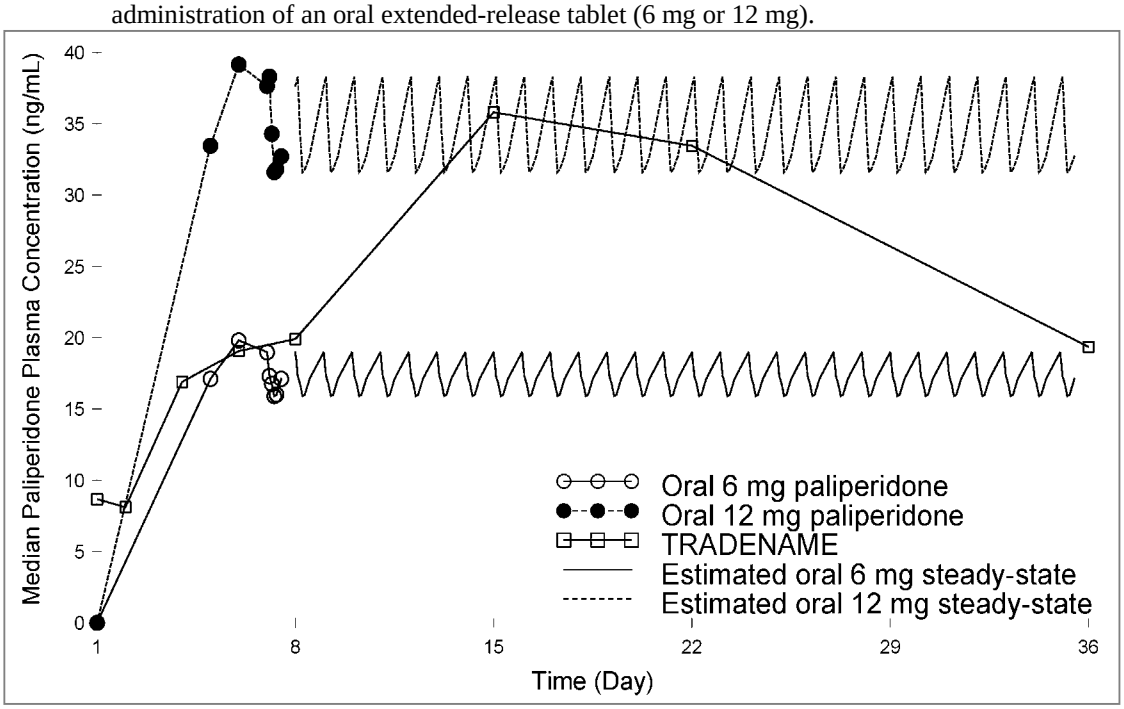
Metabolism and Elimination

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 6.5% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although in vitro studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence in vivo that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernable difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates. In vitro studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.
In vitro studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Long-Acting Paliperidone Palmitate Injection versus Oral Extended-Release Paliperidone

INVEGA® Sustenna™ is designed to deliver paliperidone over a monthly period while extended-release oral paliperidone is administered on a daily basis. Figure 2 presents the median pharmacokinetic profiles for paliperidone for 5 weeks following INVEGA® Sustenna™ administration using the recommended initiation regimen compared to the administration of an oral extended-release tablet (6 mg or 12 mg). The initiation regimen for INVEGA® Sustenna™ (150 mg/100 mg in the deltoid muscle on Day 1/Day 8) was designed to rapidly attain steady-state paliperidone concentrations when initiating therapy without the use of oral supplementation.

Figure 2 Median plasma concentration-time profiles following median pharmacokinetic profiles for paliperidone for 5 weeks following INVEGA® Sustenna™ administration using the recommended initiation regimen (initiating with paliperidone palmitate equivalent to paliperidone 150 mg/100 mg in the deltoid muscle on Day 1/Day 8) compared to the daily administration of an oral extended-release tablet (6 mg or 12 mg).



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

Special Populations

Hepatic Impairment. Paliperidone is not extensively metabolized in the liver. Although INVEGA® Sustenna™ was not studied on 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.

Renal Impairment. The dose of INVEGA® Sustenna™ should be reduced in patients with mild renal impairment; INVEGA® Sustenna™ is not recommended for use in patients with moderate or severe renal impairment (see Posology and Method of Administration). The disposition of a single oral dose 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® Sustenna™ in subjects with mild renal impairment and pharmacokinetic simulations, the recommended initiation of INVEGA® Sustenna™ for patients with mild renal impairment is with a dose of 100 mg on treatment day 1 and 75 mg one week later, both administered in the deltoid muscle; thereafter, follow with monthly (every 4 weeks) injections of 50 mg in either the deltoid or gluteal muscle, adjusted within the range of 25 to 100 mg based on patient tolerability and/or efficacy (see Posology and Method of Administration).

Elderly. No dosage adjustment is recommended based on age alone. However, dose adjustment may be required because of age-related decreases in creatinine clearance (see Renal Impairment above and Posology and Method of Administration).

Race. Population pharmacokinetics analysis of data from studies with oral paliperidone revealed no evidence of race-related differences in the pharmacokinetics of paliperidone following INVEGA® Sustenna™ administration.

Gender. No clinically significant differences were observed between men and women.

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. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any differences between smokers and non-smokers.

Preclinical Safety Data

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 7-week juvenile toxicity study in rats with oral doses of paliperidone of 0.16, 0.63, and 2.5 mg/kg/day, which are 0.12, 0.5, and 1.8 times the maximum recommended human oral dose of 12 mg/day for adolescents on a mg/m^2 basis, no effects on growth, sexual maturation, and reproductive performance were observed. Oral doses up to 2.5 mg/kg/day did not impair neurobehavioral development in males and females, except for an effect on learning and memory in female rats treated at 2.5 mg/kg/day. This effect was not observed after discontinuation of treatment.

In a 40-week study in juvenile dogs treated with oral risperidone (which is extensively converted to paliperidone) at doses of 0.31, 1.25, and 5 mg/kg/day, sexual maturation was not adversely affected at 0.31 and 1.25 mg/kg/day. Long bone growth was not affected at 0.31 mg/kg/day; effects were observed at 1.25 and 5 mg/kg/day.

Carcinogenicity

The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. There was a statistically significant increase in mammary gland adenocarcinomas in female rats at 10, 30 and 60 mg /kg/month. Male rats showed a statistically significant increase in mammary gland adenomas and carcinomas at 30 and 60 mg /kg/month which is 1.2 and 2.2 times the maximum recommended human 150 mg dose of INVEGA® Sustenna™ on a mg/kg basis.

The carcinogenic potential of oral paliperidone, an active metabolite of risperidone, was assessed based on studies with risperidone conducted in mice and rats. Risperidone was administered at doses up to 10 mg/kg/day for 18 months to mice and for 25 months to rats. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. An increase in mammary, pituitary, and endocrine pancreas tumors has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2 antagonism. The relevance of these tumor findings in rodents in terms of human risk is unknown.

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.

Impairment of 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 PARTICULARS

List of Excipients

Inactive ingredients in INVEGA® Sustenna™ are polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injection.

Incompatibilities

INVEGA® Sustenna™ 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

Observe expiry date on the outer pack.

Special Precautions for Storage

Do not store above 30°C.

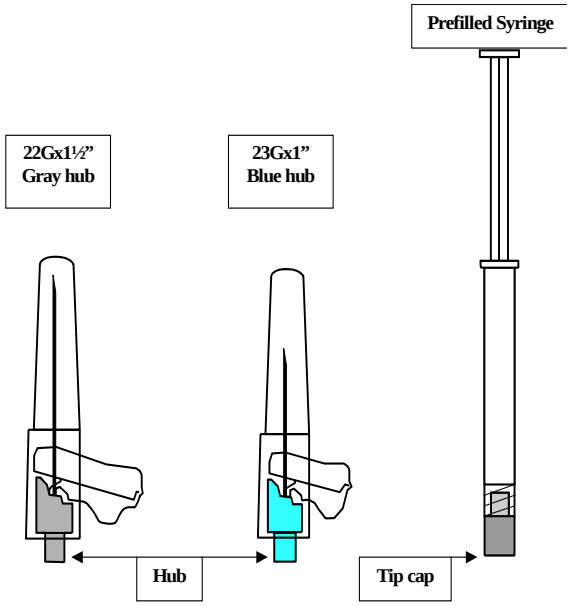
Keep out of reach of children**.**

Nature and Contents of Container

Kit containing a syringe (cyclic-olefin-copolymer) prefilled with either 25 mg(0.25 ml), 50 mg (0.5 ml), 75 mg (0.75 ml), 100 mg (1.0 ml), or 150 mg (1.5 ml) paliperidone (as 39 mg, 78 mg, 117 mg, 156 mg, or 234 mg paliperidone palmitate) suspension with a plunger stopper and tip cap (bromobutyl rubber), a 1 ½-inch 22 gauge safety needle, and a 1-inch 23 gauge safety needle.

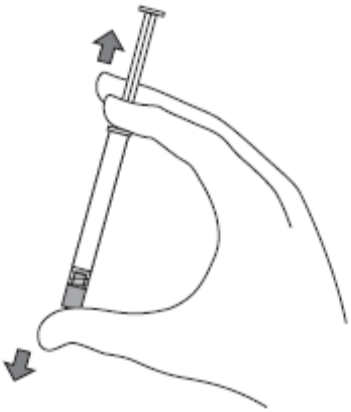
Instructions for Use and Handling and Disposal

The kit contains a prefilled syringe and 2 safety needles (a 1 ½-inch 22 gauge needle and a 1-inch 23 gauge needle) for intramuscular injection.

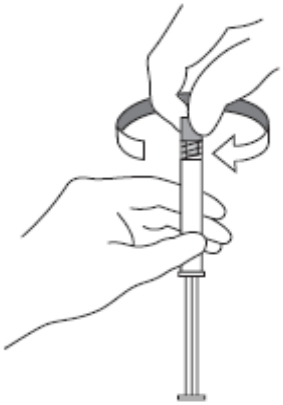


INVEGA® Sustenna™ is for single use only.

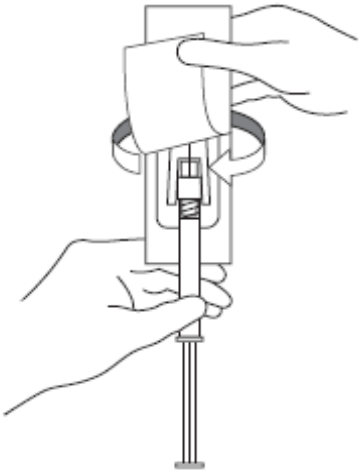
1. Shake the syringe vigorously for a minimum of 10 seconds to ensure a homogeneous suspension.



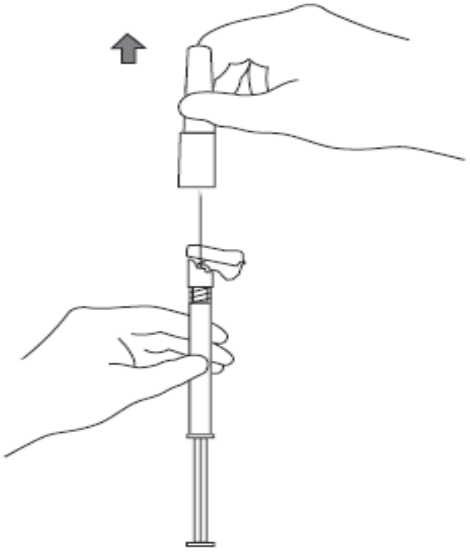
2. Select the appropriate needle.
   For DELTOID injection, if the patient weighs < 200 lb (< 90 kg), use the 1-inch **23** gauge needle (needle with **blue** colored hub); if the patient weighs ≥ 200 lb (≥ 90 kg), use the 1 ½-inch **22** gauge needle (needle with **gray** colored hub).
   For GLUTEAL injection, use the 1 ½-inch **22** gauge needle (needle with **gray** colored hub).
3. While holding the syringe upright, remove the rubber tip cap with an easy clockwise twisting motion.



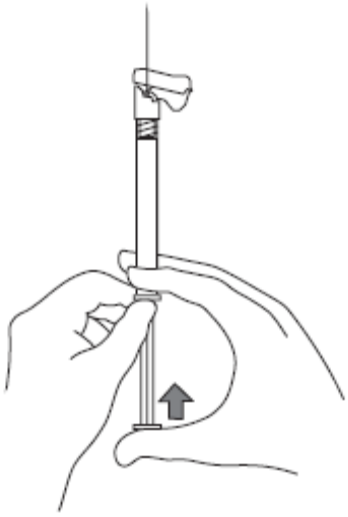
4. Peel the safety needle pouch half way open. Grasp the needle sheath using the plastic peel pouch. Attach the safety needle to the luer connection of the syringe with an easy clockwise twisting motion.



5. Pull the needle sheath away from the needle with a straight pull. Do not twist the sheath as the needle may be loosened from the syringe.

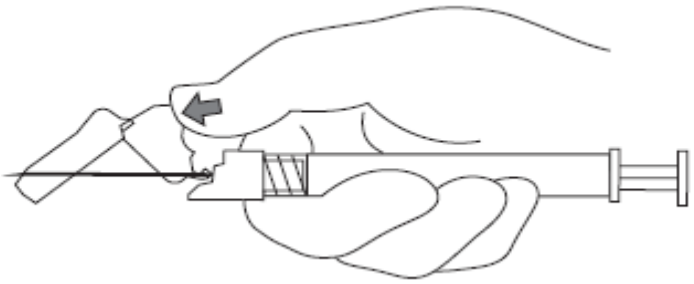


6. Bring the syringe with the attached needle in upright position to de-aerate. De-aerate the syringe by moving the plunger rod carefully forward.

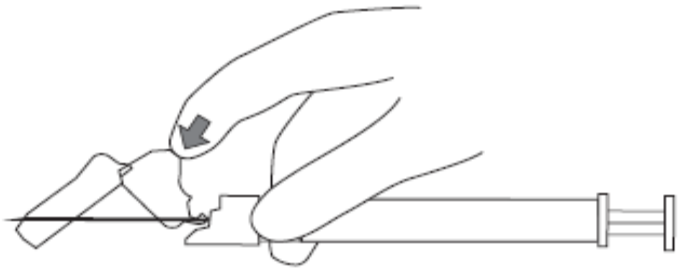


7. Inject the entire contents intramuscularly into the selected deltoid or gluteal muscle of the patient. **Do not administer intravascularly or subcutaneously.**
8. After the injection is complete, use either thumb or finger of one hand (8a, 8b) or a flat surface (8c) to activate the needle protection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

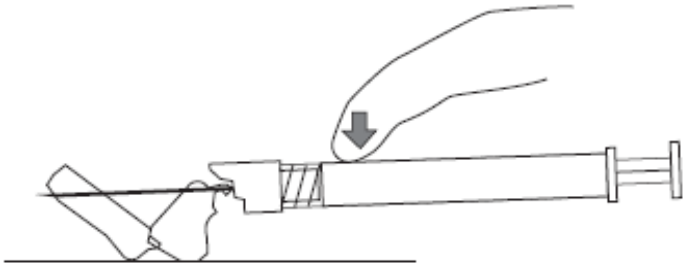
8a



8b



8c



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See outer carton.

DATE OF REVISION OF THE TEXT
July 2011