HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INVEGA® SUSTENNA® safely and effectively. See full prescribing information for INVEGA® SUSTENNA®.

INVEGA® SUSTENNA® (paliperidone palmitate) Extended-Release Injectable Suspension

Initial U.S. Approval: 2006

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA® SUSTENNA® is not approved for use in patients with dementia-related psychosis. (5.1)

----------INDICATIONS AND USAGE----------

INVEGA® SUSTENNA® is an atypical antipsychotic agent indicated for the acute and maintenance treatment of schizophrenia in adults (1)

----------DOSAGE AND ADMINISTRATION----------

- For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA® SUSTENNA®. (2.1)
- Initiate INVEGA® SUSTENNA® with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle. The recommended monthly maintenance dose is 117 mg; some patients may benefit from lower or higher maintenance doses within the recommended range of 39 mg to 234 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. (2.1)
- Administer by intramuscular injection only, using appropriate needle sizes. For deltoid injection, use 1 ½-inch 22G needle for patients ≥ 90 kg (≥ 200 lb) or 1-inch 23G needle for patients < 90 kg (< 200 lb). For gluteal injection, use 1 ½-inch 22G needle regardless of patient weight. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Prefilled syringes containing 39 mg, 78 mg, 117 mg, 156 mg, or 234 mg paliperidone palmitate. (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to paliperidone, risperidone, or to any components in the formulation (4)

----------WARNINGS AND PRECAUTIONS----------

- *Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack, including fatalities). INVEGA® SUSTENNA® is not approved for use in patients with dementia-related psychosis (5.2)
- *Neuroleptic Malignant Syndrome*: Manage with immediate discontinuation of drug and close monitoring (5.3)
- *QT Prolongation:* Increase in QT interval, avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval (5.4)
- *Tardive Dyskinesia*: Discontinue drug if clinically appropriate (5.5)
- *Hyperglycemia and Diabetes Mellitus:* Monitor glucose regularly in patients with and at risk for diabetes (5.6)
- *Weight Gain:* Significant weight gain has been reported. Monitor weight gain. (5.7)
- *Hyperprolactinemia:* Prolactin elevations occur and persist during chronic administration (5.8)
- *Orthostatic Hypotension and Syncope*: Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension (5.9)
- *Leukopenia, Neutropenia, and Agranulocytosis*: has been reported with antipsychotics, including INVEGA®, an oral form of paliperidone. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of INVEGA® SUSTENNA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.10)
- *Potential for Cognitive and Motor Impairment*: Use caution when operating machinery (5.11)
- *Seizures*: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.12)
- *Suicide*: Closely supervise high-risk patients (5.14)
- *Administration*: For intramuscular injection only. Avoid inadvertent injection into a blood vessel. (5.18)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥ 5% and occurring at least twice as often as placebo) were injection site reactions, somnolence/sedation, dizziness,akathisia, and extrapyramidal disorder. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Centrally-acting drugs: Due to CNS effects, use caution in combination. Avoid alcohol. (7.1)
- Drugs that may cause orthostatic hypotension: An additive effect may be observed when co-administered with INVEGA® SUSTENNA®. (7.1)
- Co-administration of oral paliperidone extended release with carbamazepine decreased mean steady-state C_{max} and AUC of paliperidone by approximately 37%. Adjust dose of INVEGA® SUSTENNA® if necessary. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Renal impairment: INVEGA® SUSTENNA® has not been systematically studied in patients with renal impairment. For mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min), administer 156 mg on treatment day 1 and 117 mg one week later, both administered in the deltoid muscle. Thereafter, follow with monthly injections of 78 mg. in either the deltoid or gluteal muscle. INVEGA® SUSTENNA® is not recommended for use in patients with moderate to severe renal impairment (creatinine clearance < 50 mL/min). (2.5)
- Elderly: same as for younger adults (adjust dose according to renal function status). (2.5)
- Nursing Mothers: should not breastfeed. (8.3)
- Pediatric Use: safety and effectiveness not established in patients less than 18 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: March 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNINGS – INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing
2.2 Missed Doses
2.3 Administration Instructions
2.4 Use with Oral Paliperidone or with Risperidone
2.5 Dosage in Special Populations
2.6 Maintenance Therapy
2.7 Switching from Other Antipsychotics
2.8 Instructions for Use
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
5.2 Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis
5.3 Neuroleptic Malignant Syndrome
5.4 QT Prolongation
5.5 Tardive Dyskinesia
5.6 Hyperglycemia and Diabetes Mellitus
5.7 Weight Gain
5.8 Hyperprolactinemia
5.9 Orthostatic Hypotension and Syncope
5.10 Leukopenia, Neutropenia, and Agranulocytosis
5.11 Potential for Cognitive and Motor Impairment
5.12 Seizures
5.13 Dysphagia
5.14 Suicide
5.15 Priapism
5.16 Thrombotic Thrombocytopenic Purpura (TTP)
5.17 Body Temperature Regulation
5.18 Administration
5.19 Antiemetic Effect
5.20 Use in Patients with Concomitant Illness
5.21 Monitoring: Laboratory Tests
6 ADVERSE REACTIONS
6.1 Commonly-Observed Adverse Events in Double-Blind, Placebo-Controlled Clinical Trials
6.2 Adverse Reactions Observed During the Clinical Trial Evaluation of INVEGA® SUSTENNA® and Not Listed in Table 2
6.3 Discontinuations Due to Adverse Events
6.4 Dose-Related Adverse Reactions
6.5 Demographic Differences
6.6 Extrapyramidal Symptoms (EPS)
6.7 Laboratory Test Abnormalities
6.8 Pain Assessment and Local Injection Site Reactions
6.9 Adverse Reactions Reported in Clinical Trials with Oral Paliperidone
6.10 Postmarketing Experience
6.11 Adverse Reactions Reported With Risperidone
7 DRUG INTERACTIONS
7.1 Potential for INVEGA® SUSTENNA® to Affect Other Drugs
7.2 Potential for Other Drugs to Affect INVEGA® SUSTENNA®
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
10.1 Human Experience
10.2 Management of Overdosage
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Orthostatic Hypotension
17.2 Interference with Cognitive and Motor Performance
17.3 Pregnancy
17.4 Nursing
17.5 Concomitant Medication
17.6 Alcohol
17.7 Heat Exposure and Dehydration

***Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA® SUSTENNA® (paliperidone palmitate) is not approved for the treatment of patients with dementia-related psychosis. *[See Warnings and Precautions (5.1)]*

1 INDICATIONS AND USAGE

INVEGA® SUSTENNA® (paliperidone palmitate) is indicated for the acute and maintenance treatment of schizophrenia in adults *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

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

Recommended initiation of INVEGA® SUSTENNA® is with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle. The recommended monthly maintenance dose is 117 mg; some patients may benefit from lower or higher maintenance doses within the recommended range of 39 to 234 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 Clinical Pharmacology (12.3)]*, as the full effect of the dose adjustment may not be evident for several months.

2.2 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.

Missed Dose (1 Month to 6 Weeks)

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

Missed Dose (> 6 Weeks to 6 Months)

If more than 6 weeks have elapsed since the last injection of INVEGA® SUSTENNA®, **resume the same dose the patient was previously stabilized on (unless the patient was stabilized on a dose of 234 mg, then the first two injections should each be 156 mg)** in the following manner: 1) a deltoid injection as soon as practically possible, followed by 2) another deltoid injection (same dose) one week later, and 3) resumption of either deltoid or gluteal dosing at monthly intervals.

Missed Dose (> 6 Months)

If more than 6 months have elapsed since the last injection of INVEGA® SUSTENNA®, initiate dosing as described in Section 2.1 above.

2.3 Administration Instructions

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

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

The recommended needle size for administration of INVEGA® SUSTENNA® into the gluteal muscle is the 1½-inch, 22 gauge needle. Administration should be made into the upper-outer

quadrant of the gluteal area. Gluteal injections should be alternated between the two gluteal muscles.

2.4 Use with Oral Paliperidone or with Risperidone

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®.

2.5 Dosage in Special Populations

Renal Impairment

INVEGA® SUSTENNA® has not been systematically studied in patients with renal impairment *[see Clinical Pharmacology (12.3)]*. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min), recommended initiation of INVEGA® SUSTENNA® is with a dose of 156 mg on treatment day 1 and 117 mg one week later, both administered in the deltoid muscle. Thereafter, follow with monthly injections of 78 mg in either the deltoid or gluteal muscle.

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

Hepatic Impairment

INVEGA® SUSTENNA® has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment. *[See Clinical Pharmacology (12.3)]*

Elderly

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

2.6 Maintenance Therapy

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

2.7 Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to INVEGA® SUSTENNA®, or concerning concomitant administration with other antipsychotics.

Switching from Oral Antipsychotics

For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA® SUSTENNA®.

Previous oral antipsychotics can be discontinued at the time of initiation of treatment with INVEGA® SUSTENNA®. INVEGA® SUSTENNA® should be initiated as described in Section 2.1. Patients previously stabilized on different doses of INVEGA® Extended-Release tablets can attain similar paliperidone steady-state exposure during maintenance treatment with INVEGA® SUSTENNA® monthly doses as depicted in Table 1.

Table 1. Doses of INVEGA® and INVEGA® SUSTENNA® needed to attain similar paliperidone exposure at steady-state

Formulation	INVEGA® Extended-Release Tablet	INVEGA® SUSTENNA® Injection
Dosing Frequency	Once Daily	Once every 4 weeks
Dose (mg)	12 6 3	234 117 39-78

Switching from Long-Acting Injectable Antipsychotics

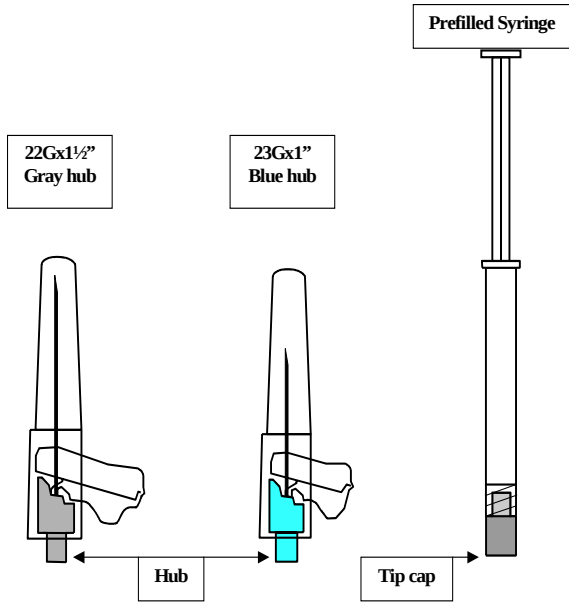
For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA® SUSTENNA®.

When switching patients from previous long-acting injectable antipsychotics, 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 in Section 2.1 is not required.

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.

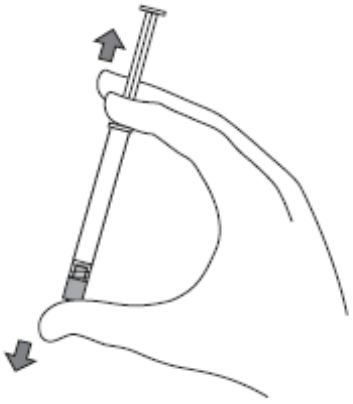
2.8 Instructions for Use

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.

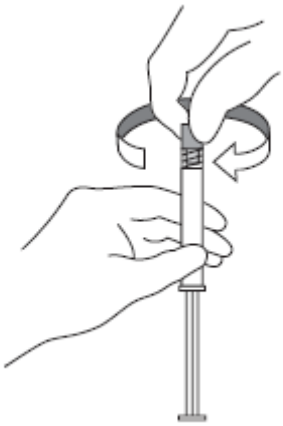


2. Select the appropriate needle.

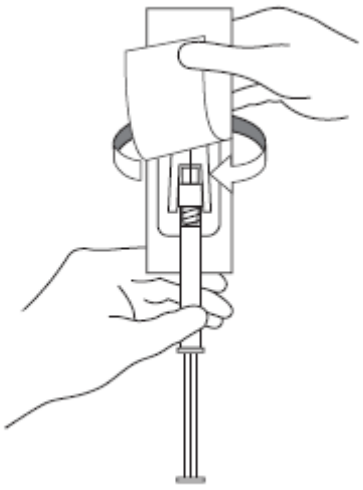
   For DELTOID injection, if the patient weighs < 200 lb (< 90 kg), use the 1-inch **23** gauge needle (needle with **blue** colored hub); if the patient weighs ≥ 200 lb (≥ 90 kg), use the 1 ½-inch **22** gauge needle (needle with **gray** colored hub).

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

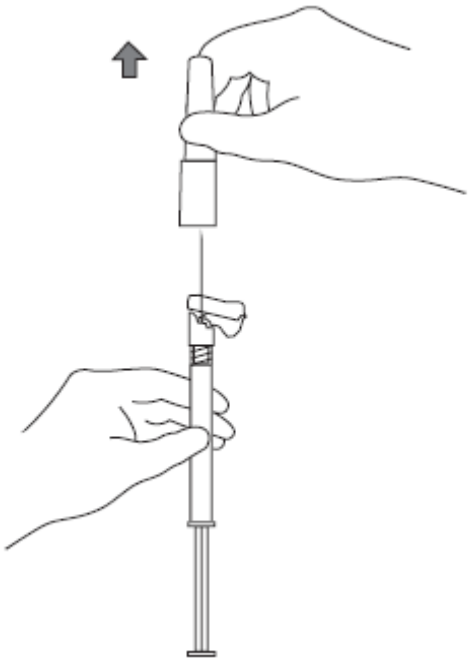
3. While holding the syringe upright, remove the rubber tip cap with an easy clockwise twisting motion.



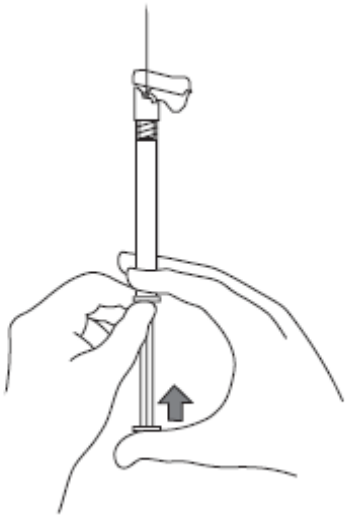
4. Peel the safety needle pouch half way open. Grasp the needle sheath using the plastic peel pouch. Attach the safety needle to the luer connection of the syringe with an easy clockwise twisting motion.



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.



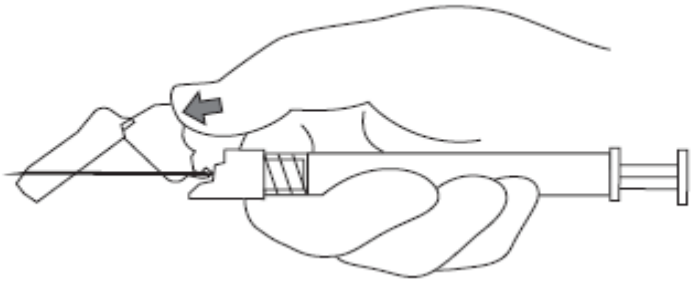
6. Bring the syringe with the attached needle in upright position to de-aerate. De-aerate the syringe by moving the plunger rod carefully forward.



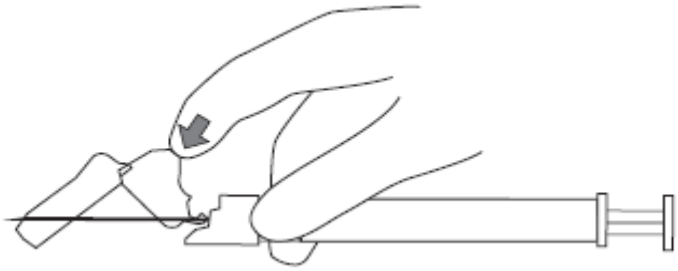
7. Inject the entire contents intramuscularly into the selected deltoid or gluteal muscle of the patient. **Do not administer intravascularly or subcutaneously.**

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.

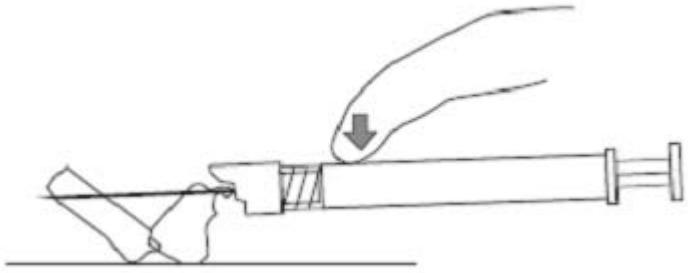
8a



8b



8c



3 DOSAGE FORMS AND STRENGTHS

INVEGA® SUSTENNA® is available as a white to off-white aqueous extended-release suspension for intramuscular injection in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate .

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. INVEGA® SUSTENNA® (paliperidone palmitate) is not approved for the treatment of dementia-related psychosis *[see Boxed Warning]*.

5.2 Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. Oral paliperidone and INVEGA® SUSTENNA® were not marketed at the time these studies were performed and are not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions (5.1)]*.

5.3 Neuroleptic Malignant Syndrome

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

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

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

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

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

5.4 QT Prolongation

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

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

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

In the QT study (n = 141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release ($C_{max\ ss}$ = 113 ng/mL) was more than 2-fold the exposure observed with the maximum recommended 234 mg dose of INVEGA® SUSTENNA® administered in the deltoid muscle (predicted median $C_{max\ ss}$ = 50 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which

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

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

In the four fixed-dose efficacy studies of INVEGA® SUSTENNA®, no subject experienced a change in QTcLD exceeding 60 msec and no subject had a QTcLD value of > 500 msec at any time point. In the 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.

5.5 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

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

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

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

If signs and symptoms of tardive dyskinesia appear in a patient treated with INVEGA®

SUSTENNA®, drug discontinuation should be considered. However, some patients may require treatment with INVEGA® SUSTENNA® despite the presence of the syndrome.

5.6 Hyperglycemia and Diabetes Mellitus

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

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

5.7 Weight Gain

Weight gain has been observed with INVEGA® SUSTENNA® and other atypical antipsychotics. In the 13-week study involving 234 mg initiation dosing, the proportion of subjects with an abnormal weight increase $\geq$ 7% showed a dose-related trend, with a 5% incidence rate in the placebo group compared with rates of 6%, 8%, and 13% in the INVEGA® SUSTENNA® 39 mg, 156 mg, and 234 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 $\geq$ 7% of body weight were 6%, 9%, and 10% in the INVEGA® SUSTENNA® 39 mg, 78 mg, and 156 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®

78 mg and 156 mg groups, respectively, met this criterion compared with 4% in the placebo group.

During the 33-week open-label period (9-week flexible-dose transition phase followed by a 24-week maintenance phase flexible-dose and minimum 12-week fixed dose) of the maintenance trial, 12% of INVEGA® SUSTENNA®-treated subjects met this criterion; the mean (SD) weight change from open-label baseline was +0.7 (4.79) kg. In the variable length double-blind phase, this criterion (weight gain of ≥ 7% from double-blind phase to endpoint) was met by 6% of INVEGA® SUSTENNA®-treated subjects compared with 3% of placebo-treated subjects; the mean weight change from double-blind baseline was +0.5 kg for INVEGA® SUSTENNA® compared with –1.0 kg for placebo. Similar results were observed in the open-label extension phase of this study.

5.8 Hyperprolactinemia

Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

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

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

5.9 Orthostatic Hypotension and Syncope

Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. Syncope was reported in < 1% (4/1293) of subjects treated with

INVEGA® SUSTENNA® in the recommended dose range of 39 mg to 234 mg in the four fixed-dose, double-blind, placebo-controlled trials compared with 0% (0/510) of subjects treated with placebo. In the four fixed-dose efficacy studies, orthostatic hypotension was reported as an adverse event by < 1% (2/1293) of INVEGA® SUSTENNA®-treated subjects compared to 0% (0/510) with placebo. Incidences of orthostatic hypotension and syncope in the long-term studies were similar to those observed in the short-term studies.

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

5.10 Leukopenia, Neutropenia, and Agranulocytosis

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

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

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

5.11 Potential for Cognitive and Motor Impairment

Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA® SUSTENNA® *[see Adverse Reactions (6.1)]*. Antipsychotics, including INVEGA® SUSTENNA®, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

5.12 Seizures

In the four fixed-dose double-blind placebo-controlled studies, <1% (1/1293) of subjects treated with INVEGA® SUSTENNA® in the recommended dose range of 39 mg to 234 mg experienced an adverse event of convulsion compared with <1% (1/510) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

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

5.13 Dysphagia

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

5.14 Suicide

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

5.15 Priapism

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

5.16 Thrombotic Thrombocytopenic Purpura (TTP)

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

5.17 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.

5.18 Administration

INVEGA® SUSTENNA® is intended for intramuscular injection, and care must be taken to avoid inadvertent injection into a blood vessel *[see Dosage and Administration (2.3)]*.

5.19 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.

5.20 Use in Patients with Concomitant Illness

Clinical experience with INVEGA® SUSTENNA® in patients with certain concomitant illnesses is limited *[see Clinical Pharmacology (12.3)]*.

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

INVEGA® SUSTENNA® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with INVEGA® SUSTENNA®, caution should be observed in patients with known cardiovascular disease *[see Warnings and Precautions (5.9)]*.

5.21 Monitoring: Laboratory Tests

No specific laboratory tests are recommended.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis *[*see *Warnings and Precautions (5.2)]*
- Neuroleptic malignant syndrome *[*see *Warnings and Precautions (5.3)]*
- QT prolongation *[see Warnings and Precautions (5.4)]*
- Tardive dyskinesia *[see Warnings and Precautions (5.5)]*

- Hyperglycemia and diabetes mellitus *[see Warnings and Precautions (5.6)]*
- Weight gain *[see Warnings and Precautions (5.7)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.8)]*
- Orthostatic hypotension and syncope *[see Warnings and Precautions (5.9)]*
- Leukopenia, neutropenia, and agranulocytosis *[see Warnings and Precautions (5.10)]*
- Potential for cognitive and motor impairment *[*see *Warnings and Precautions (5.11)]*
- Seizures *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Suicide *[see Warnings and Precautions (5.14)]*
- Priapism *[see Warnings and Precautions (5.15)]*
- Thrombotic Thrombocytopenic Purpura *[see Warnings and Precautions (5.16)]*
- Disruption of body temperature regulation *[see Warnings and Precautions (5.17)]*
- Avoidance of inadvertent injection into a blood vessel *[see Warnings and Precautions (5.18)]*
- Antiemetic effect *[see Warnings and Precautions (5.19)]*
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies *[see Warnings and Precautions (5.20)]*
- Diseases or conditions that could affect metabolism or hemodynamic responses *[see Warnings and Precautions (5.20)]*

Throughout this section, a distinction is made between adverse events and adverse reactions. Adverse events are events reported by the clinician investigator and there is no attempt to assign causality to the study drug. Adverse reactions are adverse events that are considered to be reasonably associated with the use of INVEGA® SUSTENNA® (adverse drug reactions) based on a predetermined method of assessment, e.g., a comparison of adverse event rates for drug and placebo groups for the event of interest. It is not possible to reliably establish causality by considering individual adverse event reports for drug-treated patients. Thus, the section overall is

labeled Adverse Reactions, however, individual subsections are labeled adverse reactions or adverse events, depending on what is included in the subsection.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most common (at least 5% in any INVEGA® SUSTENNA® group) and likely drug-related (adverse events for which the drug rate is at least twice the placebo rate) adverse reactions from the double-blind, placebo-controlled trials were injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder**.**

The data described in this section are derived from a clinical trial database consisting of a total of 3817 subjects with schizophrenia who received at least one dose of INVEGA® SUSTENNA® in the recommended dose range of 39 mg to 234 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 maintenance trial (of whom 205 continued to receive INVEGA® SUSTENNA® during the double-blind placebo-controlled phase of this study), and 1675 received INVEGA® SUSTENNA® in five non-placebo controlled trials (three noninferiority active-comparator trials, one long-term open-label pharmacokinetic and safety study, and an injection site [deltoid-gluteal] cross-over trial). One of the 13-week studies included a 234 mg INVEGA® SUSTENNA® initiation dose followed by treatment with either 39 mg, 156 mg, or 234 mg every 4 weeks.

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

The majority of all adverse reactions were mild to moderate in severity.

6.1 Commonly-Observed Adverse Events in Double-Blind, Placebo-Controlled Clinical Trials

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

Table 2. Incidence of Treatment Emergent Adverse Events in ≥ 2% of INVEGA® SUSTENNA®-Treated Subjects with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials

System Organ Class Adverse Event	Placebo[a] (N=510)	39 mg (N=130)	78 mg (N=302)	156 mg (N=312)	234/39 mg[b] (N=160)	234/156 mg[b] (N=165)	234/234 mg[b] (N=163)
Total percentage of subjects with adverse event	70	75	68	69	63	60	63
Gastrointestinal disorders							
Abdominal discomfort/abdominal pain upper	2	2	4	4	1	2	4
Constipation	5	3	5	5	2	4	1
Diarrhea	2	0	3	2	1	2	2
Dry mouth	1	3	1	0	1	1	1
Nausea	3	4	4	3	2	2	2
Toothache	1	1	1	3	1	2	3
Vomiting	4	5	4	2	3	2	2
General disorders and administration site conditions							
Asthenia	0	2	1	<1	0	1	1
Fatigue	1	1	2	2	1	2	1
Injection site reactions	2	0	4	6	9	7	10
Infections and infestations							
Nasopharyngitis	2	0	2	2	4	2	2
Upper respiratory tract infection	2	2	2	2	1	2	4
Urinary tract infection	1	0	1	<1	1	1	2
Injury, poisoning and procedural complications							
Skin laceration	<1	2	<1	0	1	0	0
Investigations							
Alanine aminotransferase increased	2	0	2	1	1	1	1
Weight increased	1	4	4	1	1	1	2
Musculoskeletal and connective tissue disorders							
Back pain	2	2	1	3	1	1	1
Musculoskeletal stiffness	1	1	<1	<1	1	1	2
Myalgia	1	2	1	<1	1	0	2
Pain in extremity	1	0	2	2	2	3	0
Nervous system disorders							
Akathisia	3	2	2	3	1	5	6
Dizziness	1	6	2	4	1	4	2
Extrapyramidal disorder	1	5	2	3	1	0	0
Headache	12	11	11	15	11	7	6
Somnolence/sedation	3	5	7	4	1	5	5
Psychiatric disorders							
Agitation	7	10	5	9	8	5	4
Anxiety	7	8	5	3	5	6	6
Insomnia	15	15	15	13	12	10	13
Nightmare	<1	2	0	0	0	0	0
Suicidal ideation	2	0	1	2	2	2	1
Respiratory, thoracic and mediastinal disorders							
Cough	1	2	3	1	0	1	1
Vascular disorders							
Hypertension	1	2	1	1	1	1	0

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

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

[b] Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. *[See Clinical Studies (14)]*

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

6.2 Adverse Reactions Observed During the Clinical Trial Evaluation of INVEGA® SUSTENNA® and Not Listed in Table 2

The following additional adverse reactions occurred in INVEGA® SUSTENNA®-treated subjects in the above four fixed-dose, double-blind, placebo-controlled trials, in the double-blind phase of the maintenance trial, or in INVEGA® SUSTENNA®-treated subjects with schizophrenia who participated in other clinical trials, and were not reported in Table 2. They were determined to be adverse reactions based upon reasons to suspect causality such as timing of onset or termination with respect to drug use, plausibility in light of the drug's known pharmacology, occurrence at a frequency above that expected in the treated population or occurrence of an event typical of drug-induced adverse reactions.

Cardiac disorders: atrioventricular block first degree, bradycardia, bundle branch block, electrocardiogram QT prolonged, palpitations, postural orthostatic tachycardia syndrome, tachycardia

Ear and labyrinth disorders: vertigo

Endocrine disorders: hyperprolactinemia

Eye disorders: eye movement disorder, eye rolling, oculogyric crisis, vision blurred

Gastrointestinal disorders: salivary hypersecretion

Immune system disorders: hypersensitivity

Investigations: blood cholesterol increased, blood glucose increased, blood triglycerides increased, electrocardiogram abnormal

Metabolism and nutrition disorders: decreased appetite, hyperglycemia, hyperinsulinemia, increased appetite

Musculoskeletal and connective tissue disorders: joint stiffness, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, nuchal rigidity

Nervous system disorders: bradykinesia, cerebrovascular accident, convulsion, dizziness postural, drooling, dysarthria, dyskinesia, dystonia, hypertonia, lethargy, neuroleptic malignant syndrome, oromandibular dystonia, parkinsonism, psychomotor hyperactivity, syncope, tardive dyskinesia

Psychiatric disorders: restlessness

Reproductive system and breast disorders: amenorrhea, breast discharge, erectile dysfunction, galactorrhea, gynecomastia, menstrual disorder, menstruation delayed, menstruation irregular, sexual dysfunction

Skin and subcutaneous tissue disorders: drug eruption, pruritus, pruritus generalized, rash, urticaria

Vascular disorders: orthostatic hypotension

6.3 Discontinuations Due to Adverse Events

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

6.4 Dose-Related Adverse Reactions

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

6.5 Demographic Differences

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

6.6 Extrapyramidal Symptoms (EPS)

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

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

	Percentage of Subjects			
		INVEGA® SUSTENNA®		
Scale	Placebo (N=262)	39 mg (N=130)	78 mg (N=223)	156 mg (N=228)
Parkinsonism[a]	9	12	10	6
Akathisia[b]	5	5	6	5
Dyskinesia[c]	3	4	6	4
Use of Anticholinergic Medications[d]	12	10	12	11

a: For Parkinsonism, percent of subjects with Simpson-Angus Total score > 0.3 at endpoint (Total score defined as total sum of items score divided by the number of items)
b: For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at endpoint
c: For Dyskinesia, percent of subjects with a score ≥ 3 on any of the first 7 items or a score ≥ 2 on two or more of any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint
d: Percent of subjects who received anticholinergic medications to treat emergent EPS

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

	Percentage of Subjects			
		INVEGA® SUSTENNA®		
EPS Group	Placebo (N=262)	39 mg (N=130)	78 mg (N=223)	156 mg (N=228)
Overall percentage of subjects with EPS-related adverse events	10	12	11	11
Parkinsonism	5	6	6	4
Hyperkinesia	2	2	2	4
Tremor	3	2	2	3
Dyskinesia	1	2	3	1
Dystonia	0	1	1	2

Parkinsonism group includes: Extrapyramidal disorder, hypertonia, musculoskeletal stiffness, parkinsonism, drooling, masked facies, muscle tightness, hypokinesia
Hyperkinesia group includes: Akathisia, restless legs syndrome, restlessness
Dyskinesia group includes: Dyskinesia, choreoathetosis, muscle twitching, myoclonus, tardive dyskinesia
Dystonia group includes: Dystonia, muscle spasms

The results across all phases of the maintenance trial exhibited comparable findings. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, the proportions of Parkinsonism and akathisia assessed by incidence of rating scales were higher in the INVEGA® SUSTENNA® 156 mg group (18% and 11%, respectively) than in the INVEGA® SUSTENNA® 78 mg group (9% and 5%, respectively) and placebo group (7% and 4%, respectively).

In the 13-week study involving 234 mg initiation dosing, the incidence of any treatment-emergent EPS-related adverse events was similar to that of the placebo group (8%), but exhibited a dose-related pattern with 6%, 10%, and 11% in the INVEGA® SUSTENNA® 234/39 mg, 234/156 mg, and 234/234 mg groups, respectively. Hyperkinesia was the most frequent category of EPS-related adverse events in this study, and was reported at a similar rate between the

placebo (4.9%) and INVEGA® SUSTENNA® 234/156 mg (4.8%) and 234/234 mg (5.5%) groups, but at a lower rate in the 234/39 mg group (1.3%).

Dystonia

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

6.7 Laboratory Test Abnormalities

In the pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials, a between-group comparison revealed no medically important differences between INVEGA® SUSTENNA® and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no differences between INVEGA® SUSTENNA® and placebo in the incidence of discontinuations due to changes in hematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements. However, INVEGA® SUSTENNA® was associated with increases in serum prolactin *[see Warnings and Precautions (5.8)]*. The results from the 13-week study involving 234 mg initiation dosing, the 9-week, fixed-dose, double-blind, placebo-controlled trial, and the double-blind phase of the maintenance trial exhibited comparable findings.

6.8 Pain Assessment and Local Injection Site Reactions

In the pooled data from the two 13-week, fixed-dose, double-blind, placebo-controlled trials, the mean intensity of injection pain reported by subjects using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 10.9 to 9.8; 39 mg: 10.3 to 7.7; 78 mg: 10.0 to 9.2; 156 mg: 11.1 to 8.8). The results from both the 9-week, fixed-dose, double-blind, placebo-controlled trial and the double-blind phase of the maintenance trial exhibited comparable findings.

In the 13-week study involving 234 mg initiation dosing, occurrences of induration, redness, or swelling, as assessed by blinded study personnel, were infrequent, generally mild, decreased over time, and similar in incidence between the INVEGA® SUSTENNA® and placebo groups. Investigator ratings of injection pain were similar for the placebo and INVEGA® SUSTENNA® groups. Investigator evaluations of the injection site after the first injection for redness, swelling, induration, and pain were rated as absent for 69-100% of subjects in both the INVEGA®

SUSTENNA® and placebo groups. At Day 92, investigators rated absence of redness, swelling, induration, and pain in 95-100% of subjects in both the INVEGA® SUSTENNA® and placebo groups.

6.9 Adverse Reactions Reported in Clinical Trials with Oral Paliperidone

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

Cardiac disorders: bundle branch block left, sinus arrhythmia

Gastrointestinal disorders: abdominal pain, flatulence, small intestinal obstruction

General disorders and administration site conditions: edema, edema peripheral

Immune system disorders: anaphylactic reaction

Infections and infestations: rhinitis

Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal pain, torticollis, trismus

Nervous system disorders: cogwheel rigidity, grand mal convulsion, parkinsonian gait, transient ischemic attack

Psychiatric disorders: sleep disorder

Reproductive system and breast disorders: breast engorgement, breast tenderness/breast pain, retrograde ejaculation

Respiratory, thoracic and mediastinal disorders: nasal congestion, pharyngolaryngeal pain, pneumonia aspiration

Skin and subcutaneous tissue disorders: rash papular

Vascular disorders: hypotension, ischemia

6.10 Postmarketing Experience

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

6.11 Adverse Reactions Reported With Risperidone

Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with oral risperidone and risperidone long-acting injection can be found in the ADVERSE REACTIONS sections of the package inserts for those products.

7 DRUG INTERACTIONS

Since paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3)]*, results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

7.1 Potential for INVEGA® SUSTENNA® to Affect Other Drugs

Given the primary CNS effects of paliperidone *[see Adverse Reactions (6.1)]*, 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, an additive effect may be observed when INVEGA® SUSTENNA® is administered with other therapeutic agents that have this potential *[see Warnings and Precautions (5.9)]*.

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

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

7.2 Potential for Other Drugs to Affect INVEGA® SUSTENNA®

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

Co-administration of oral paliperidone extended release once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of

paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone. A minor decrease in the amount of drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. On initiation of carbamazepine, the dose of INVEGA® SUSTENNA® should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA® SUSTENNA® should be re-evaluated and decreased if necessary.

Paliperidone is metabolized to a limited extent by CYP2D6 *[see Clinical Pharmacology (12.3)]*. In an interaction study in healthy subjects in which a single 3 mg dose of oral paliperidone extended release was administered concomitantly with 20 mg per day of paroxetine (a potent CYP2D6 inhibitor), paliperidone exposures were on average 16% (90% CI: 4, 30) higher in CYP2D6 extensive metabolizers. Higher doses of paroxetine have not been studied. The clinical relevance is unknown.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well controlled studies of INVEGA® SUSTENNA® in pregnant women.

There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate during the period of organogenesis at doses up to 160 mg/kg, which is 10 times the maximum recommended human 234 mg dose of INVEGA® SUSTENNA® on a mg/m^2 basis.

In studies in pregnant rats and rabbits in which paliperidone was given orally during the period of organogenesis, there were no increases in fetal abnormalities up to the highest doses tested (10 mg/kg/day in rats and 5 mg/kg/day in rabbits, which are each 8 times the maximum recommended human dose [12 mg/day] of orally administered paliperidone [INVEGA®] on a mg/m^2 basis).

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, increases in pup deaths were seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m^2 basis (see RISPERDAL® package insert).

Use of first generation antipsychotic drugs during the last trimester of pregnancy has been associated with extrapyramidal symptoms in the neonate. These symptoms are usually self-limited. It is not known whether paliperidone, when taken near the end of pregnancy, will lead to similar neonatal signs and symptoms.

Non-teratogenic Effects

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

INVEGA® SUSTENNA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of INVEGA® SUSTENNA® on labor and delivery in humans is unknown.

8.3 Nursing Mothers

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.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

This drug is known to be substantially excreted by the kidney and clearance is decreased in

patients with renal impairment *[see Clinical Pharmacology (12.3)]*, who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2.5)]*.

8.6 Renal Impairment

INVEGA® SUSTENNA® has not been systematically studied in patients with renal impairment *[see Clinical Pharmacology (12.3)]*. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min), recommended initiation of INVEGA® SUSTENNA® is with a dose of 156 mg on treatment day 1 and 117 mg one week later, both administered in the deltoid muscle. Thereafter, follow with monthly injections of 78 mg in either the deltoid or gluteal muscle.

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

8.7 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.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

INVEGA® SUSTENNA® (paliperidone) is not a controlled substance.

9.2 Abuse

Paliperidone has not been systematically studied in animals or humans for its potential for abuse.

9.3 Dependence

Paliperidone has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

10 OVERDOSAGE

10.1 Human Experience

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

While experience with paliperidone overdose is limited, among the few cases of overdose

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

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

10.2 Management of Overdosage

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

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

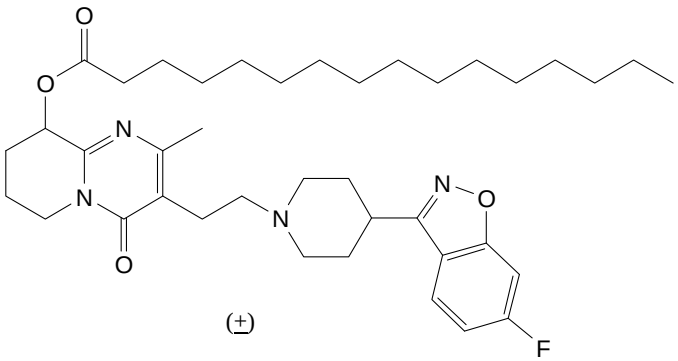
Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in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

Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of paliperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

11 DESCRIPTION

INVEGA® SUSTENNA® contains paliperidone palmitate. The active ingredient, paliperidone palmitate, is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. INVEGA® SUSTENNA® contains a racemic mixture of (+)- and (-)- paliperidone palmitate. The chemical name is (9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-

4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimadin-9-yl hexadecanoate. Its molecular formula is $C_{39}H_{57}FN_4O_4$ and its molecular weight is 664.89. The structural formula is:



Paliperidone palmitate is very slightly soluble in ethanol and methanol, practically insoluble in polyethylene glycol 400 and propylene glycol, and slightly soluble in ethyl acetate.

INVEGA® SUSTENNA® is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate. The drug product hydrolyzes to the active moiety, paliperidone, resulting in dose strengths of 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg of paliperidone, respectively. The inactive ingredients are polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3)]*. Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown, but it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

12.2 Pharmacodynamics

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

adrenergic receptors and H_1 histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar *in vitro.*

12.3 Pharmacokinetics

Absorption and Distribution

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

Following intramuscular injection of single doses (39 mg - 234 mg) in the deltoid muscle, on average, a 28% higher C_{max} was observed compared with injection in the gluteal muscle. The two initial deltoid intramuscular injections of 234 mg on day 1 and 156 mg on day 8 help attain therapeutic concentrations rapidly. The release profile and dosing regimen of INVEGA® SUSTENNA® results in sustained therapeutic concentrations. The AUC of paliperidone following INVEGA® SUSTENNA® administration was dose-proportional over a 39 mg-234 mg dose range, and less than dose-proportional for C_{max} for doses exceeding 78 mg . The mean steady-state peak:trough ratio for an INVEGA® SUSTENNA® dose of 156 mg was 1.8 following gluteal administration and 2.2 following deltoid administration.

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

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

Metabolism and Elimination

In a study with oral immediate-release ^{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 discernable

difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

In vitro studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

The median apparent half-life of paliperidone following INVEGA® SUSTENNA® single-dose administration over the dose range of 39 mg - 234 mg ranged from 25 days - 49 days.

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. The initiation regimen for INVEGA® SUSTENNA® (234 mg/156 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.

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

Renal Impairment

INVEGA® SUSTENNA® has not been systematically studied in patients with renal impairment. Based on a limited number of observations with INVEGA® SUSTENNA® in subjects with mild renal impairment and pharmacokinetic simulations, the dose of INVEGA® SUSTENNA® should be reduced in patients with mild renal impairment; INVEGA® SUSTENNA® is not recommended in patients with moderate or severe renal impairment *[see Dosage and Administration (2.5)]*. Although INVEGA® SUSTENNA® was not studied in patients with moderate or severe renal impairment, 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 mL/min to < 80 mL/min), 64% in moderate (CrCl = 30 mL/min to < 50 mL/min), and 71% in severe (CrCl = 10 mL/min to < 30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC_{inf}) of 1.5 fold, 2.6 fold, and 4.8 fold, respectively, compared to healthy subjects. Based on a limited number of observations with INVEGA® SUSTENNA® in subjects with mild renal impairment and pharmacokinetic simulations, the recommended initiation of INVEGA® SUSTENNA® for patients with mild renal impairment is with a dose of 156 mg on treatment day 1 and 117 mg on treatment day 8; thereafter, follow with monthly injections of 78 mg *[see Dosage and Administration (2.5)]*.

Hepatic Impairment

INVEGA® SUSTENNA® has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone in subjects with moderate hepatic impairment (Child-Pugh class B), no dose adjustment is required in patients with mild or moderate hepatic impairment *[see Dosage and Administration (2.5)]*. In the study with oral paliperidone in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects, although total paliperidone exposure decreased because of a decrease in protein binding. Paliperidone has not been studied in patients with severe hepatic impairment.

Elderly

No dosage adjustment is recommended based on age alone. However, dose adjustment may be required because of age-related decreases in creatinine clearance *[see Renal Impairment above and Dosage and Administration (2.5)]*.

Race

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

Gender

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

Smoking

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of intramuscularly injected paliperidone palmitate 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 0.6, 2, and 4 times, respectively, the maximum recommended human 234 mg dose of INVEGA® SUSTENNA® on a mg/m^2 basis. A no-effect dose was not established. Male rats showed an increase in mammary gland adenomas, fibroadenomas, and carcinomas at 47 mg and 94 mg/kg/month. A carcinogenicity study in mice has not been conducted with paliperidone palmitate.

Carcinogenicity studies of risperidone, which is extensively converted to paliperidone in rats, mice, and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. 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 on a mg/m^2 basis (see RISPERDAL® package insert). 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-receptor antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents in terms of human risk is unknown *[see Warnings and Precautions (5.8)]*.

Mutagenesis

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

Impairment of Fertility

Fertility studies of paliperidone palmitate have not been performed.

In a study of fertility conducted with orally administered paliperidone, the percentage of treated female rats that became pregnant was not affected at doses of paliperidone of up to 2.5 mg/kg/day. However, pre- and post-implantation loss were increased, and the number of live embryos was slightly decreased, at 2.5 mg/kg, a dose that also caused slight maternal toxicity. These parameters were not affected at a dose of 0.63 mg/kg, which is half of the maximum recommended human dose (12 mg/day) of orally administered paliperidone (INVEGA®) on a mg/m^2 basis.

The fertility of male rats was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day, although sperm count and sperm viability studies were not conducted with paliperidone. In a subchronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested (0.31 mg/kg - 5.0 mg/kg) resulted in decreases in serum testosterone and in sperm motility and concentration. Serum testosterone and sperm parameters partially recovered, but remained decreased after the last observation (two months after treatment was discontinued).

14 CLINICAL STUDIES

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.

In a 13-week study (n=636) comparing three fixed doses of INVEGA® SUSTENNA® (initial deltoid injection of 234 mg followed by 3 gluteal or deltoid doses of either 39 mg/4 weeks, 156 mg/4 weeks or 234 mg/4 weeks) to placebo, all three doses of INVEGA® SUSTENNA® were superior to placebo in improving the PANSS total score.

In another 13-week study (n=349) comparing three fixed doses of INVEGA® SUSTENNA® (78 mg/4 weeks, 156 mg/4 weeks, and 234 mg/4 weeks) to placebo, only 156 mg/4 weeks of INVEGA® SUSTENNA® was superior to placebo in improving the PANSS total score.

In a third 13-week study (n=513) comparing three fixed doses of INVEGA® SUSTENNA® (39 mg/4 weeks, 78 mg/4 weeks, and 156 mg/4 weeks) to placebo, all three doses of INVEGA® SUSTENNA® were superior to placebo in improving the PANSS total score.

In the 9-week study (n=197) comparing two fixed doses of INVEGA® SUSTENNA® (78 mg/4 weeks and 156 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 in schizophrenia was established in a longer-term double-blind, placebo-controlled, flexible-dose study involving adult subjects who met DSM-IV criteria for schizophrenia. This study included a minimum 12-

week fixed-dose stabilization phase, and a randomized, placebo-controlled phase to observe for relapse. During the double-blind phase, patients were randomized to either the same dose of INVEGA® SUSTENNA® they received during the stabilization phase, i.e., 39 mg, 78 mg, or 156 mg administered every 4 weeks, or to placebo. 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 showed a statistically significantly longer time to relapse in patients treated with INVEGA® SUSTENNA® compared to placebo, and the study was stopped early because maintenance of efficacy was demonstrated.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

INVEGA® SUSTENNA® is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate. The kit contains a prefilled syringe and 2 safety needles (a 1 ½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle).

39 mg paliperidone palmitate kit (NDC 50458-560-01)

78 mg paliperidone palmitate kit (NDC 50458-561-01)

117 mg paliperidone palmitate kit (NDC 50458-562-01)

156 mg paliperidone palmitate kit (NDC 50458-563-01)

234 mg paliperidone palmitate kit (NDC 50458-564-01)

Storage and Handling

Store at room temperature (25°C, 77°F); excursions between 15°C and 30°C (between 59°F and 86°F) are permitted.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following issues with patients for whom they prescribe INVEGA® SUSTENNA®. See FDA-approved patient labeling.

17.1 Orthostatic Hypotension

Patients should be advised that there is risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (5.9)]*.

17.2 Interference with Cognitive and Motor Performance

As INVEGA® SUSTENNA® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that INVEGA® SUSTENNA® therapy does not affect them adversely *[see Warnings and Precautions (5.11)]*.

17.3 Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with INVEGA® SUSTENNA® *[see Use in Specific Populations (8.1)]*.

17.4 Nursing

Patients should be advised not to breast-feed an infant during treatment with INVEGA® SUSTENNA® *[see Use in Specific Populations (8.3)]*.

17.5 Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions *[see Drug Interactions (7)]*.

17.6 Alcohol

Patients should be advised to avoid alcohol while taking INVEGA® SUSTENNA® *[see Drug Interactions (7.1)]*.

17.7 Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.17)]*.

INVEGA® SUSTENNA® (paliperidone palmitate) Extended-Release Injectable Suspension

Manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

Manufactured for:
Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

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