CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-264

LABELING

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 Cmax 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 breast feed. (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: [INSERT MM/YYYY OF FDA APPROVAL]

FULL PRESCRIBING INFORMATION: CONTENTS*

*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

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