Real-World Outcomes of Paliperidone Palmitate Compared to Daily Oral Antipsychotic Therapy in Schizophrenia: A Randomized, Open-Label, Review Board-Blinded 15-Month Study


Study objective
To compare the effects of once-monthly paliperidone palmitate (INVEGA SUSTENNA®) with daily oral antipsychotics on treatment failure in adults with schizophrenia¹

INDICATION
INVEGA SUSTENNA® (paliperidone palmitate) is indicated for the treatment of:
• Schizophrenia.

IMPORTANT SAFETY INFORMATION

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 the treatment of patients with dementia-related psychosis.

Real-world is defined by patient selection and clinically meaningful outcome measures.¹

Please see Important Safety Information on pages 7 to 8 and full Prescribing Information, including Boxed WARNING, in pocket.
Designed to reflect real-world issues in the treatment of schizophrenia\textsuperscript{1}

Paliperidone Palmitate Research in Demonstrating Effectiveness study (N=444)\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Clinical trial features</th>
<th>Real-world design elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Prospective</td>
<td>✓ Flexible treatment interventions</td>
</tr>
<tr>
<td>✓ Randomized</td>
<td>✓ Included patients who are typically excluded from clinical trials</td>
</tr>
<tr>
<td>✓ Open-label with blinded Event Monitoring Board</td>
<td>✓ Comorbid substance abuse\textsuperscript{†}</td>
</tr>
<tr>
<td>✓ A 15-month, head-to-head trial vs commonly prescribed oral antipsychotics*</td>
<td>✓ History of incarceration\textsuperscript{‡}</td>
</tr>
<tr>
<td>✓ Medication adherence was monitored but not required to complete the trial</td>
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</tr>
</tbody>
</table>

Key patient characteristics\textsuperscript{1}:

- Mean age: 38.1 years
- Patients with comorbid substance abuse: 59.5%
- Mean time since release from last incarceration: 42.2 days

Real-world is defined by patient selection and clinically meaningful outcome measures.\textsuperscript{1}

\textsuperscript{1}The 7 oral antipsychotics (included in the comparative arm) account for 74% of oral schizophrenia treatment during the study period.\textsuperscript{2}

\textsuperscript{2}Except for patients who had abused intravenous drugs within 3 months of screening or had an opiate dependence disorder (\textit{DSM-IV}).\textsuperscript{1}

\textsuperscript{3}Patients must have been arrested \textgeq 2 times in previous 2 years, with \textgeq 1 event leading to incarceration; released from most recent custody within 90 days of the screening visit.\textsuperscript{1}

The study was not powered to compare the efficacy of INVEGA SUSTENNA® with that of individual oral antipsychotics.

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A 15-month study of INVEGA SUSTENNA® (paliperidone palmitate) vs commonly prescribed oral antipsychotics1

Study overview1

• Patients assigned to the INVEGA SUSTENNA® group were initiated with 2 injections in the deltoid muscle that were given approximately 1 week apart: 234 mg on day 1 and 156 mg on day 8 (± 4 days)1
  – Flexible monthly maintenance dosing for INVEGA SUSTENNA® was started on day 38 within a range of 78 mg to 234 mg (recommended target maintenance dose was 156 mg)1

• Oral antipsychotic doses were given and adjusted within the range of the package insert1

Primary endpoint1:
• Time to first treatment failure, defined as 1 of the following:
  – Psychiatric hospitalization
  – Arrest/incarceration
  – Discontinuation of antipsychotic treatment due to safety or tolerability concerns
  – Treatment supplementation with another antipsychotic due to inadequate efficacy
  – Increased psychiatric services to prevent an imminent psychiatric hospitalization
  – Discontinuation of antipsychotic treatment due to inadequate efficacy
  – Suicide

Key secondary endpoint1:
• Time to first psychiatric hospitalization or arrest/incarceration

IMPORTANT SAFETY INFORMATION

Contraindications: Paliperidone is contraindicated in patients with a known hypersensitivity to either paliperidone, risperidone, or to any excipients of the formulation.
INVEGA SUSTENNA® (paliperidone palmitate) significantly delayed time to first treatment failure >6 months longer than commonly prescribed oral antipsychotics¹

Primary endpoint: Time to first treatment failure for INVEGA SUSTENNA® vs commonly prescribed oral antipsychotics¹

>6 months longer than commonly prescribed oral antipsychotics

- Median time to first treatment failure in the INVEGA SUSTENNA® group was 416 days vs 226 days in the oral antipsychotic group¹
- Fewer patients experienced a treatment failure event taking INVEGA SUSTENNA® vs those patients taking oral antipsychotics (39.8% vs 53.7%, respectively)¹

The study was not powered to compare the efficacy of INVEGA SUSTENNA® with that of individual oral antipsychotics.

*Data from randomization until end of randomly assigned treatment (28 days after last injection of INVEGA SUSTENNA® or 1 day after last dose of oral antipsychotic).¹

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Time to first hospitalization or arrest/incarceration was significantly longer with INVEGA SUSTENNA® than with commonly prescribed oral antipsychotics\(^1\)

Secondary endpoint: Median time to first psychiatric hospitalization or arrest/incarceration\(^1\)

- Median time to first psychiatric hospitalization or arrest/incarceration was not reached in the INVEGA SUSTENNA® group (>450 days). Median time to first psychiatric hospitalization or arrest/incarceration in the oral antipsychotic group was 274 days\(^1\)

IMPORTANT SAFETY INFORMATION

**Cerebrovascular Adverse Reactions:** Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attacks), including fatalities, were reported at a higher incidence in elderly patients with dementia-related psychosis taking risperidone, aripiprazole, and olanzapine compared to placebo. No studies have been conducted with oral paliperidone, INVEGA SUSTENNA®, or the 3-month paliperidone palmitate extended-release injectable suspension in elderly patients with dementia. These medicines are not approved for the treatment of patients with dementia-related psychosis.
Safety and tolerability of INVEGA SUSTENNA® (paliperidone palmitate) vs commonly prescribed oral antipsychotics

Treatment-emergent adverse events in ≥5% of subjects (N=444)

<table>
<thead>
<tr>
<th>TEAE, n (%)</th>
<th>INVEGA SUSTENNA® (n=226)</th>
<th>Oral antipsychotics (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>194 (85.8)</td>
<td>174 (79.8)</td>
</tr>
<tr>
<td>Injection-site pain</td>
<td>42 (18.6)</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>38 (16.8)</td>
<td>25 (11.5)</td>
</tr>
<tr>
<td>Weight increased</td>
<td>27 (11.9)</td>
<td>13 (6.0)</td>
</tr>
<tr>
<td>Akathisia</td>
<td>25 (11.1)</td>
<td>15 (6.9)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>24 (10.6)</td>
<td>16 (7.3)</td>
</tr>
<tr>
<td>Depression</td>
<td>17 (7.5)</td>
<td>14 (6.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (7.5)</td>
<td>6 (2.8)</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>17 (7.5)</td>
<td>0</td>
</tr>
<tr>
<td>Sedation</td>
<td>15 (6.6)</td>
<td>16 (7.3)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>15 (6.6)</td>
<td>18 (8.3)</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>15 (6.6)</td>
<td>8 (3.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>15 (6.6)</td>
<td>12 (5.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (6.2)</td>
<td>18 (8.3)</td>
</tr>
<tr>
<td>Libido decreased</td>
<td>13 (5.8)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13 (5.8)</td>
<td>10 (4.6)</td>
</tr>
<tr>
<td>Back pain</td>
<td>13 (5.8)</td>
<td>8 (3.7)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>10 (4.4)</td>
<td>15 (6.9)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>10 (4.4)</td>
<td>15 (6.9)</td>
</tr>
<tr>
<td>Toothache</td>
<td>10 (4.4)</td>
<td>12 (5.5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (2.2)</td>
<td>11 (5.0)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>8 (3.5)</td>
<td>13 (6.0)</td>
</tr>
</tbody>
</table>

Data from randomization until end of randomly assigned treatment (28 days after last injection of INVEGA SUSTENNA® or 1 day after last dose of oral antipsychotic).

The safety of INVEGA SUSTENNA® reflected what was seen in previous double-blind, placebo-controlled clinical trials in adult patients with schizophrenia.

• Percentage of patients who discontinued due to adverse events was 11.9% in the INVEGA SUSTENNA® group and 7.8% in the oral antipsychotic group

• There were no unexpected safety concerns related to vital signs, physical examination findings, or clinical laboratory test results with INVEGA SUSTENNA®

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Cerebrovascular Adverse Reactions: Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attacks), including fatalities, were reported at a higher incidence in elderly patients with dementia-related psychosis taking risperidone, aripiprazole, and olanzapine compared to placebo. No studies have been conducted with oral paliperidone, INVEGA SUSTENNA®, or the 3-month paliperidone palmitate extended-release injectable suspension in elderly patients with dementia. These medicines are not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with the use of antipsychotic medications, including paliperidone. Clinical manifestations include muscle rigidity, fever, altered mental status, and evidence of autonomic instability (see full Prescribing Information). Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and close medical monitoring, and treatment of any concomitant serious medical problems.

QT Prolongation: Paliperidone causes a modest increase in the corrected QT (QTc) interval. Avoid the use of drugs that also increase QTc interval and in patients with risk factors for prolonged 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 torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.

Tardive Dyskinesia (TD): TD is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medications. The risk of developing TD and the likelihood that dyskinetic movements will become irreversible are believed to increase with duration of treatment and total cumulative dose, but can develop after relatively brief treatment at low doses. Elderly female patients appeared to be at increased risk for TD, although it is impossible to predict which patients will develop the syndrome. Prescribing should be consistent with the need to minimize the risk of TD (see full Prescribing Information). Discontinue drug if clinically appropriate. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus: Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, have been reported in patients treated with all atypical antipsychotics (APS). Patients starting treatment with APS who have or are at risk for diabetes mellitus should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia during treatment should also undergo fasting blood glucose testing. All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia. Some patients require continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Continued on next page
Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Orthostatic Hypotension and Syncope: INVEGA SUSTENNA® may induce orthostatic hypotension in some patients due to its alpha-adrenergic blocking activity. INVEGA SUSTENNA® should be used with caution in patients with known cardiovascular disease, cerebrovascular disease or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, treatment with antihypertensive medications). Monitoring should be considered in patients for whom this may be of concern.

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

Leukopenia, Neutropenia and Agranulocytosis have been reported with antipsychotics, including INVEGA SUSTENNA®. In patients with a history of clinically significant low white blood cell count (WBC)/absolute neutrophil count (ANC) or drug-induced leukopenia/neutropenia, perform a complete blood count frequently during the first few months of therapy. Consider discontinuing INVEGA SUSTENNA® at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue INVEGA SUSTENNA® in patients with severe neutropenia (absolute neutrophil count <1000/mm³) and follow their WBC until recovery.

Hyperprolactinemia: As with other drugs that antagonize dopamine D₂ receptors, INVEGA SUSTENNA® elevates prolactin levels, and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to risperidone, which is associated with higher levels of prolactin elevation than other antipsychotic agents.

Potential for Cognitive and Motor Impairment: Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA SUSTENNA®. INVEGA SUSTENNA® has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities that require mental alertness such as operating hazardous machinery, including motor vehicles, until they are reasonably certain that INVEGA SUSTENNA® does not adversely affect them.

Seizures: INVEGA SUSTENNA® should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold. Conditions that lower seizure threshold may be more prevalent in patients 65 years or older.

Administration: For intramuscular injection only by a healthcare professional using only the needles provided in the INVEGA SUSTENNA® kit. Care should be taken to avoid inadvertent injection into a blood vessel.

Drug Interactions: Strong CYP3A4/P-glycoprotein (P-gp) inducers: Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, St. John’s Wort) during a dosing interval for INVEGA SUSTENNA®. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended-release tablets.

Pregnancy/Nursing: Advise patients that INVEGA SUSTENNA® may cause extrapyramidal and/or withdrawal symptoms in a neonate and to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with INVEGA SUSTENNA®.

Commonly Observed Adverse Reactions for INVEGA SUSTENNA®: The most common adverse reactions in clinical trials in patients with schizophrenia (≥5% and twice placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia and extrapyramidal disorder.

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CONCLUSION

“The PRIDE study demonstrated the superiority of once-monthly paliperidone palmitate [INVEGA SUSTENNA®] over daily oral antipsychotics in delaying time to treatment failure in an innovative randomized study that reflects real-world management of schizophrenia.”

— Alphs et al

The study was not powered to compare the efficacy of INVEGA SUSTENNA® with that of individual oral antipsychotics.

For more information, please contact your sales representative.

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