D2 and 5HT 2A blocker

Once daily dosing

No liver metabolism

Half-life is 24 hours

Steady state after 4 daily doses

1.5-12 mg/day

Evidence

- Joshi
    - 8-week, prospective, open-label, monotherapy, bipolar spectrum, youth, 15 kids
    - 3-6 mg/d (mostly 3)
    - Positive efficacy
    - Weight gain: 0-10 pounds (average: 4 pounds)

SE:

- Sleepiness 13%
- Muscle restlessness 9%
- Headache 9%
- Insomnia 9%
- Weight gain

In 6-week pivotal trials, INVEGA® (paliperidone) demonstrated powerful efficacy in patients with schizophrenia exhibiting a wide range of symptoms.[1] Patients in the trials were randomized to INVEGA®, placebo, and/or an active comparator.

INVEGA® is also indicated for the maintenance treatment of schizophrenia.

Patient Characteristics at Baseline (Pooled)[1]

In the 6-week pivotal trials, all patients were experiencing acute psychotic episodes, with a Positive and Negative Syndrome Scale (PANSS) total score of 70 to 120.

- Mean age: 36-39 years
- Race: White (61%); African American (22%); Asian (9%); other (8%)
- Gender: Male (63%); female (37%)
- Mean weight: 168.0-172.8 lbs

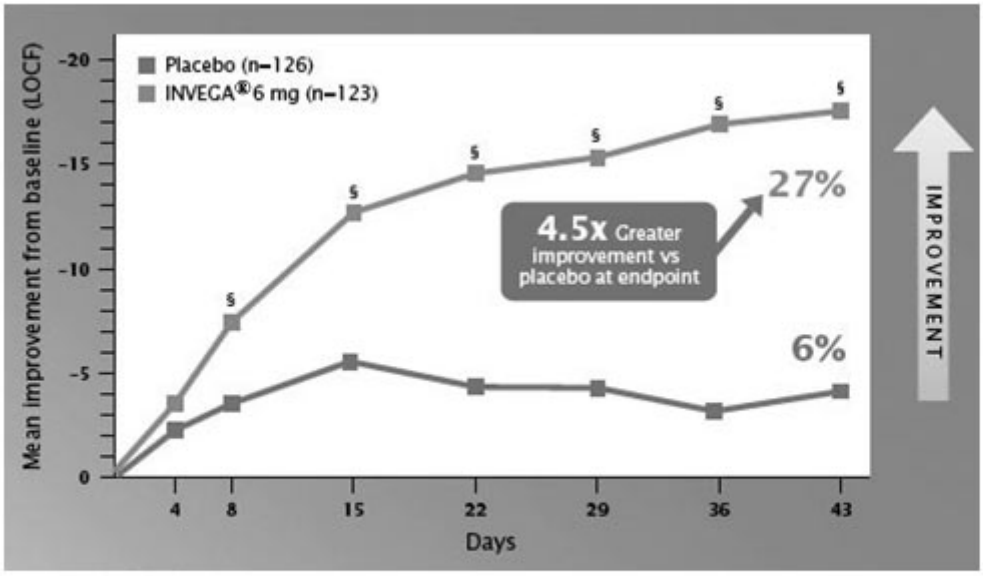
- Prior hospitalization: None (12%); once or twice (41%); three times or more (48%)

Clinical Efficacy

INVEGA® demonstrated significant symptom improvement, based on PANSS total scores, in a pivotal 6-week trial.[2] Efficacy was evaluated using the 5 PANSS factors:

- Positive symptoms
- Negative symptoms
- Uncontrolled hostility/excitement
- Anxiety/depression
- Disorganized thoughts

Improvement in PANSS Total Score Over 6 Weeks[2,3]



§ $P<0.05$ vs placebo.
Represents percent change from baseline. Mean change from baseline at end point was 4.1 for placebo and 17.9 for INVEGA®. LOCF=last observation carried forward.
Data on file[1] and adapted from Kane et al.[2]

In the trials, INVEGA® was proven effective for both acute and maintenance treatment of schizophrenia.[1]

- In all 3 pivotal studies, INVEGA® demonstrated significant improvements in PANSS total scores at all doses (3 mg, 6 mg, 9 mg, 12 mg) versus placebo ($P<0.001$)[1]
- In a longer-term trial, INVEGA® demonstrated maintenance of symptom control by delaying time to relapse*

*Results from a 6-week, double-blind, placebo-controlled study involving 628 patients with acute schizophrenia who received once-daily INVEGA® (6 mg, 9 mg, 12 mg), placebo, or active comparator.[2]

Hepatic Metabolism and Excretion

- CYP450 isoenzymes play a limited role in the overall metabolism of INVEGA®.
- Less than 10% of the dose is metabolized by each of the 4 identified metabolic pathways (dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission)
- The dose is primarily excreted unchanged via the kidneys

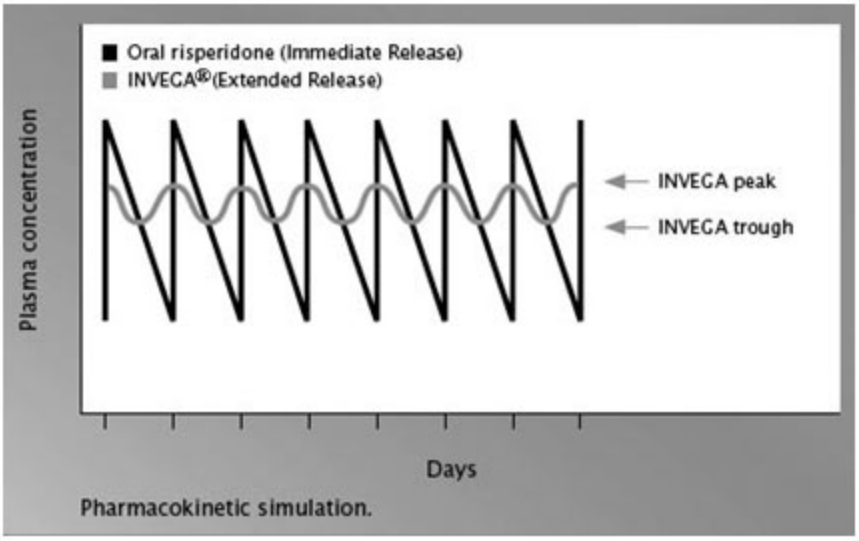
Safety and Tolerability

- Mean weight change was similar to placebo in 6-week clinical trials[3]
    - The proportion of patients gaining ≥7% of body weight with INVEGA® was 7% (3 mg), 6% (6 mg), 9% (9 mg), and 9% (12 mg) vs 5% (placebo) in 6-week trials, and 20% (average 10.8 mg) vs 12% (placebo) in a longer-term, flexible-dose trial
- No medically important differences versus placebo were seen in the number of patients with changes in lipids (including HDL, LDL, triglycerides, and total cholesterol) in 6-week trials and a longer-term clinical trial[1,3*]
    - As with other drugs that antagonize dopamine D_2 receptors, INVEGA® elevates prolactin levels and the elevation persists during chronic administration
- INVEGA® 3-mg and 6-mg doses were comparable with placebo across all EPS scales and rates of adverse events in 6-week trials
    - Total EPS-related adverse events in the higher 9-mg and 12-mg treatment groups were 25% and 26%, respectively, versus 11% for the placebo group in 6-week trials
- Discontinuation rates due to adverse reactions with INVEGA® were similar to those with placebo (3% vs 1% with placebo)

*Laboratory Test Abnormalities in Clinical Trials

Innovative Delivery System

INVEGA® utilizes OROS® extended-release technology for reduced peak/trough fluctuations.[4*]



*__Correlation to clinical effect has not been established.__
OROS is a registered trademark of ALZA Corporation.

Additional Benefits

- No dosage adjustments are required for patients with mild to moderate hepatic impairment
    - The effect of severe hepatic impairment is unknown. Clinical experience with INVEGA® in patients with certain concomitant illnesses is limited.
- Pharmacokinetic analyses show no difference in exposure or clearance of INVEGA® between extensive metabolizers and poor metabolizers of CYP2D6 substrates
- INVEGA® is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by the CYP450 enzymes
- In patients with renal impairment, dosing must be individualized according to renal function status. The maximum recommended dose of INVEGA® is 6 mg for patients with mild renal impairment and 3 mg for patients with moderate to severe renal impairment.
    - Given the primary CNS effects of INVEGA®, INVEGA® should be used with caution in combination with other centrally acting drugs and alcohol. INVEGA® 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® is administered with other therapeutic agents that have this potential.
    - The use of INVEGA® should be avoided in combination with other drugs that are known to prolong QTc.
    - In a study in healthy subjects, when a single dose of INVEGA® 3 mg was given with 20 mg of paroxetine, paliperidone exposures were on average 16% higher (90% CI: 4, 30) in CYP2D6 extensive metabolizers. Higher does of paroxetine have not been studied. The clinical relevance is unknown.

Convenient, Flexible, Once-Daily Dosing

- No initial dose titration is necessary; many patients can start with the recommended 6-mg dose
- Available in 3 tablet strengths (3 mg, 6 mg, 9 mg)
- Provides dosing flexibility for patients who may benefit from higher or lower doses (3 mg to 12 mg)
- Due to the extended-release formulation, morning administration is recommended

INVEGA® (paliperidone) extended-release tablets are indicated for the acute and maintenance treatment of schizophrenia.

IMPORTANT SAFETY INFORMATION for INVEGA®

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. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen 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. INVEGA® (paliperidone) is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular Adverse Events (CAEs): **CAEs, including fatalities, have been reported in elderly patients with dementia-related psychosis taking atypical antipsychotics in clinical trials. INVEGA is not approved for treating these patients.**

Neuroleptic Malignant Syndrome (NMS): **NMS, a potentially fatal symptom complex, has been reported with the use of antipsychotic medications, including INVEGA. 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 medical monitoring, and treatment of any concomitant serious medical problems.**

QT Prolongation: **INVEGA causes a modest increase in the corrected QT (QTc) interval. INVEGA should be avoided in combination with other drugs that are known to prolong the QTc interval, in patients with congenital long QT syndrome or a history of cardiac arrhythmias. Certain circumstances may increase the risk 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. Elderly patients appeared to be at increased risk for TD. Prescribing should be consistent with the need to minimize the risk of TD. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.**

Hyperglycemia and Diabetes: **Hyperglycemia, some cases extreme and associated with ketoacidosis, hyperosmolar coma or death has been reported in patients treated with atypical antipsychotics (APS). Patients starting treatment with APS who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.**

Hyperprolactinemia: **As with other drugs that antagonize dopamine D_2 receptors, INVEGA elevates prolactin levels and the elevation persists during chronic administration.**

Potential for Gastrointestinal Obstruction: **INVEGA should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing. Rare instances of obstructive symptoms have been reported in patients with known strictures taking nondeformable formulations. INVEGA should only be used in patients who are able to swallow the tablet whole.**

Orthostatic Hypotension: **INVEGA may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period. Monitoring should be considered in patients for whom this may be of concern. INVEGA should be used with caution in patients with known cardiovascular disease, and conditions that would predispose patients to hypotension.**

Potential for Cognitive and Motor Impairment: **INVEGA has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that INVEGA does not affect them adversely.**

Seizures: **INVEGA should be used cautiously in patients with a history of seizures.**

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

Maintenance Treatment: **Physicians who elect to use INVEGA for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.**

Drug Interactions: **Given the primary CNS effects of INVEGA, INVEGA should be used with caution in combination with other centrally acting drugs and alcohol.**

Extrapyramidal Symptoms (EPS): **Total EPS-related adverse events in the higher 9-mg and 12-mg treatment groups were 25% and 26%, respectively, versus 11% for the placebo group.**

Weight Gain: **The proportion of subjects having a weight gain of ≥7% body weight were comparable to placebo (5%) for 3 mg (7%) and 6 mg (6%). A higher incidence was seen for 9 mg (9%) and 12 mg (9%).**

Renal Impairment: **Dosing must be individualized according to the patient's renal function status. The maximum recommended dose of INVEGA is 6 mg for patients with mild renal impairment and 3 mg for patients with moderate to severe renal impairment (see Dosing for Special Populations).**

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 Dosing for Special Populations).**

Commonly observed adverse reactions: **The most commonly observed adverse reactions, occurring at an incidence of ≥5% and at least 2 times placebo, were akathisia and extrapyramidal disorder.**

Long-Term Safety of Paliperidone Extended Release in Adolescents with Schizophrenia: An Open-Label, Flexible Dose Study
Adam Savitz, Rosanne Lane, Isaac Nuamah, Jaskaran Singh, David Hough, Srihari Gopal
Journal of Child and Adolescent Psychopharmacology 2015, 25 (7): 548-57
OBJECTIVE: The purpose of this study was to evaluate the long-term safety and tolerability of paliperidone extended-release (ER) in adolescents with schizophrenia.

METHODS: This was a 2 year open-label, multicenter study in adolescents (12-17 years of age, inclusive) with schizophrenia. Eligible patients were initially treated with 6mg/day paliperidone ER, and the dose could be adjusted between 1.5 and 12mg/day based on clinical need. Safety parameters were treatment-emergent adverse events (TEAEs), weight, Tanner staging, blood chemistry (including prolactin, glucose, insulin, and lipid levels), and extrapyramidal symptom (EPS) scales. The main efficacy endpoint was change from baseline to endpoint in Positive and Negative Syndrome Scale for Schizophrenia (PANSS) total score.
RESULTS: Of 400 enrolled patients (mean age, 15.4 years; boys, 61%), 220 were completers. Median (range) exposure was 604.5 (2-765) days. TEAEs were reported in 85.3% of patients; most frequently reported TEAEs included somnolence, increased weight, headache, insomnia, nasopharyngitis, akathisia, schizophrenia exacerbation, and tremor. No deaths were reported. There were no clinically significant mean changes in growth-adjusted z score for change in weight, height, or body mass index (BMI). Tanner ratings showed normal maturation. Most frequently occurring EPS-related events were related to Parkinsonism (15.5%) and hyperkinesia (13.8%). No cases of tardive dyskinesia were reported. Hyperprolactinemia (based on laboratory values) was noted in 56% of patients and 9.3% of patients had prolactin-related TEAEs. A low percentage of patients (4.3%, n=14) had a shift from normal or impaired fasting glucose to high levels. Mean (SD) decrease (improvement) in PANSS total score from baseline to endpoint was -19.1 (21.89). The majority of patients had a ≥20% improvement in PANSS total score (responders) from initial treatment with paliperidone ER. Overall, 41.7% of patients achieved remission during the study.
CONCLUSIONS: Paliperidone ER was generally tolerable, and exhibited efficacy in the maintenance treatment of schizophrenia in adolescents in this large 2 year study.

Invega in youth with anger outbursts

- 2016
- Brazilian study
- 15 patients
- open-label
- diagnoses of depression, bipolar disorder, ADHD, and DMDD
- 6 mg/day