

Invega (paliperidone) STEPS

July 11, 2007

Recommendations

No head to head trials comparing paliperidone to risperidone or any other atypical anti-psychotic are available. Paliperidone would be expected to be similar to risperidone in effectiveness and tolerability. Paliperidone and risperidone are similarly priced, although generic risperidone is expected to be available in December 2007. Risperidone is approved for more indications and is available in multiple dosage forms. Given that there is no data to show that paliperidone is better tolerated or more efficacious, risperidone would still be recommended as the preferred agent in the inpatient setting.

Approved: December 20, 2006

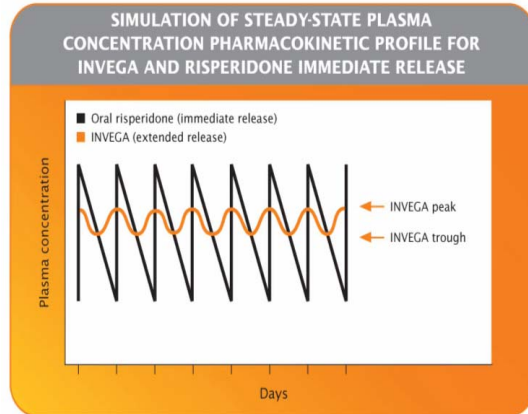
Invega is indicated for the acute and maintenance treatment of schizophrenia. It is the major metabolite of risperidone and is formulated using OROS[®] (osmotic controlled-release system) technology. This system employs osmosis to provide precise, consistent plasma drug concentrations throughout the day. The exact mechanism of action in schizophrenia is unknown, but paliperidone is believed to antagonize dopamine type 2 and serotonin type 2 receptors, similar to other available agents.

Safety =/-

- **Sound/Look alike names:** Neumega, Invagesic
- **Drug Interactions**
 - Antihypertensives: paliperidone may cause additive effects
 - CNS depressants, alcohol: paliperidone may cause additive CNS depression
 - Levodopa: paliperidone may antagonize the dopamine effects
 - Drugs known to prolong the QT interval should be used with caution: Class IA or Class III antiarrhythmic medications, or certain antibiotics (i.e. fluoroquinolones, macrolides)
 - Not extensively metabolized by cytochrome P450 and is not expected to cause clinically relevant pharmacokinetic drug interactions. Risperidone is a substrate and inhibitor of CYP 2D6 and 3A4.
- **Hepatic Function:** A dose adjustment is not needed in patients with mild to moderate hepatic impairment.
- **Renal Function:** For patients with mild renal impairment (CrCl 51 – 79ml/min), the maximum daily dose is 6mg once daily. For patients with moderate to severe renal impairment (CrCl 10-49ml/min), the maximum daily dose is 3mg.
- **Elderly:** No dosage adjustment needed based on age alone. Do not use in elderly patients with dementia – related psychosis due to an increased mortality (black-box warning for all atypical anti-psychotics)
- **Pediatric:** Efficacy not established in patients younger than 18 years
- **Pregnancy:** Category C
- **Lactation:** In human studies of risperidone, paliperidone was excreted in milk. Do not use in breastfeeding women
- **Contraindications:** Known hypersensitivity to paliperidone, risperidone or any components of the formulation
- **Precautions:** Similar to risperidone
 - Modest increase in the QTc interval – use with caution
 - Neuroleptic malignant syndrome
 - Tardive dyskinesia
 - Orthostatic hypotension – use with caution in patients with known cardiovascular disease
 - Diabetes mellitus: Hyperglycemia, and in some rare cases extreme hyperglycemia with ketoacidosis, coma or death, have occurred with all atypical antipsychotics. Monitor patients with diabetes closely.
 - Seizures: All atypical antipsychotics have the potential to lower the seizure threshold
 - Gastrointestinal: Obstructive symptoms have been reported in patients taking non-deformable formulations
 - Increases prolactin levels
 - Increased mortality in elderly patient with dementia-related psychosis when treated with atypical antipsychotics (**black box warning**)

Tolerability =

- Theorized to have fewer side effects due to consistency of drug levels throughout the day. No trials to confirm this hypothesis.



- Most common adverse events:** tachycardia (12%), sedation (9%), anxiety (7%). Other adverse reactions: dizziness (5%), nausea (4%), QT prolongation (4%), tremor (3%), akathisia (3%), dry mouth (3%)
- Dose-related side effects:** Somnolence, salivary hypersecretion, akathisia, extrapyramidal disorder, and parkinsonism
- Prolactin elevating effect:** Pharmacokinetic studies reveal similar increases in serum prolactin between paliperidone and risperidone
- Metabolic effects:** Substantial weight gain and development of hyperglycemia and diabetes were not reported in short-term clinical trials, although metabolic effects are likely to be similar to risperidone. There tended to be a higher incidence of weight gain in those taking the 9 or 12mg dose (9% of patients taking the 12mg dose had a >7% weight gain compared to 6% taking the 6mg dose)
- Would expect adverse effect profile to be similar to risperidone. Based on a comparison of prescribing information, Invega may have less extrapyramidal effects and anxiety, but more tachycardia than risperidone.

Comparison of Adverse Effects of Atypical Anti-Psychotics

Drug	Diabetes	EPS	↑ prolactin	QTc prolongation	Weight Gain
Aripiprazole (Abilify®)	+/-	+	+/-	+/-	+/-
Clozapine (Clozaril®)*	++++	+/-	+/-	+	++++
Olanzapine (Zyprexa®)	++++	+	+/-	+	++++
Paliperidone (Invega®)**	++	+++	+++	+	++
Quetiapine (Seroquel®)	++	+/-	+/-	+	+++
Risperidone (Risperdal®)	++	+++	+++	+	++
Ziprasidone (Geodon®)	+/-	+	+	++	+/-

* Clozapine is also associated with myocarditis and agranulocytosis

**Limited experience; likely to be similar to risperidone

Efficacy =/-

- Pharmacokinetics:** The peak concentration occurs after about 24 hours. Steady state concentrations can be achieved after 4 to 5 days. Bioavailability is only 28%. Food increases the peak concentration by as much as 60%. There is little hepatic metabolism, it is excreted 60% unchanged by the kidneys. The elimination half-life is about 23 hours. Because the drug delivery system maintains levels constant for 24 hours, Invega is hypothesized to prevent relapse and have fewer side effects compared to other medications. No trials have been performed to confirm this theory.
- Indications:** Schizophrenia. Invega does not have an indication for bipolar disease, although company representatives state that all the necessary studies have been completed and it is effective.

- **Clinical trials:** No head to head trials comparing Invega to risperidone or any other atypical anti-psychotic. All currently available clinical data was funded by Janssen Pharmaceutica. Studies are six weeks in duration – no long term data.

Prevention of Symptom Recurrence

J Clin Psychopharmacol. 2007 Feb;27(1):6-14.

Multi-center, double-blinded, placebo-controlled trial, n = 530. Primary efficacy variable was time to relapse after stabilization. 53% of placebo patients and 25% of paliperidone patients experienced recurrence.

Treatment of acute schizophrenia

Schizophr Res. 2007 Feb;90(1-1):147-61.

Multi-center, double blind, randomized study of 630 patients with schizophrenia, all experiencing an acute episode (Positive and Negative Syndrome Scale total score between 70-120). Patients received either placebo, paliperidone 6mg, paliperidone 12mg or olanzapine 10mg once daily. Olanzapine was used to provide a concurrent active control group in order to detect a “failed trial”. Paliperidone and olanzapine were not statistically compared. Paliperidone was superior to placebo in decreasing the PANSS score, and improving personal and social functioning. The adverse effect most commonly causing discontinuation was tachycardia. No glucose-related or QT prolongation adverse effects were reported.

“Virtual” comparison of paliperidone ER to risperidone

Poster at the 45th Annual Meeting of the American College of Neuropsychopharmacology (December 3-7, 2006)

Individual patient-level data from both paliperidone ER and risperidone studies was combined into one database for analysis. Paliperidone ER 6-12mg/day was compared to risperidone 4-6mg/day and risperidone 2-4mg/day. Paliperidone was similarly efficacious to the risperidone 4-6mg/day group and more efficacious than the risperidone 2-4mg/day group. In both groups, paliperidone ER was associated with lower rates of akathisia, restlessness, insomnia, somnolence, dizziness and GI effects, but had higher rates of tachycardia. Mean weight change was greater with risperidone (1.3 +/- 3.7kg) as compared to paliperidone ER (0.7 +/- 2.7kg) (p=0.024). Although the p value is significant, the weight ranges of the two agents overlap.

Price =

Paliperidone vs Risperidone

Drug	Paliperidone ER (Invega)	Risperidone (Risperdal)**
Dose (cost/day)* -prices from drugstore.com-	3mg daily (\$10.37) 6mg daily (\$10.93) 9mg daily (\$16.39)	1mg BID (\$8.90) 2mg BID (\$13.58) 3mg BID (\$17.82)

*Doses are not necessarily equivalent. Company states that there is no specific dosage conversion between paliperidone and risperidone and advises that practitioners use clinical judgment when switching to paliperidone




**A generic risperidone is expected to be available by December 2007

Cost Comparison of Available Atypical Anti-Psychotics

Drug	Usual Maintenance Dose	Cost/day (drugstore.com)
Aripiprazole (Abilify [®])	10mg daily	\$11.49
Clozapine (Clozaril [®])	100mg tid	\$5.10 (generic)
Olanzapine (Zyprexa [®])	15mg daily	\$17.32
Paliperidone (Invega [®])	6mg daily	\$10.93
Quetiapine (Seroquel [®])	200mg bid	\$13.13
Risperidone (Risperdal [®])	4mg daily	\$10.30
Ziprasidone (Geodon [®])	40mg bid	\$11.03

Simplicity +

- The osmotic drug delivery system (OROS) allows for once daily oral dosing and sustains drug levels for prolonged periods of time.
- The biologically inert components of the tablet remain intact during GI transit and are eliminated in the stool as a tablet shell
- Invega may be taken without regard to meals, although food does increase bioavailability. Invega must be swallowed whole and not crushed, chewed or divided
- There may be an advantage for those patients on several medications, since this drug is not metabolized by and does not interfere with the CYP 450 system.
- Available as 3mg, 6mg, and 9mg oral tablets. Risperidone is available as tablets, injection, oral solution, and orally disintegrating tablet.
- Initial and target dose is 6mg daily in the morning. Invega does not require dose titration as does risperidone. The initial dose can be increased if necessary by 3mg daily no more frequently than every five days. Recommended dosing range is 3 –12mg daily. Dosing in the evening was associated with increased variability in gastrointestinal transit time (approximately one-third of patients will expel the tablet prior to full release of the medication).

INVEGA DOSE DESCRIPTION AND PACKAGING	
Dose	Color
3 mg 	White
6 mg 	Beige
9 mg 	Pink

Tablets not shown actual size.