INVEGA® (paliperidone ER)
INVEGA - Dosing - Dosage and Administration

SUMMARY

- **Availability: INVEGA (paliperidone)** Extended-Release Tablets are available in 1.5 mg, 3 mg, 6 mg, and 9 mg strengths.[1]
- **Dose**:
  - **Adult:** The recommended dose of INVEGA is 6 mg once daily. Initial dose titration is not required. Although it has not been systematically established that doses above 6 mg have additional benefits, there was a general trend for greater effects with higher doses. This must be weighed against the dose-related increase in adverse reactions. Thus, some patients may benefit from higher dose, up to 12 mg/day, and for some patients, a lower dose of 3 mg/day may be sufficient. Dose increases above 6 mg/day should be made only after clinical reassessment and generally should occur at intervals of more than 5 days (in schizophrenia) and 4 days (in schizoaffective disorder). When dose increases are indicated, increments of 3 mg/day are recommended. The maximum recommended dose is 12 mg/day.[1]
  - **Adolescent:** The recommended starting dose of INVEGA tablets is 3 mg once daily. Initial dose titration is not required. Dose increases, if considered necessary, should be made only after clinical reassessment and should occur at increments of 3 mg/day at intervals of more than 5 days. In the adolescent schizophrenia study, there was no clear enhancement in efficacy at the higher doses. The maximum dose in patients <51 kg is 6 mg/day, while the maximum dose in patients ≥51 kg is 12 mg/day.[1]
- **DO NOT Split Tablets:** INVEGA must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.[1]
- **Administration Time:** INVEGA should be administered once daily.[1] Morning dosing leads to a 24-hour transit time in most individuals. Dosing in the evening is associated with increased variability in gastrointestinal transit time.[2]
- **With or Without Food:** INVEGA can be taken with or without food. However, the presence of food at the time of INVEGA administration may increase exposure to paliperidone.[1] Pharmacokinetic studies have found an increase in the area under the curve (AUC) and maximum concentration (C_{max}) in the fed vs fasted state.[3] INVEGA was dosed in the morning without regard to the timing of meals in all the pivotal studies.[1]
- **Use in Renal Impairment:** Dosing must be individualized according to the patient's renal function status. For patients with mild renal impairment (creatinine clearance 50 to <80 mL/min), the recommended initial dose is 3 mg once daily, and the maximum recommended dose is 6 mg once daily. For patients with moderate to severe renal impairment (creatinine clearance 10 to <50 mL/min), the recommended initial dose is 1.5 mg once daily, and the maximum recommended dose is 3 mg once daily.[1]
- **Hepatic Impairment:** No dose adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh Classification A and B). The effect of severe hepatic impairment is unknown.[1]
- **Use with Risperidone:** Concomitant use of INVEGA with risperidone has not been studied. Since paliperidone is the major active metabolite of risperidone, consideration should be given to the additive paliperidone exposure if risperidone is coadministered with INVEGA.

- **Elderly:** No dosage adjustment is recommended based on age only. However, because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status.[1]
- **Race, Gender, or Smoking Status:** No dosage adjustment is recommended based on race, gender, or smoking status.[1]

PRODUCT LABELING

Please refer to the following sections of the enclosed Full Prescribing Information that are relevant to your inquiry: DOSAGE AND ADMINISTRATION, USE IN SPECIFIC POPULATIONS, and CLINICAL PHARMACOLOGY.

PUBLISHED LITERATURE

Sathyan et al (2000)[2] conducted a study that investigated the effect of dosing time on the total gastrointestinal (GI) transit time of non-disintegrating tablets, such as OROS systems. Pooled OROS delivery system data (n=1163) regarding transit times after morning administration showed a distribution with peak times clustered around 24 and 48 hours. Conversely, night administration of OROS systems (n=80) resulted in transit times clustered around 12 and 36 hours, suggesting that transit times after administration may be related to the bowel movement habits of patients. The transit time of OROS systems was compared to bowel movement patterns for the general population and a correlation was observed. Because the GI transit time of non-disintegrating tablets is determined by the frequency of defecation, as well as the location of the tablet in the GI tract, a tablet is more likely to be excreted if it is located further down the GI tract. The transit time data for OROS systems suggest that a tablet is more likely to be excreted the next morning if it is dosed the previous morning.

Schizoaffective Disorder - Adult

Two publications are summarized below describing the modal daily dose of INVEGA when studied with flexible dosing (3-12 mg/day), higher dosing (9-12 mg/day), and lower dosing (3-6 mg/day).

Canuso et al (2010)[4] conducted a 6-week, international, double-blind, randomized, placebo-controlled, flexible-dose study of 304 adult patients with schizoaffective disorder. Patients in the INVEGA group received a starting dose of 6 mg/day adjusted within a range of 3-12 mg/day up to day 15. The mean modal daily dose of INVEGA was 8.6 mg/day. Overall, 1.4%, 35.1%, 29.9%, and 33.6% of patients had 3 mg, 6 mg, 9 mg, and 12 mg of INVEGA as their INVEGA daily dose, respectively. PANSS total scores significantly improved in the INVEGA group (-20.0) versus the placebo group (-10.8) at endpoint, and the mean difference was -9.1 (95% CI [confidence interval], -13.8, -4.5; P=0.0001).

Canuso et al (2010)[5] conducted a 6-week, double-blind, randomized, placebo-controlled study of 313 adult patients with schizoaffective disorder. Patients received higher dose of INVEGA (12 mg/day with an option to reduce the dose to 9 mg/day), or lower dose of INVEGA (6 mg/day with an option to reduce the dose to 3 mg/day), or placebo. Patients who reduced their dose due to tolerability reasons had the option to return to their originally assigned dose within the first 15 days. No dose adjustments were permitted after the day 15 visit. Overall, 13.3% and 12.4% of subjects had their dose reduced in the higher and lower dose groups, respectively. Only the higher dose group (mean modal dose 11.6 mg/day) was able to demonstrate a significant change versus placebo on the primary endpoint of total PANSS scores (P<0.001). The lower dose group (mean modal dose 5.7 mg/day) did not separate from placebo on total PANSS score (P=0.083).

Schizophrenia - Adult

Meltzer et al (2008)[6] conducted a pooled analysis of three 6-week, international, multicenter, double-blind, randomized, fixed-dose, placebo-controlled studies[7-9] to evaluate the safety and efficacy of INVEGA in patients with schizophrenia (N=1,306). Patients were randomly assigned to receive 3 mg (n=123), 6 mg (n=234), 9 mg (n=245), 12 mg (n=240), or 15 mg/day (n=113) of INVEGA or placebo (n=351). Overall, mean PANSS total scores, all PANSS factor scores, and rate of treatment response (defined as a 30% improvement in PANSS score) were significantly improved from baseline to endpoint for all doses of INVEGA than for placebo. Higher response rates were observed with individual doses of ≥6 mg/day.

Kramer et al (2007)[10] conducted an international, randomized, double-blind, placebo-controlled, parallel-group study evaluating the safety and efficacy of flexibly dosed INVEGA (3 mg, 6 mg, 9 mg, 12 mg, and 15 mg) in delaying symptom recurrence in patients with schizophrenia (N=207). Before patients were randomized in the flexible-dose double-blind phase, there was a screening period; an 8-week, open-label, run-in phase (flexible dosing); and a 6-week, open-label stabilization phase (fixed dosing). Distribution of the INVEGA Mode Daily Dose provides an overview of the doses patients received during the different phases of the study. The INVEGA mean dose and mean modal dose during the double-blind phase were both 10.8 mg/day. Time to pre-defined recurrence with INVEGA was significantly longer in both the interim analysis (P=0.005) and the final analysis (n=205, P<0.001).

Distribution of the INVEGA Mode Daily Dose[10]

	Run-in Phase - Flexible Dosing/Open-Label (Starting dose of 9 mg/day; Range 3-15 mg/day)	Stabilization Phase - Open-Label (Patients remained on previous dose during run-in phase)	Placebo-Controlled Phase - Double-Blind (Patients started at their stabilization phase dose)
Mode daily dose distribution (dose, %)	3 mg or 6 mg/day, 8% 9 mg/day, 45% 12 mg or 15 mg/day, 47%	9 mg/day, 33% 12 mg/day, 26% 15 mg/day, 30%	9 mg/day, 38% 12 mg/day, 22% 15 mg/day, 28%

Schizophrenia - Adolescent

Singh et al (2011)[11] conducted a randomized, placebo-controlled, multi-center, 6-week, double-blind study in 201 adolescents (mean age: 15-16 years) with schizophrenia. Patients were randomly assigned to receive either placebo or 1 of 3 weight-based, fixed-dose regimens of INVEGA. Patients weighing between 29 kg and <51 kg received either INVEGA 1.5 mg (low-treatment group), 3 mg (medium-treatment), or 6 mg (high-treatment) per day. Patients weighing ≥51 kg received either INVEGA 1.5 mg (low-treatment), 6 mg (medium-treatment), or 12 mg (high-treatment) per day. Overall, this study demonstrated the efficacy of INVEGA in adolescents with schizophrenia in the dose range of 3 to 12 mg/day. Doses within this broad range were shown to be effective, however, there was no clear enhancement of efficacy at the higher doses.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 22 April 2024.

OTHER RELEVANT LITERATURE

Additional publications identified during a literature search have been referenced.[12,13]

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