INVEGA® (paliperidone ER)
Dosing of INVEGA - Higher Doses

SUMMARY

- This information is intended to be a concise summary of representative clinical data; not all available published literature is incorporated into this response.
- The maximum recommended dose of INVEGA is 12 mg/day.[1]
- The pharmacokinetics (PK) of INVEGA are dose-proportional over the dose range of 3 to 15 mg/day.[2]
- The clinical trials that established the short-term efficacy of INVEGA in the treatment of schizophrenia included treatment arms that received a fixed dose of INVEGA (3, 6, 9, 12, and 15 mg/day).[3–5] All doses significantly improved Positive and Negative Syndrome Scale (PANSS) scores compared to placebo.[6] An analysis of dose response for efficacy demonstrated modest evidence of enhanced efficacy of INVEGA at higher doses (eg, 12 mg and 15 mg daily). There was also no clinically relevant relationship between INVEGA dosage and the incidence of serious adverse events.[3–6]
- During additional studies in patients with schizophrenia and a flexible-dosing design, patients received up to 15 mg/day of INVEGA. The results from these studies were not stratified by dose.[7,8]
- The short-term efficacy of INVEGA in the treatment of schizoaffective disorder was established in 2 placebo-controlled, 6-week trials. The maximum dose studied in these trials was 12 mg once daily.[1]
- The effects of INVEGA (12 and 18 mg/day), and quetiapine (400 mg twice daily) on QT interval were evaluated in a randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Both INVEGA and quetiapine slightly prolonged the QTcLD interval (population specific linear-derived method) and the changes were comparable between groups. There were no clinically significant cardiovascular events or adverse events that suggested proarrhythmic potential.[9]
- There have been case reports of adverse effects, such as motor tics and stroke, occurring in patients treated with INVEGA 15 mg/day for a short period of time.[10,11]

CLINICAL STUDIES

Pooled Analysis of 3 Similarly Designed Studies

Meltzer et al (2008)[6] presented the results from a pooled analysis of 3 similarly designed studies[3–5] assessing the efficacy and safety of INVEGA in patients (n=1306) with an acute episode of schizophrenia (PANSS score, 70-120).

Study Design/Methods

- Six-week, multicenter, double-blind, randomized, fixed-dose, placebo-controlled study
- Patients were randomly assigned to receive once-daily INVEGA (3, 6, 9, 12, or 15 mg) or placebo for 6 weeks.
- Primary endpoint: The difference between INVEGA and placebo in the change from baseline to endpoint in the PANSS total score in the intent-to-treat (ITT) population
- Secondary endpoints: PANSS Marder factor scores, clinical response (≥30% improvement from baseline in PANSS total score), Personal and Social Performance (PSP) score, and Clinical Global Impression-Severity (CGI-S) score
- Patients receiving at least 1 dose of study medication were included in the safety analysis, which consisted of spontaneous adverse event (AE) reporting, Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), Simpson-Angus Rating Scale (SAS), clinical laboratory values, ECG, and body weight.

Results

- Demographics and baseline characteristics of the ITT population (n=1306) were comparable across all groups. The average age among the total ITT population receiving INVEGA ranged from 36.3 years to 39.4 years and was 39 years for the placebo group. Approximately two-thirds of all patients were male.

Efficacy

- More patients in the INVEGA 15 mg group completed the study (71%) compared to patients in the other INVEGA groups (range, 55-64%) or placebo group (39%).
- Patients treated with INVEGA achieved statistically significantly greater improvements in the mean PANSS total score, clinical response, mean PSP total score (see Table: Outcome Measures: Change From Baseline to Endpoint), and all Marder factor scores than patients receiving placebo ($P \leq 0.001$).

Outcome Measures: Change From Baseline to Endpoint[6]

	Placebo (n=351)	INVEGA 3 mg (n=123)	INVEGA 6 mg (n=234)	INVEGA 9 mg (n=245)	INVEGA 12 mg (n=240)	INVEGA 15 mg (n=113)
Change in mean PANSS total score	-4.8	-15.0[a]	-16.9[a]	-16.8[a]	-20.6[a]	-19.9[a]
Clinical response, %	27.4	39.8[b]	53.2[b]	48.2[b]	56.7[b]	52.7[b]
Change in mean PSP total score	0.5	8.3[a]	9.0[a]	7.8[a]	9.5[a]	12.2[a]

Abbreviations: PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance.
[a]$P<0.001$ vs placebo.
[b]$P \leq 0.001$ vs placebo.

- An analysis of dose response for efficacy demonstrated modest evidence of enhanced efficacy of INVEGA at higher doses (eg, 12 mg and 15 mg daily).
- The largest LSM difference among pairwise comparison between INVEGA dose groups for changes from baseline to endpoint in PANSS total scores was between the 3 mg group and either the 12 mg or 15 mg INVEGA treatment groups (approximately -5.5).
- Smaller LSM differences were observed between the 6 mg or 9 mg groups compared with the 12 mg or 15 mg groups.

Safety

- Seventy-seven percent of patients in the INVEGA 15 mg group reported an AE, compared with 66-76% of patients in the other INVEGA groups, and 66% of patients in the placebo group.
- The most frequently (≥10% of patients in any treatment group) reported TEAEs were headache (INVEGA 15 mg, 18%; INVEGA 3-12 mg, 11-14%; placebo, 12%), akathisia (INVEGA 15 mg, 10%; INVEGA 3-12 mg, 3-10%; placebo, 4%), and insomnia (INVEGA 15 mg, 12%; INVEGA 3-12 mg, 11-14%; placebo, 14%).
- Extrapyramidal symptom (EPS)-related AEs occurred in 24% of patients in the INVEGA 15 mg group compared to 10-26% of patients in other INVEGA groups and 11% of patients in the placebo group.
- A higher proportion of patients receiving doses of INVEGA above 6 mg/day experienced EPS-related and other AEs (see Table: Potential Dose-Related Adverse Events).

Potential Dose-Related Adverse Events[6]

%	Placebo (n=351)	INVEGA 3 mg (n=123)	INVEGA 6 mg (n=234)	INVEGA 9 mg (n=245)	INVEGA 12 mg (n=240)	INVEGA 15 mg (n=113)
Somnolence	3	5	3	7	5	6
Orthostatic hypotension	1	2	1	2	4	3
Akathisia	4	4	3	8	10	10
Dystonia	1	1	1	5	5	2
Extrapyramidal disorder	2	5	2	7	7	8
Hypertonia	1	2	1	4	3	4
Parkinsonism	2	3	3	7	6	6
Salivary hypersecretion	<1	0	1	<1	0	2

- One to 2% of patients receiving INVEGA 3-12 mg and placebo experienced potential prolactin-related AEs, with a higher incidence in the INVEGA 15 mg group (4%).
- Clinically meaningful changes in laboratory tests and ECG results were not observed.
- The average weight gain was 0.6-1.1 kg in patients treated with INVEGA within the 3-12 mg dose range and 1.9 kg in the 15 mg group. There was a weight loss of 0.4 kg in the placebo group.

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 20 September 2023.

REFERENCES

1. INVEGA (paliperidone) [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc;https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVEGA-pi.pdf.

2. Boom S, Talluri K, Janssens L, et al. Single- and multiple-dose pharmacokinetics and dose proportionality of the psychotropic agent paliperidone extended release. *J Clin Pharmacol*. 2009;49(11):1318-1330.

3. Davidson M, Emsley R, Kramer M, et al. Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): results of a 6-week, randomized, placebo-controlled study. *Schizophr Res*. 2007;93(1-3):117-130.

4. Kane J, Canas F, Kramer M, et al. Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. *Schizophr Res*. 2007;90(1-3):147-161.

5. Marder S, Kramer M, Ford L, et al. Efficacy and safety of paliperidone extended-release tablets: results of a 6-week, randomized, placebo-controlled study. *Biol Psychiatry*. 2007;62(12):1363-1370.

6. Meltzer H, Bobo W, Nuahmah I, et al. Efficacy and tolerability of oral paliperidone extended-release tablets in the treatment of acute schizophrenia: pooled data from three 6-week, placebo-controlled studies. *J Clin Psychiatry*. 2008;69(5):817-829.

7. Kramer M, Simpson G, Maciulis V, et al. Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2007;27(1):6-14.

8. Emsley R, Berwaerts J, Eerdekens M, et al. Efficacy and safety of oral paliperidone extended-release tablets in the treatment of acute schizophrenia: pooled data from three 52-week open-label studies. *Int Clin Psychopharmacol*. 2008;23(6):343-356.

9. Hough DW, Natarajan J, Vandebosch A, et al. Evaluation of the effect of paliperidone extended release and quetiapine on corrected QT intervals. *Int Clin Psychopharmacol*. 2011;26(1):25-34.

10. Hsieh MH, Chiu NY. Paliperidone-associated motor tics. *Gen Hosp Psychiat*. 2014;36(3):360.e7-360.e8.

11. Chang CC, Wang WF, Lai TJ. Possible paliperidone-related pons infarction. *J Neuropsychiatry Clin Neurosci*. 2014;26(1):E15-E16.