INVEGA® (paliperidone ER)
INVEGA - OROS Technology

SUMMARY

- Osmotic-controlled release system (OROS®) is an advanced drug delivery system that uses osmotic pressure to deliver medications, including paliperidone, at a precise, controlled rate for up to 24 hours. The OROS formulation for INVEGA (paliperidone) Extended-Release (ER) Tablets results in minimal fluctuations in plasma concentrations.[1]
- Morning dosing leads to a 24-hour transit time in most individuals. Dosing in the evening is associated with increased variability in gastrointestinal (GI) transit time.[2]
- Patients should be informed that INVEGA should 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.[3]
- INVEGA uses the OROS delivery system that results in a gradually controlled ascending release of paliperidone. This release profile allows for small 24-hour peak-to-trough fluctuations in plasma concentrations at steady state. As a result, a lower incidence of treatment-emergent adverse events (TEAEs) was observed in a six day pharmacokinetic (PK) study comparing INVEGA 12 mg/day with risperidone IR 2-4 mg/day.[7]
- The OROS formulation enhances the initial tolerability of INVEGA, which permits initiation of treatment at an effective dose without dose titration.[4]
- In the three 6-week pivotal trials in schizophrenia[5], INVEGA demonstrated a therapeutic effect from the first observation point (Day 4).[6]
- A study using positron emission tomography (PET) to measure dopamine D_2-receptor occupancy found that fluctuation in D_2-receptor occupancy was 6-fold larger with the paliperidone immediate-release (IR) formulation when compared with the INVEGA formulation.[6]
- In a double-blind (DB), randomized, single-period study evaluating the PK of INVEGA 3 mg and 9 mg in healthy Chinese adults (n=24), the median time to reach maximum plasma concentration (t_{max}) was 22.2 hours for INVEGA 3 mg and 24.8 hours for INVEGA 9 mg. The geometric mean half-life ($t_{½}$) was 22.8 hours for INVEGA 3 mg and 21.4 hours for INVEGA 9 mg.[8]
- In a single- and multiple-dose PK study evaluating the plasma concentration profiles of INVEGA over the dose range of 3-15 mg in 30 healthy subjects the plasma concentrations of paliperidone gradually increased to reach maximum plasma concentration (C_{max}) approximately 24 hours following a single dose. The t_{max} (approximately 24 hours) and $t_{1/2}$ (22-23 hours) were comparable for all dose levels.[9]
- The OROS formulation of paliperidone results in a lower bioavailability compared with IR formulation paliperidone (28% vs. ~100%). The lower bioavailability of the OROS formulation most likely results from reduced absorption of paliperidone in the colon.[10]
- Additional information on INVEGA PK is available upon request.

BACKGROUND

INVEGA uses osmotic pressure to deliver paliperidone at a controlled rate. The delivery system, which resembles a capsule-shaped tablet in appearance, consists of an osmotically active trilayer core surrounded by a subcoat and semipermeable membrane. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There are two precision laser-drilled orifices on the drug-layer dome of the tablet. Each tablet strength has a different colored water-dispersible overcoat and print markings. In an aqueous environment, such as the GI

tract, the water-dispersible color overcoat erodes quickly. Water then enters the tablet through the semipermeable membrane that controls the rate at which water enters the tablet core, which, in turn, determines the rate of drug delivery. The hydrophilic polymers of the core hydrate and swell, creating a gel containing paliperidone that is then pushed out through the tablet orifices. The biologically inert components of the tablet remain intact during GI transit and are eliminated in the stool as a tablet shell, along with insoluble core components.

OROS® is a registered trademark of ALZA corporation.

PHARMACOKINETICS

Conley et al (2006)[1] conducted a review of various OROS technologies and their application in various therapeutic areas. This technology is designed to optimize the desired delivery profile of a drug for a specific indication.

The OROS formulation of INVEGA is designed to ensure a gradual rise in blood concentrations. This allows for initiation of treatment with a therapeutically effective dose from Day 1 without the need for dose titration. In addition, the OROS technology results in minimal fluctuations in plasma concentrations over 24 hours and is dosed once-daily.

INVEGA should be administered in the morning. A study by **Sathyan et al (2000)**[2] investigated the effect of dosing time on the total GI transit time of nondisintegrating 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 bowel movement habits of patients. The transit time of OROS systems were compared to bowel movement patterns for the general population and a correlation was observed. Because GI transit time of nondisintegrating 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.

Rossenu et al (2006)[10] conducted a study to evaluate the PK of paliperidone intravenous (IV), paliperidone IR, and OROS INVEGA.

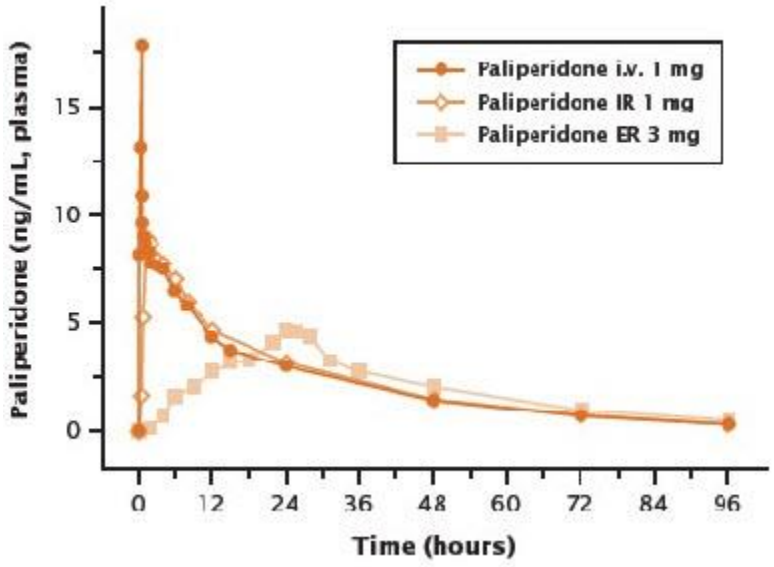
Study Design/Methods

- Single-dose, 5-period cross-over study in healthy subjects (n=20) receiving:
  - Paliperidone IV (1 mg 30-minute infusion)
  - Paliperidone IR (1 mg oral solution)
  - OROS INVEGA (3 mg) (INVEGA was administered at 3 times the dose of the other formulations due to differences in bioavailability)

Results

- The slow ascending concentration-time curve profile of INVEGA may allow for initiation of treatment at an effective dose with once-daily administration. See Figure: Mean Plasma Concentration-Time Plot and Table: Mean PK Parameters for a comparison of the 3 paliperidone formulations.

Mean Plasma Concentration-Time Plot[10]



Abbreviations: ER, extended release; IR, immediate release; IV, intravenous.

Mean PK Parameters[10]

Parameter	Paliperidone IV 1 mg	Paliperidone IR 1 mg	INVEGA 3 mg
t_{max}, h	0.5	1.8	23.5
C_{max}, ng/mL	17.8	9.4	4.9
AUC_{∞}, ng•h/mL	233	241	210
$t_{1/2}$, h	24.6	25.2	25.2
CL/F[a], mL/min	83.2	76.5	356

Abbreviations: AUC_{∞}, area under the plasma concentration-time curve from 0 to infinite time; CL, clearance; CL/F, total clearance of drug after extravascular administration; C_{max}, maximum plasma concentration; ER, extended release; IR, immediate release; IV, intravenous; PK, pharmacokinetics; $t_{1/2}$, terminal half-life; t_{max}, time to reach maximum plasma concentration.
[a]For IV treatment, CL/F is equal to CL.

- The absolute bioavailability of paliperidone IR and ER were 106% and 28%, respectively.
- The absolute bioavailability of the IR formulation indicates limited first-pass effect for paliperidone, and the lower absolute bioavailability of the ER formulation could stem from reduced absorption of paliperidone in the colon.
- A list of common (≥10% of patients in any group) adverse events (AEs) are presented in the Table: Incidence of Common TEAEs.

Incidence of Common TEAEs[10]

Adverse Event, %	Paliperidone IV 1 mg (n=20)	Paliperidone IR 1 mg (n=20)	INVEGA 3 mg (n=20)
Somnolence	60	55	30
Postural hypotension	45	20	15
Fatigue	5	10	15

Headache	15	10	10
Menstrual disorder	0	10	0
Abbreviations: IR, immediate release; IV, intravenous; TEAE, treatment-emergent adverse event.			

Karlsson et al (2005)[11] conducted 2 studies to evaluate the PK and dopamine D_2 and serotonin $(5\text{-HT})_{2A}$ receptor occupancy of paliperidone IR 1 mg (study 1) and INVEGA 6 mg (study 2) in healthy subjects.

Study Design/Methods

- Two open-label, single-dose studies

Results

- The PK of paliperidone and receptor occupancy of D2 and 5-HT_{2A} are presented in the Table Paliperidone PK and D_2 and 5-HT_{2A} Receptor Occupancy.
- Paliperidone occupies central D_2 and $5HT_{2A}$ receptors. They authors predicted that INVEGA, corresponding to a D_2 receptor occupancy of >60%, will be effective on psychotic and affective symptoms at doses above 3 mg/day.

Paliperidone PK and D2 and 5-HT_{2A} Receptor Occupancy[11]

Measure	Paliperidone IR 1 mg[a] (n=3)	INVEGA 6 mg[a] (n=4)
Median C_{max} (range), ng/mL	6.0 (5.3-6.1)	11.3 (7.7-16.5)
Median t_{max} (range), h	4.2 (4.1-8.1)	24.1 (23.1-29.0)
Median D_2 receptor occupancy, %	48 at 2.5 h postdose	64 at 22 h postdose 53 at 46 h postdose
Median 5-HT_{2A} receptor occupancy, %	65 at 4.5 h postdose	Not measured
Abbreviations: 5-HT, serotonin; C_{max}, maximum plasma concentration; IR, immediate release; PK, pharmacokinetics; t_{max}, time to reach maximum plasma concentration. [a]Initial studies have shown that INVEGA bioavailability is approximately 33% of paliperidone IR.		

PK/CLINICAL DATA/TOLERABILITY

Rossenu et al (2007)[7] conducted a study to compare the PK and tolerability of INVEGA 12 mg (highest recommended dose) with 2 mg titrated up to 4 mg of risperidone IR (the most commonly use and recommended dose in schizophrenia) in patients with schizophrenia.

Study Design/Methods

- Multiple-dose, DB, randomized, parallel-group study in patients with schizophrenia (n=113). Patients were assigned to one of three groups:
  - PBO on day 1 and INVEGA 12 mg on days 2 to 6
  - INVEGA 12 mg on days 1 to 6
  - Risperidone IR 2 mg on day 1 and risperidone IR 4 mg on days 2 to 6

Results

- The peak-to-trough variation of the plasma concentration of the active moiety (risperidone and paliperidone) among patients receiving risperidone exceeded the

peak-to-trough variation in the plasma concentration of paliperidone among patients receiving paliperidone by three-fold (125% vs. 38%, respectively).
- The OROS formulation reduced peak to trough fluctuation which may have improved tolerability.
- The incidence of TEAEs was 39% in the INVEGA treatment groups compared with 50% in the risperidone IR groups.

Kramer et al (2006)[6] conducted a post-hoc analysis of pooled data from 3 similarly designed 6-week, multicenter, DB, randomized, fixed-dose, placebo (PBO)-controlled studies[5] in patients with acute schizophrenia.

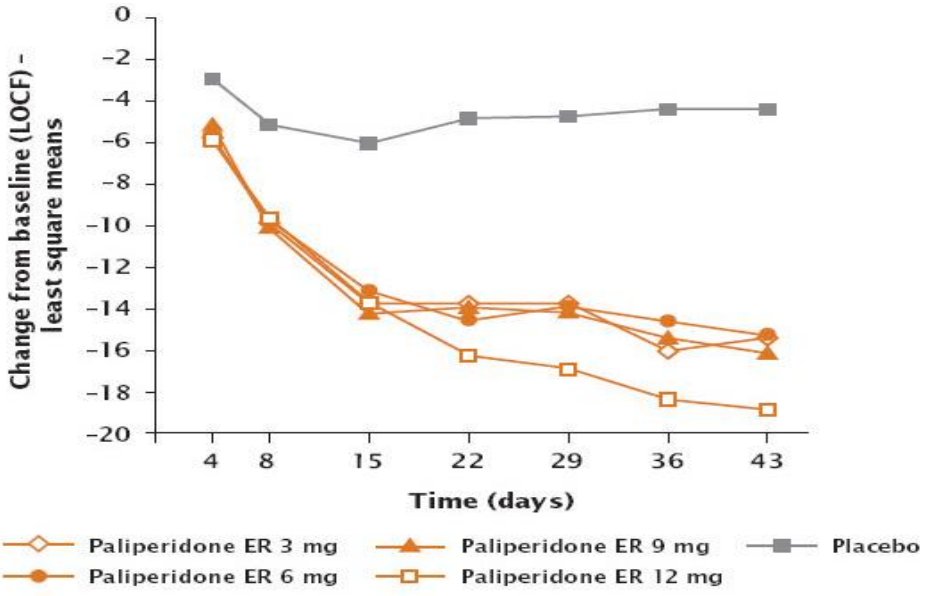
Study Design/Methods

- Patients with acute schizophrenia (n=1192) were randomly assigned to receive INVEGA 3 mg, 6 mg, 9 mg, 12 mg or PBO for 6 weeks.
- The analysis included an assessment of the onset of therapeutic effect.

Results

- Mean Positive and Negative Syndrome Scale (PANSS) total scores in the INVEGA groups improved significantly compared with PBO from Day 4 (first observation point) onward ($P<0.05$). (See Figure: Change From Baseline in the PANSS Total Scores in the Intent-to-Treat Population Over Time) From Week 2 onward, all INVEGA groups, except the 6 mg group, achieved significant clinical response (≥30% improvement on PANSS total score) compared with PBO ($P<0.05$).

Change From Baseline in the PANSS Total Scores in the Intent-to-Treat Population Over Time[6]



Abbreviations: ER, extended release; LOCF, last observation carried forward; PANSS, Positive and Negative Syndrome Scale.

Cleton et al (2007)[4] conducted a study to assess the orthostatic tolerability of INVEGA 12 mg with risperidone IR 2 mg in patients with schizophrenia.

Study Design/Methods

Multiple-dose, DB, randomized, PBO- and active-controlled, parallel-group study in patients with schizophrenia (n=112). Patients were assigned to a 6-day trial with one of three groups:

- PBO on day 1 and INVEGA 12 mg from days 2-6
- INVEGA 12 mg on days 1-6
- Risperidone IR 2 mg on day 1 and risperidone IR 4 mg on days 2-6

Results

- The mean change from baseline to day 1 in orthostatic systolic blood pressure was -1.16, -0.16, and -0.15 mmHg for INVEGA 12 mg, risperidone IR 2 mg, and PBO, respectively.
    - According to prespecified limits, the results indicated that INVEGA was noninferior to risperidone IR with respect to initial orthostatic tolerability.
- The incidence of orthostatic hypotension over the first 5 days of active treatment was 39% across both INVEGA groups and 53% in the risperidone IR group.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, DERWENT Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 26 May 2023.

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