INVEGA® (paliperidone ER)
INVEGA - Pharmacokinetics

SUMMARY

- INVEGA (paliperidone) Extended-Release Tablets utilize OROS® osmotic drug-release technology. The osmotic delivery system results in relatively smooth plasma paliperidone drug concentrations with small 24-hour peak-to-trough fluctuations at steady-state compared with IR (immediate-release) formulations.[1]
- Following a single dose, the plasma concentrations of paliperidone gradually rise to reach peak plasma concentration (C_{max}) approximately 24 hours after dosing.[2,3]
- The pharmacokinetics (PK) of paliperidone following INVEGA administration are dose-proportional within the recommended clinical dose range (3 to 12 mg).[2,3]
- The absolute oral bioavailability of paliperidone is 28% with a volume of distribution of 487 L. The plasma protein binding of racemic paliperidone is 74%.[2]
- The terminal elimination half-life of paliperidone is approximately 23 hours and steady-state concentrations of paliperidone are attained within 4-5 days of dosing in most subjects.[2,3]
- INVEGA can be taken without regard to food. The presence of food at the time of INVEGA administration may increase exposure to paliperidone. Clinical trials establishing the safety and efficacy of INVEGA were carried out in patients without regard to the timing of meals.[2,4]
- No dosage adjustments is recommended in patients with mild to moderate hepatic impairment.[2,5]
- The dose of INVEGA should be individualized according to the patient's renal function status.[6]

BACKGROUND - OROS TECHNOLOGY

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 gastrointestinal 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 gastrointestinal transit and are eliminated in the stool as a tablet shell, along with insoluble core components.[2]

Conley et al (2006)[7] 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.

PUBLISHED LITERATURE

Double-Blind, Randomized, Single Period Study

Tianmai et al (2010)[8] evaluated the PK of INVEGA 3 mg and 9 mg in 24 healthy Chinese subjects.

Study Design/Methods

Double-blind, randomized, single-period study in healthy Chinese subjects (18 to 55 years of age). Subjects received a single dose of either INVEGA 3 mg or 9 mg. Blood and urine samples were collected before dosing and over a 96-hour period following a single oral dose of INVEGA.

Results

Pharmacokinetics

The time course of plasma paliperidone concentrations demonstrated a one-compartmental model. Median t_{max} (time to reach maximum plasma concentration) occurred at 22.2 hours for the INVEGA 3-mg dose and 24.8 hours for the 9-mg dose. Geometric mean $t_{1/2}$ (half-life) was 22.8 hours for the 3-mg dose and 21.4 hours for the 9-mg dose. Significant dose-dependent differences were seen for C_{max}, AUC_{0-t} (area under the plasma-concentration time curve to time t), and $AUC_{0-\infty}$ (area under the plasma-concentration time curve to infinity).

Safety

Adverse events (AEs) reported in at least 5% of subjects were somnolence, dizziness, asthenia, headache, feeling flustered, and nausea. Somnolence and dizziness were dose related.

Single and Multiple Dose Pharmacokinetic Study

Boom et al (2009)[3] evaluated plasma concentration profiles of INVEGA over the dose range of 3 to 15 mg in 30 healthy subjects. A second study, a dose-proportionality study (N=50), evaluated five different single oral doses of INVEGA (3, 6, 9, 12, and 15 mg/day).

Study Design/Methods

Healthy subjects were enrolled in the single- and multiple-dose PK study (aged 18 to 45 years) and the dose-proportionality study (aged 18 to 55 years). In the single-dose phase, INVEGA 3 mg/day was administered followed by a 6-day sampling period. In the multiple-dose phase, INVEGA 3 mg/day was administered for 7 days followed by a 6-day sampling period. In the dose-proportionality study, five different single oral doses of INVEGA (3, 6, 9, 12, and 15 mg/day) were administered in random order followed by a 10- to 14-day washout period between each dose.

Results

Pharmacokinetics

The dose-proportionality study included only men, while the single-and multiple-dose study included both men and women. PK parameters (C_{max}, $t_{1/2}$, and CL/F) were similar between studies, which indicated that the PK of INVEGA were probably not influenced by sex.

On the first dosing day, plasma concentrations gradually ascended, with maximum concentrations occurring at 24 hours and minimal fluctuations in plasma concentrations on

subsequent treatment days. In the multiple-dose phase, steady state was achieved after four once-daily doses. Paliperidone ER showed a 3.47-fold accumulation upon steady state, and this was mainly caused by the controlled-release characteristics of the formulation. The results of the dose-proportionality study indicate that paliperidone ER is dose proportional over the dose range of 3 to 15 mg. The t_{max} (approximately 24 hours) and $t_{1/2}$ (22 to 23 hours) were similar between all dose levels.

Safety

In the single-dose study, the most common AEs were hypotension and headache. During multiple-dose administration, hypotension, postural dizziness, and headache were the most common AEs. In the dose-proportionality study, the most commonly reported AEs were headache, fatigue, dizziness, and somnolence. Eight subjects experienced extrapyramidal symptom-related AEs.

Single-Dose, Parallel Group Study

Boom et al (2009)[5] conducted a single-dose, parallel-group study in 10 patients with moderate hepatic impairment (Child-Pugh class B: total score of 7 to 9) and 10 demographically matched (for age, weight, sex, and ethnicity) patients with normal hepatic function.

Study Design/Methods

All participants received 1 mg of paliperidone IR as an oral solution under fasting conditions. Blood and urine samples were collected before dosing and over a 96-hour period following paliperidone administration.

Results

Pharmacokinetics

Patients with hepatic impairment achieved lower total plasma concentrations than healthy patients (i.e., total exposure was somewhat reduced). After the reduced protein binding was taken into account, unbound plasma paliperidone concentrations were similar between the two groups. As unbound plasma concentrations of the drug are believed to be most relevant for efficacy and safety, no dose adjustment is required in patients with hepatic impairment, according to the PK data in this study.

All other PK parameters were similar between the two groups.

Safety

After a single oral dose of 1 mg of paliperidone IR, the only AEs reported in more than one patient in either group were hyperprolactinemia and dizziness (the latter occurred in two hepatically impaired patients).

Randomized, Double-Blind, Parallel Group Phase I Study

Berwaerts et al (2010)[9] compared the PK between INVEGA 12 mg/day and risperidone 4 mg/day in patients with schizophrenia (N=76).

Study Design/Methods

6-day, randomized, double-blind, parallel-group, Phase I study. Patients (aged 18 to 75 years) with stable schizophrenia who received risperidone for at least one month prior to entering the study were eligible to participate. Patients were randomized to receive INVEGA

12 mg (n=38) on Days 1 to 6 or risperidone 2 mg (n=38) on Day 1 and 4 mg on Days 2 to 6. PK measurements included plasma concentrations of risperidone, paliperidone, and risperidone plus paliperidone (i.e., the active moiety).

Results

Pharmacokinetics

The C_{max} of paliperidone ER on Day 6 was 19% lower than the pharmacologically active fraction of risperidone IR (46.1 vs 56.8 ng/mL, respectively), while the AUC_{0-24h} was similar between treatment groups (896 vs 760 ng·h/mL, respectively). The fluctuation index was 38% for paliperidone and 125% for the active fraction of risperidone IR. Steady state was achieved by Day 6 for both treatment groups.

Safety

The most commonly reported AEs (incidence of ≥5%) in patients receiving INVEGA (groups combined) were extrapyramidal disorder (12%) and insomnia, hyperkinesia, and headache (each 5%). The most commonly reported AEs (incidence of ≥5%) in risperidone-treated patients were insomnia (18%), anxiety (11%), extrapyramidal disorder (8%), tachycardia (8%), and hyperkinesia (5%).

Study Reviewing the Peak to Trough Fluctuation in Plasma Concentration of Long-Acting Antipsychotics and Their Oral Equivalents

Sheehan et al (2012)[10] conducted a study reviewing the peak-to-trough fluctuation in plasma concentration of long-acting injectable antipsychotics and their oral equivalents. Selected Pharmacokinetic Parameters provides the time to maximum plasma concentration (T_{max}) and the terminal half-life ($T_{½}$) for long-acting injectable antipsychotics and their oral equivalents.

Selected Pharmacokinetic Parameters[10]

Drug	Tmax	T½
Long-Acting Injectable Antipsychotics		
Haloperidol Decanoate	6 days	21 days
Olanzapine Pamoate	4 days	30 days
Paliperidone Palmitate	13 days	37 days[b]
Risperidone Long-Acting Injection	35 days[b]	4.5 days[b]
Zuclopenthixol Decanoate	3 days	7.4 days
Oral Antipsychotics		
Haloperidol	4.9 hours	25.6 hours
Oral Olanzapine	6 hours	30 hours
Oral Risperidone[a]	1.3 hours	19.5 hours
Paliperidone ER	24 hours	23 hours

Abbreviation: T½, Terminal Half-life.
a: Risperidone - data reported for the active moiety (risperidone + (9-OH-risperidone)
b: Where a range was reported, the midpoint of the range is presented here.

Study Investigating the Effect of Dosing Time on the Total Gastrointestinal Transit Time of Nondisintegrating Tablets

Sathyan et al (2000)[11] conducted a study investigating the effect of dosing time on the total gastrointestinal (GI) transit time of nondisintegrating tablets, such as the OROS system. Pooled OROS delivery system data (n=1163) regarding transit times after morning administration showed a distribution with peak times clustered around 24 to 48 hours.

Conversely, night administration of OROS systems (n=80) resulted in transit times clustered around 12 to 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.

Effects of Smoking Status on Pharmacokinetics

Schoretsanitis et al (2020)[12] conducted a retrospective analysis of the pharmacokinetics of oral paliperidone in patients treated between 2007 and 2015 to analyze the effects of smoking status on plasma levels and dose-corrected-plasma concentrations (C/D) in a naturalistic population. The sample included 55 smokers and 37 nonsmokers who did not differ in sex, age, body weight or daily paliperidone dose. No group differences were detected in plasma concentrations (P=0.50) or C/D (P=0.96) between smokers and non-smokers.

UNPUBLISHED LITERATURE

Pharmacokinetic Simulations Examining the Effect of Different Adherence Rates

Devane et al (2009)[13] performed PK simulations to examine the effect of three different adherence rates on the plasma concentration of paliperidone ER and risperidone in 4,000 virtual patients receiving 12 weeks of either INVEGA 6 mg/day or risperidone 4 mg/day.

Study Design/Methods

The simulation used data from two population PK models:

- Paliperidone ER developed from 21,183 individual plasma drug concentrations
- Risperidone developed from 5,359 plasma drug concentrations

The investigators defined the target drug concentration range as the concentration that corresponds to 70% to 80% of D_2 receptor occupancy.

- Paliperidone: 10 to 17 ng/mL
- Active moiety of risperidone (risperidone + 9-hydroxy-risperidone): 26 to 46 ng/mL

Results

In simulations that assumed 100% compliance for both paliperidone ER and risperidone, 24.2% of virtual patients receiving paliperidone ER and 4.7% of those receiving risperidone showed consistent plasma concentrations in the target range. In a simulation that assumed 67% compliance (two doses deleted within a window of six days prior to evaluation), 10.4% of paliperidone ER-treated virtual patients and 2.6% of risperidone-treated patients had plasma concentrations consistently in the target range. In a simulation that assumed 33% compliance, plasma concentrations of paliperidone ER and risperidone remained within the target range for 3.4% and 1.0% of virtual patients, respectively.

Study Comparing the PK and Tolerability of INVEGA and Risperidone IR

Rossenu et al (2007)[14] conducted a study comparing 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).

Study Design/Methods

Multiple-dose, double-blind, randomized, parallel-group study in patients with schizophrenia (n=113). Patients were assigned to one of three groups:

- Placebo 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).

Safety

The incidence of treatment-emergent AEs was 39% in the INVEGA treatment groups compared with 50% in the risperidone IR groups.

Study Comparing the Effects of Renal Impairment on Plasma and Urine PK

Thyssen et al (2007)[6] compared the effects of renal impairment on plasma and urine PK of orally administered INVEGA 3 mg between subjects with varying degrees of impairment and healthy subjects with normal renal function (N=48).

Study Design/Methods

Single-dose, parallel-group study in subjects aged 18 to 75 years. The subjects were divided into four groups:

- normal renal function group (creatinine clearance ≥80 mL/min)
- mild renal impairment group (creatinine clearance 50 to ≤80 mL/min)
- moderate renal impairment group (creatinine clearance 30 to <50 mL/min)
- severe renal impairment group (creatinine clearance <30 mL/min)

Results

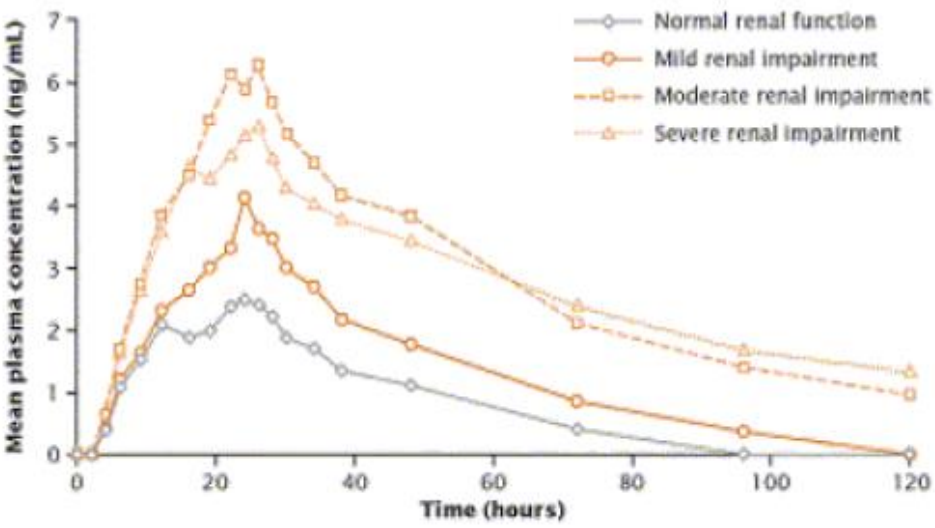
Patient Characteristics

Mean age: 57.3 years and all groups were balanced for age, weight, BMI, sex, and ethnicity.

Pharmacokinetics

Plasma protein binding did not significantly differ among the four groups (mean: 26.8% to 30.1%). Please see: Mean Paliperidone Plasma Concentration-time Plot for a graphical comparison of the drug disposition.

Mean Paliperidone Plasma Concentration-time Plot[6]



Please refer to Table: Paliperidone Pharmacokinetic Parameters (mean) for a comparison of the PK among the four groups of subjects. The volume of distribution decreased by 25% to 30% in renally impaired subjects compared with that in healthy subjects

Paliperidone Pharmacokinetic Parameters (mean)[6]

	Healthy Subjects (n=12)	Mild Renal Impairment (n=11)	Moderate Renal Impairment (n=12)	Severe Renal Impairment (n=10)
C_{max}, ng/mL	2.63	4.29	6.65	5.55
AUC_{∞}, ng.h/mL	114	169	416	429
t_{max}[a], h	20.5	24.0	24.0	24.0
$t_{1/2}$, h	23.2	23.6	40.2	51.0
CL/F, mL/min	561	433	271	217
CL_R, mL/min	70.5	49.2	21.9	12.9
CL_{NR}, mL/min	491	384	268	204
Ae, % dose	13.2	15.2	9.80[b]	7.47

Abbreviations: C_{max}, peak plasma concentration; AUC_{∞}, area under the plasma-concentration-time curve from time zero to infinity; t_{max}, time to reach peak plasma concentration; $t_{1/2}$, elimination half-life; CL/F, apparent total plasma clearance; CL_R, renal clearance; CL_{NR}, non-renal clearance; Ae, amount renally excreted.
[a] Median (range)
[b] n=11

Safety

AEs were reported for 91% of subjects with normal renal function, 83% of those with mild renal impairment, 100% of those with moderate renal impairment, and 100% of those with severe renal impairment. No patients reported severe or serious AEs, and no subjects discontinued treatment because of AEs.

Open Label Study Comparing Single and Multiple Dose INVEGA Between Healthy Elderly Patients and Healthy Young Patients

Cleton et al (2007)[15] compared single- (Day 1) and multiple-dose (Days 6 to 12) PK of 3 mg INVEGA between healthy elderly subjects (n=30) and young healthy adults (n=30).

Study Design/Methods

An open-label study was conducted with healthy elderly subjects (aged ≥65 years) and young healthy adults (aged 18 to 45 years) received INVEGA 3 mg on Day 1 and on Days 6 to 12.

Results

Patient Characteristics

The elderly (men, 57%; mean age, 71.0 years; mean creatinine clearance, 60 mL/min) and young subjects (men, 50%; mean age, 29.0 years; mean creatinine clearance, 101 mL/min) were matched as closely as possible for sex and weight. Fifty-four subjects completed the study.

Pharmacokinetics

After a single dose of INVEGA 3 mg, the time concentrations were similar between elderly and young adult subjects during the absorption phase, somewhat higher in elderly subjects during the elimination phase, and higher in elderly subjects throughout the profile after multiple dosing. The PK of paliperidone ER 3 mg suggested linearity and time independency of the PK process in both young and elderly healthy subjects. The higher paliperidone concentrations observed during the elimination phase did not signify the requirement for dose adjustment in elderly subjects. he recommended dose range for elderly patients with normal renal function should not differ from the recommended dose range (3 to 12 mg) for younger adult patients with normal renal function.

Safety

After a single dose of INVEGA 3 mg, the most common AEs (≥20% incidence in either the young or elderly subject group) were hypotension (measured in the supine position) (0% elderly; 23% young), orthostatic hypotension (20% elderly; 7% young), headache (7% elderly; 23% young), and leg pain (27% elderly; 10% young). After repeated-dose administration of INVEGA 3 mg, the most common AEs were hypotension (measured in the supine position) (14% elderly; 50% young), orthostatic hypotension (29% elderly; 14% young), headache (21% elderly; 25% young), and postural dizziness (7% elderly; 43% young). One serious AE occurred in an elderly subject (silent inferior myocardial infarction that resolved and was considered possibly related to study medication). None of the subjects had an increase in QTc interval of >60 msec compared with that recorded at screening, and none of the subjects had a QTc interval >500 msec.

Two Open-Label, Single-Dose Studies

Karlsson et al (2005)[1] conducted two studies to evaluate the PK and dopamine D_2 and serotonin 5-HT_{2A} receptor occupancy of paliperidone IR 1 mg (Study 1; n=3) and INVEGA 6 mg (Study 2; n=4) in healthy patients.

Study Design/Methods

Two open-label, single-dose studies were conducted in healthy patients.

Results

See: Paliperidone Pharmacokinetics and D2 and 5-HT_{2A} Receptor Occupancy.

Paliperidone Pharmacokinetics and D_2 and 5-HT_{2A} Receptor Occupancy[1]

Measure	Paliperidone IR 1 mg[a] (n=3)	Paliperidone ER 6 mg[a] (n=4)
Median C_{max} (ng/mL) (range)	6.02 (5.34-6.14)	11.3 (7.73-16.5)
Median T_{max} (h) (range)	4.2 (4.1-8.1)	24.1 (23.1-29.0)
Median % D_2 receptor occupancy	48 at 2.5h post-dose	64 at 22h post-dose; 53 at 46h post-dose
Median % 5-HT_{2A}-receptor occupancy	65 at 4.5h post-dose	Not measured
[a] Initial studies have shown that paliperidone ER's bioavailability is approximately 33% of paliperidone IR.		

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 16 January 2024. Several published references regarding the PK of paliperidone were identified.[16,17]

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