INVEGA® (paliperidone ER)
Drug Interaction of INVEGA - Anticonvulsants and Mood Stabilizers

SUMMARY

- Given the primary CNS effects of paliperidone, INVEGA should be used with caution in combination with other centrally acting drugs and alcohol.[1]
- **Carbamazepine:**
  - Co-administration of INVEGA 6 mg once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease was caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone.[1]
  - A minor decrease in the amount of drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration.[1]
  - The dose of INVEGA may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy.[1]
- **Valproate:**
  - Co-administration of a single dose of INVEGA 12 mg with divalproex sodium ER tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone. Dosage reduction for INVEGA should be considered when INVEGA is coadministered with valproate after clinical assessment.[1]
  - In a drug interaction study, coadministration of INVEGA (12 mg once daily for 5 days) with divalproex sodium ER tablets (500-2000 mg once daily) did not affect the steady-state pharmacokinetics (area under the plasma concentration-time curve over 24 hours [AUC_{24h}] and maximum plasma concentration at steady state [$C_{max,ss}$]) of valproate in 13 patients stabilized on valproate. In a clinical study, subjects on stable doses of valproate had comparable valproate average plasma concentrations when INVEGA 3-15 mg/day was added to their existing valproate treatment.[1]
- **Lithium:** A pharmacokinetic interaction is unlikely.[1]

PRODUCT LABELING

Please refer to the following section(s) of the INVEGA Full Prescribing Information that are relevant to your inquiry: DRUG INTERACTIONS.

PUBLISHED LITERATURE

Mood Stabilizers

Berwaerts et al (2011)[2] conducted a 6-week, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of INVEGA in combination with a mood stabilizer for the treatment of an acute manic or mixed episode in patients with bipolar I disorder. A total of 300 patients were randomized to receive either a combination treatment of flexibly-dosed INVEGA (3-12 mg/day; starting dose: 6 mg/day) and a mood stabilizer (either lithium or valproate) or receive a mood stabilizer as monotherapy. Mood stabilizer dosing was based on plasma concentration remaining within the therapeutic range (0.6-1.2 mEq/L for lithium and 50-125 µg/mL for valproate). Baseline characteristics were similar between groups, with a mean age of 40 years, and 54% being male. The mood stabilizer used more frequently in both the combination therapy and monotherapy groups was valproate (61% and 63%, respectively). Mean final dose of INVEGA was 8.1 mg/day.

Treatment-emergent adverse events (TEAEs) were more frequently reported in the combination treatment group compared to the monotherapy group (70% vs 54%,

respectively). Adverse events that occurred more commonly (≥5%) and had a higher incidence (≥3% difference) in the combination group than the monotherapy group were somnolence (9% vs 5%), akathisia (8% vs 1%), weight increased (9% vs 4%), and increased appetite (5% vs 2%). Discontinuation due to TEAEs were higher in the combination group than the monotherapy group (8% vs 1%, respectively). Serious TEAEs were reported in 5% of patients in both treatment groups, with worsening of mania being the most common event. Weight increase was reported by 9% of patients in the combination group and 4% in the monotherapy group, with a mean body-weight change being 1.8 kg and 0.7 kg, respectively. A prolactin-related TEAE occurred in 1 patient in the combination therapy group (sexual dysfunction) with normal serum prolactin levels. Patients in the combination group experienced a mean increase in serum prolactin from baseline (25.8 ng/mL in men; 80.5 ng/mL in women), while the monotherapy group experienced a decrease from baseline (-3.1 ng/mL in men; -7.8 ng/mL in women).

Carbamazepine

Kerbusch-Herben et al (2014)[3] conducted an open-label, multiple-dose, 2-treatment, 2-period sequential study which investigated the effect of repeated administration of carbamazepine on the steady-state pharmacokinetics of INVEGA in patients with schizophrenia or bipolar I disorder.

A total of 64 patients (43 men and 21 women, median age: 42 years, schizophrenia diagnosis: n=62) received the following treatments in a fixed sequential manner, without washout between treatments: (1) INVEGA 6 mg once daily for 7 days, and (2) INVEGA 6 mg once daily with carbamazepine controlled-release 200 mg twice daily for 21 days (days 8-28).

After coadministration with carbamazepine, paliperidone AUC_{24h} and C_{max} at steady-state decreased by approximately 37% each vs treatment with INVEGA alone. In addition, there was a 35.5% increase in renal clearance of paliperidone and a 14% decrease in the amount of paliperidone excreted unchanged in the urine over a 24-hour period following coadministration with carbamazepine.

After receiving INVEGA monotherapy (30%) and in combination with carbamazepine (24%) the overall incidence of adverse events (AEs) was similar. The most common (≥5%) AEs after administration of INVEGA monotherapy were headache (11%) and extrapyramidal disorder (5%); following administration of INVEGA with carbamazepine weight increase (5%) was the most common AE reported.

Yasui-Furukori et al (2013)[4] evaluated the effects of carbamazepine on the pharmacokinetics of paliperidone in patients with schizophrenia (N=6). Patients initially received paliperidone 6-12 mg/day for 8-24 weeks. Coadministered agents included flunitrazepam (2-4 mg/day, n=3), biperiden (4-6 mg/day, n=2), and sennoside (12-48 mg/day, n=2). Carbamazepine 100 mg twice daily was added for 2-4 weeks followed by an increase to 200 mg twice daily then 300 mg twice daily for 2-4 weeks. The addition of carbamazepine significantly reduced the plasma concentrations of paliperidone. The plasma concentrations of paliperidone at baseline and with coadministration of carbamazepine 200, 400, and 600 mg/day were 45.8±11.7 ng/mL, 26.9±13.7, 17.1±8.2, and 15.9±7.6 ng/mL, respectively. The concentration of paliperidone with coadministration of carbamazepine 200, 400, and 600 mg/day were 55.7%±20.7%, 36.1%±12.2%, and 33.6%±10.4%, respectively, of baseline. Approximately 2-3 months following the start of carbamazepine 5 of the 6 patients deteriorated. The paliperidone dose was increased from 6 to 12 mg daily however, the coadministration of carbamazepine was ultimately discontinued in 3 of these 5 patients.

Akamine et al (2015)[5] reported the case of a 53-year-old female patient with schizophrenia and hypertension who was receiving paliperidone 12 mg/day and amlodipine 5 mg/day. When carbamazepine 200-600 mg/day was added, the plasma concentrations of paliperidone and amlodipine greatly decreased in a dose-dependent fashion (paliperidone by 35%-48% and amlodipine by 36%-68%). The concentration of carbamazepine also decreased after administration of 600 mg/day vs 200 mg/day or 400 mg/day. There was no change in the patient's psychotic symptoms following the addition of carbamazepine. However, the patient's mean blood pressure increased from 138.4 mmHg to 160.1 mmHg after administration of carbamazepine 600 mg/day and returned to normal upon discontinuation.

Valproate

Remmerie et al (2016)[6] conducted 2 phase 1, open-label, 2-treatment, single-sequence studies to evaluate the effects of repeated doses of valproic acid (VPA), in the form of divalproex sodium ER, on the pharmacokinetics of a single dose of INVEGA in healthy volunteers (study 1), and the effect of multiple doses of INVEGA on the steady-state pharmacokinetics of valproic acid (VPA) in patients with schizophrenia, bipolar I disorder, or schizoaffective disorder (study 2).

In study 1, volunteers received 2 consecutive treatment regimens (n=24; mean age: 39 years). Treatment A consisted of a single dose of INVEGA 12 mg (day 1). Treatment B consisted of 2 tablets of divalproex sodium ER 500 mg once daily on days 5 to 18 and a single dose of INVEGA 12 mg on day 15.

In study 2, patients received 2 consecutive treatment regimens (n=17; 76% male; mean age: 39.5 years; bipolar diagnosis: 82.4%). Treatment A consisted of divalproex sodium ER once daily on days 1-7. Treatment B consisted of divalproex sodium ER once daily + INVEGA 12 mg once daily on days 8-12. Divalproex sodium ER doses were based upon each patient's prescreening therapeutic VPA dose and remained unchanged throughout the treatment period.

Effect of VPA on PK of INVEGA: In study 1, mean paliperidone C_{max} and AUC values were increased by 51% and 51-52%, respectively, with INVEGA+VPA treatment versus treatment with INVEGA alone (Table: Analysis of Variance by Treated for Pharmacokinetics Parameters of Paliperidone and Valproic Acid). Median time to peak concentration (t_{max}) of paliperidone was 24 hours for both treatments (range: 9-27 hours INVEGA monotherapy; 15-27 hours INVEGA+VPA) and the mean elimination half-life was approximately 24 hours.

Analysis of Variance by Treated for Pharmacokinetics Parameters of Paliperidone and Valproic Acid[6]

Parameters	N	Intrasubject CV (%)	Geometric Mean		Ratio, % (90% CI) (Test/Reference)
			Paliperidone Alone (Reference)	Paliperidone + VPA (Test)	
Healthy Participants					
C_{max} (ng/mL)	23	29.3	11.7	17.7	151.5 (130.6-175.7)
AUC_{last} (ng•h/mL)	23	26.9	438.1	657.4	150.1 (131.0-172.0)
AUC_{∞} (ng•h/mL)	23	27.1	475.4	721.7	151.8 (132.3-174.2)

Abbreviations: AUC_{∞}, area under the plasma concentration-time curve from time 0 to infinite time; AUC_{last}, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; Ratio, ratio of geometric means (paliperidone ER + VPA/paliperidone ER alone); VPA, divalproex sodium extended-release.

Effect of INVEGA on the PK of VPA: In both studies, bioequivalence was demonstrated in VPA exposure. When administered with a single dose (study 1) or multiple doses (study 2) of INVEGA, respectively, compared to VPA alone, the $C_{max,ss}$ and area under the plasma concentration-time curve during a dosing interval (AUC_T) of VPA were similar (See Table. Analysis of Variance by Treated for Pharmacokinetics Parameters of Valproic Acid and Paliperidone).

Analysis of Variance by Treated for Pharmacokinetics Parameters of Valproic Acid and Paliperidone[6]

Parameters	N	Intrasubject CV (%)	Geometric Mean		Ratio, % (90% CI) (Test/Reference)
			VPA Alone (Reference)	Paliperidone + VPA (Test)	
Healthy Participants					
$C_{max,ss}$ (µg/mL)	23	7.2	80.0	82.5	103.1 (99.4-106.9)
AUC_T (µg•h/mL)	23	6.4	1663.3	1693.9	101.8 (98.6-105.2)
Patients with Schizophrenia					
$C_{max,ss}$ (µg/mL)	13	8.7	80.0	78.1	97.6 (91.8-103.6)
AUC_T (µg•h/mL)	13	8.2	1533.9	1495.5	97.5 (92.1-103.2)

Abbreviations: AUC_T, area under the plasma concentration-time curve during a dosing interval; CI, confidence interval; $C_{max,ss}$, maximum observed plasma concentration at steady state; CV, coefficient of variation; Ratio, ratio of geometric means (paliperidone ER + VPA/ paliperidone ER alone); VPA, divalproex sodium extended-release.

Treatment with INVEGA, VPA, and INVEGA + VPA was well-tolerated. In study 1, the most commonly reported TEAEs (≥10%) for the INVEGA vs INVEGA + VPA treatment groups, respectively were: headache (29% vs 13%), dizziness (17% vs 9%), and somnolence (4% vs 9%). For VPA alone, the most commonly reported TEAEs were dizziness (4%) and somnolence (22%). In study 2, the most commonly reported TEAEs (≥10%) in the INVEGA + VPA period were sedation (19%), weight gain (19%) and somnolence (13%).

UNPUBLISHED LITERATURE

Fu et al (2010)[7] reported results from 2, 6-week, multicenter, international, randomized, double-blind, placebo-controlled, parallel-group studies in adult patients (n=414 INVEGA, n=200 placebo) with schizoaffective disorder. Patients who had been receiving stable doses of concomitant antidepressants (AD), except monoamine oxidase inhibitors, and/or mood stabilizer (MS; valproate, lithium, or lamotrigine) continued treatment with these medications, provided that the medication had been given at a stable dose 30 days prior to screening. The modal dose of INVEGA was 8.4 mg/day in the monotherapy group and 8.8 mg/day in the adjunctive therapy group. Of the total intent-to-treat population, 275 patients received INVEGA or placebo adjunctively with a MS/AD. Of this group, 140 patients (51.0%) received MS without AD. The types and frequencies of adverse events were similar in patients receiving INVEGA as monotherapy and as an adjunct to MS/AD. INVEGA as monotherapy or as an adjunct to MS or AD was tolerable across these subpopulations.

OTHER RELEVANT LITERATURE

Citations for review articles discussing INVEGA efficacy and safety, including drug interactions, have been included in the References section for your convenience.[8-11]

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, DERWENT® (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 20 May 2024.

REFERENCES

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