INVEGA® (paliperidone ER)
INVEGA - Differences from Oral Risperidone

SUMMARY

- Paliperidone is the major active metabolite of RISPERDAL® (risperidone) and INVEGA® (paliperidone) Extended-Release Tablets is the only atypical antipsychotic using OROS® (osmotic controlled release system) technology. OROS technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours.[1] Due to the OROS technology, peak-to-trough variation in plasma concentrations is substantially lower with INVEGA than with RISPERDAL.[2,3]
- INVEGA is metabolized by four primary metabolic pathways, none of which accounts for more than 10% of the dose, and 59% of the dose is excreted largely unchanged in urine.[1] In contrast, RISPERDAL is extensively metabolized in the liver.[4]
- Cytochrome P450 enzymes (2D6) are minimally involved in the metabolism of paliperidone, unlike risperidone, the potential for clinically significant pharmacokinetic drug interactions with drugs that induce or inhibit these enzymes [eg, paroxetine, fluoxetine] is minimal.[1,5]
- INVEGA is currently the only antipsychotic to include effectiveness on personal and social functioning compared with placebo in the US Prescribing Information.[1]
- According to the results of a "virtual" comparison, INVEGA 6-12 mg/day may be similarly efficacious to risperidone 4-6 mg/day with some tolerability benefits.[6]
- The recommended dose of INVEGA is 6 mg once daily. Unlike RISPERDAL, INVEGA can be initiated at an effective dose without the need for initial titration. Additionally, no dose adjustment is recommended with INVEGA for patients with mild to moderate hepatic impairment.[1]

BACKGROUND

The Food and Drug Administration (FDA) approved INVEGA as a New Chemical Entity. Based on FDA's standard definition of therapeutic equivalents[7], INVEGA and RISPERDAL are not considered by FDA to be therapeutically equivalent, as they do not contain the same active ingredient. They are also not administered in the same range of dose strengths or according to the same recommended regimen.

SUMMARY OF DIFFERENCES BETWEEN INVEGA AND RISPERIDONE

Most Common Adverse Events

INVEGA: The most commonly observed adverse reactions in INVEGA clinical trials occurring at an incidence of ≥5% and at least 2 times placebo in the treatment of schizophrenia were: Adults – extrapyramidal symptoms, tachycardia, and akathisia; Adolescents (12-17 years of age) were: somnolence, akathisia, tremor, dystonia, cogwheel rigidity, anxiety, weight increased, and tachycardia. The most commonly observed adverse reactions in clinical trials occurring at an incidence of ≥5% and at least 2 times placebo in the treatment of schizoaffective disorder were: Adults – extrapyramidal symptoms, somnolence, dyspepsia, constipation, weight increased, and nasopharyngitis.[1]

RISPERDAL: The most common adverse reactions in clinical trials (incidence of ≥5% and twice placebo) were parkinsonism, akathisia, dystonia, tremor, sedation, dizziness, anxiety, blurred vision, nausea, vomiting, upper abdominal pain, stomach discomfort, dyspepsia, diarrhea, salivary hypersecretion, constipation, dry mouth, increased appetite, increased weight, fatigue, rash, nasal congestion, upper respiratory tract infection, nasopharyngitis, and pharyngolaryngeal pain.[4]

Formulation

INVEGA is the only atypical antipsychotic using OROS technology to deliver an antipsychotic, paliperidone. OROS technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours.[1] The specific OROS technology employed in INVEGA was specifically engineered to vary the amount of medication delivered over the release period in order to improve the consistency of a patient's plasma levels of paliperidone. Due to the OROS technology, peak-to-trough variation in plasma concentrations is substantially lower with INVEGA than with RISPERDAL (38% vs 125%).[2,3] For many medications, it is hypothesized that tolerability and/or efficacy are affected by pharmacokinetic characteristics and not simply by total drug exposure.[8] INVEGA can be dosed once daily, and unlike RISPERDAL, can be initiated at an effective dose without the need for initial titration.[1]

Pharmacokinetics

Pharmacokinetic differences between INVEGA and RISPERDAL include oral bioavailability (28% vs 70%), plasma level fluctuations (38% vs 125%)[2, 3] and time to reach peak plasma concentrations following a single dose (24 hours vs 1 hour), respectively.[1, 4] In addition, steady-state peak-to-trough concentrations varies between oral paliperidone and oral risperidone, with the plasma concentration ratios being 1.47 and 3.30, respectively.[3] An additional article, discussing atypical antipsychotic pharmacokinetics, has been referenced for your convenience.[9]

Further, unlike RISPERDAL, the active ingredient of INVEGA has limited hepatic metabolism. INVEGA is metabolized by four primary metabolic pathways, none of which accounts for more than 10% of the dose, and 59% of the dose is excreted largely unchanged into urine. In contrast to dosing recommendations in the RISPERDAL Prescribing Information, no dose adjustment is recommended with INVEGA for patients with mild to moderate hepatic impairment.[1,4,10]

P-glycoprotein is an endogenous transporter pump that can affect the pharmacokinetics of drugs. Among other activities, P-glycoprotein can impact transport of medication from the bloodstream across the blood-brain barrier into the central nervous system. Research suggests that paliperidone and risperidone are not similar substrates of P-glycoprotein.[11]

Drug-Drug Interactions

Cytochrome P450 enzymes (2D6) are minimally involved in the metabolism of paliperidone, unlike risperidone, the potential for clinically significant pharmacokinetic drug interactions with drugs that induce or inhibit these enzymes [e.g., paroxetine, fluoxetine] is minimal.[1,5]

Receptor Binding

Although there is extensive literature on the neuroreceptor physiology of antipsychotic medications, according to the approved prescribing information, the mechanism of action of paliperidone and other drugs proven effective in schizophrenia is defined as unknown. Similar to RISPERDAL, INVEGA is a centrally active dopamine D_2 antagonist and serotonergic 5-HT_{2A} antagonistic. INVEGA is also active as an antagonist at α_1 and α_2 adrenergic receptors and H_1 histaminergic receptors. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors.[1]

The relative efficacy of risperidone and paliperidone in the regulation of several receptor signaling pathways coupled to human D_2, 5-HT_{2A}, 5-HT_{2C}, and H_1 receptors was evaluated.[12] Although there are some similarities in binding affinities for many receptors, risperidone and paliperidone may differ in their profile of cellular signaling pathways resulting in a possible

difference in therapeutic efficacy or adverse effect profile. Further research is needed to determine the impact on specific clinical effects.

Preclinical data suggest paliperidone and risperidone may exert distinct effects on serotonin and norepinephrine neuronal activity.[13]

Personal and Social Performance

INVEGA is currently the only antipsychotic to include effectiveness on personal and social functioning compared to placebo, as assessed by the Personal and Social Performance (PSP) scale, in the US prescribing information. The PSP is a validated clinician-rated scale that measures personal and social functioning in the domains of socially useful activities (e.g., work and study), personal and social relationships, self-care, and disturbing and aggressive behaviors. The PSP scale has not been included as an outcome measure in oral RISPERDAL clinical trials.

Additional Prescribing Information Differences

While the WARNINGS and PRECAUTIONS sections of the INVEGA and RISPERDAL Prescribing Information are generally similar, the INVEGA Prescribing Information includes additional WARNINGS and PRECAUTIONS (QT Prolongation and Potential for Gastrointestinal Obstruction).[1] The RISPERDAL Prescribing Information includes 1 additional WARNING and PRECAUTION (Patients with Phenylketonuria) for patients on RISPERDAL M-TAB.[4] (Please note that RISPERDAL M-TAB was discontinued in 2018.)

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 06 June 2023.

REFERENCES

1. INVEGA (paliperidone) [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-d30da9a4-d8a4-4e37-b8e8-d52589dfe597.
2. Berwaerts J, Cleton A, Rossenu S, et al. A comparison of serum prolactin concentrations after administration of paliperidone extended-release and risperidone tablets in patients with schizophrenia. *J Psychopharmacol*. 2010;24(7):1011-1018.
3. Sheehan JJ, Reilly KR, Fu DJ, et al. Comparison of the peak-to-trough fluctuation in plasma concentration of long-acting injectable antipsychotics and their oral equivalents. *Innov Clin Neurosci*. 2012;9(7-8):17-23.
4. RISPERDAL (risperidone) [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-7df7969a-275a-4705-94b7-f7a07c3e33a4.
5. Berwaerts J, Cleton A, Herben V, et al. The effects of paroxetine on the pharmacokinetics of paliperidone extended-release tablets. *Pharmacopsych*. 2009;42(4):158-163.
6. Turkoz I, Bossie C, Lindenmayer JP, et al. Paliperidone ER and oral risperidone in patients with schizophrenia: a comparative database analysis. *BMC Psychiatry*. 2011;11(21):1-10.
7. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Silver Springs, MD: U.S. Food and Drug Administration. June 2019. https://www.accessdata.fda.gov/scripts/cder/ob/. Accessed August 13, 2019.
8. Ereshefsky L, Mascarenas CA. Comparison of the effects of different routes of antipsychotic administration on pharmacokinetics and pharmacodynamics. *J Clin Psychiatry*. 2003;64(suppl 16):18-23.

9. Preskorn SH. Psychopharmacology. Clinically important differences in the pharmacokinetics of the ten newer "atypical" antipsychotics: part 2. Metabolism and elimination. *J Psychiatr Pract*. 2012;18(5):361-368.

10. Preskorn SH. Clinically important differences in the pharmacokinetics of the ten newer "atypical" antipsychotics: part 3. Effects of renal and hepatic impairments. *J Psychiatr Pract*. 2012;18(6):430-437.

11. Nakagami T, Yasui-Furukori N, Saito M, et al. Effect of verapamil on pharmacokinetics and pharmacodynamics of risperidone: In vivo evidence of involvement of p-glycoprotein in risperidone disposition. *Clin Pharmacol Ther*. 2005;78(1):43-51.

12. Clarke WP, Chavera TA, Silva M, et al. Signaling profile differences: paliperidone versus risperidone. *Br J Pharmacol*. 2013;170(3):532-545.

13. Dremencov E, El Mansari, M, Blier P. Distinct electrophysiological effects of paliperidone and risperidone on the firing activity of rat serotonin and norepinephrine neurons. *Psychopharmacology*. 2007;194(1):63-72.