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# Clinical and pharmacological review on novel atypical antipsychotic drug: Paliperidone

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**ABSTRACT**

Paliperidone is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. Chemically, it is the major metabolite of the widely used atypical antipsychotic drug, resperidone. Paliperidone is indicated for acute and maintenance treatment of schizophrenia. Paliperidone-ER (sold as INVEGA) is the first oral atypical antipsychotic with an extended release, which is achieved by osmotic-controlled release oral delivery system. Paliperidone is a centrally active dopamine Type 2 ($D_2$) antagonist which is metabolized by dealkylation, hydroxylation, dehydrogenation and benzisoxazole scission.Paliperidone gradually rise to reach peak plasma concentration (Cmax ) approximately 24 hours after dosing. The maximum pharmacokinetics of paliperidone administration are dose-proportional within the recommended clinical dose range (3 to 12 mg).The terminal elimination half-life of paliperidone is approximately 23 hours

**Key words:** Paliperidone, risperidone, antipsychotic, schizophrenia.

## INTRODUCTION

Paliperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidine-4-one is an atypical antipsychotic which is indicated in the treatment of schizophrenia as well as manic and mixed episodes occurring in conjuction with Bipolar I Disorder and depression[1-2]. Paliperidone is a risperidone with an extra hydroxyl group i.e, 9-hydroxyrisperidone. Paliperidone-extended release (ER) is achieved by the osmotic-controlled release (OROS), a well established technology already in use for CNS drugs[1]. Paliperidone exhibits powerful efficacy for many patients experiencing symptoms of schizophrenia including those who may benefit from a change in therapy.

### Chemical structure

### Systematic (IUPAC) name[7]

3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidine-4-one

### Physical properties

### Solubility

Paliperidone is a white to yellow non-hygroscopic powder. It is sparingly soluble in 0.1N HCl and methylene chloride. It is insoluble in water, 0.1N Sodium Hydroxide and hexane; and slightly soluble in N,N-dimethylformamide.

### Stability

Paliperidone remains stable at normal conditions of temperature and pressure.

**Identification**

The identification of paliperidone includes tests for appearance (visual examination), identification by IR (Ph. Eur) and HPLC, heavy metals (USP), residue on ignition and sulphated ash (USP ), water content by (Karl-Fischer), assay (HPLC), related substances (HPLC), residual solvents (GC) and particle size (Laser diffraction)[2].

**Dosage forms and strengths[1]**

INVEGA® Extended-Release Tablets are available in 3 mg (white), 6 mg (beige), and 9 mg (pink). All tablets are capsule shaped and are imprinted with either "PALI 3", "PALI 6", or "PALI 9".

**Dose and Administration**

The recommended dose of paliperidone Extended-Release Tablets (INVEGA) is 6 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from higher doses; up to 12 mg/day, and for some patients, a lower dose of 3 mg/day may be sufficient. When dose increases are indicated, small increments of 3 mg/day are recommended. The maximum recommended dose is 12 mg/day[1].

Paliperidone ER tablet can be taken with or without food. It must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed.

**Pharmacology**

**Mechanism of action**

The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown, but it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 ($D_2$) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

**Pharmacodynamics**

**Primary pharmacodynamics**

Paliperidone is a centrally active dopamine Type 2 ($D_2$) antagonist and with predominant serotonin Type 2 ($5HT_{2A}$) activity. Paliperidone is also active as an antagonist at $\alpha_1$ and $\alpha_2$ adrenergic receptors and $H_1$ histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone has no affinity for cholinergic muscarinic or $\beta_1$- and $\beta_2$-adrenergic receptors[3].

The binding profiles for paliperidone, its enantiomers and risperidone are comparable. Several *in vivo* studies were performed in rats and dogs. In rats, paliperidone was slightly less potent than risperidone at early time intervals, but became equipotent at later time intervals, probably reflecting a slower rate of brain penetration. In dogs, paliperidone, its enantiomers and risperidone were roughly equipotent against apomorphine-induced emesis[2].

**Secondary pharmacodynamics**

Dopamine secreted in the portal hypophyseal circulation inhibits prolactin release. By antagonizing this tonic inhibitory action of endogenous dopamine, D2 receptor antagonists elevate prolactin release. Anti-adrenergic and anti-histaminergic effects are suspect to elicit hypotensive and sedative effects. Hyperprolactinemia is expected due to the $D_2$-receptor antagonism.

**Pharmacokinetics**

Paliperidone is presented as a prolonged-release formulation. The goal of the development program was to identify an extended-release formulation that would enhance the initial tolerability and permit initiation of treatment at an effective dose without the need for initial dose titration. Invega prolonged release tablets are based on the patented OROS® (Oral Osmotic System) Push-Pull™ technology delivery system, designed to deliver the paliperidone active substance in a controlled manner over 24 hours, thereby achieving an effective once-a-day treatment for schizophrenia[10].

Following a single dose, the plasma concentrations of paliperidone gradually rise to reach peak plasma concentration (Cmax ) approximately 24 hours after dosing. The maximum pharmacokinetics of paliperidone administration are dose-proportional within the recommended clinical dose range (3 to 12 mg).The terminal elimination half-life of paliperidone is approximately 23 hours.Steady-state concentrations of paliperidone are attained within 4-5 days of dosing in most subjects.

**Absorption-Bioavailability**

The absolute oral bioavailability of paliperidone found to be is 28%.The ER OROS tablets have been designed to deliver paliperidone over a 24-hour period. Paliperidone showed some preference for the secretary direction, and the efflux ratio decreased with increasing concentration, indicating involvement of an efflux transporter[10]. When apical pH increased from 6.0 to 8.0, there was a gradual increase in absorptive permeation. P-gp inhibitors (quinidine, verapamil and imipramine) had a limited effect on the transport of paliperidone, with increased absorptive and decreased secretary transport, while inhibitors of other transporters had no effect.

The absolute bioavailability is 28% for the ER OROS formulation and is 106% (complete) for the oral solution. The lower bioavailability for the ER OROS formulation is probably due to a higher fraction of paliperidone released in the colon, where the absorption is lower. Since paliperidone has an absolute bioavailability of more than 90% it can be classified as a highly permeable compound. Clinical trials establishing the safety and efficacy of paliperidone were carried out in 24 subjects without regard to the timing of meals. While paliperidone can be taken without regard to food; the presence of food at the time of paliperidone administration may increase exposure to paliperidone

**Tissue distribution and protein binding**

Paliperidone was rapidly and widely distributed and crossed the blood-brain barrier; in brain, it was preferentially distributed to the frontal cortex and striatum. Based on a population analysis, the apparent volume of distribution of paliperidone is 487 Liters. In plasma protein binding studies it was shown that in all species tested, including human, paliperidone is bound to a maximum of 85 %. In human plasma, Paliperidone and its enantiomers were predominately bound to $\alpha$1-acid glycoprotein and albumin. In patients with moderate hepatic impairment, plasma protein binding was reduced, mainly because of a reduction in $\alpha$1-acid glycoprotein and albumin plasma concentrations[3-6].

**Metabolism and excretion**

The metabolism of 14-C paliperidone and its separate enantiomers when studied in subcellular liver fractions in vitro suggested that paliperidone was metabolized to a very limited extent in human liver matrices. *In vitro*, a total of eight metabolites were identified, with pathways of primary importance including *N*-dealkylation and alicyclic hydroxylation. The major compound observed in primary hepatocyte cultures was paliperidone (20-90%). Based on the metabolism rate alone, there were no major quantitative differences observed between enantiomers and all metabolites observed with paliperidone were also seen with the individual enantiomers. Paliperidone is not metabolised to a large extent. Almost 60% of the dose was identified as unchanged paliperidone in urine. Four metabolites were identified in urine, each of which accounted for up to a maximum of 6.5% of the dose, while 7% of the urinary radioactivity remained unidentified. Two small metabolites were identified in faeces.

The main elimination route of paliperidone is renal excretion and about half of this is through active secretion in the renal tubules. One week following administration of a single oral dose of 1 mg immediate-release C-14 paliperidone to 5 healthy volunteers, 51% - 67% of the dose was excreted unchanged into urine, 26% - 41% of the dose was recovered as metabolites, and 6% - 12% of the dose was not recovered. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces. Four primary metabolic pathways have been identified *in vivo*, none of which could be shown to account for more than 10% of the dose: dealkylation, hydroxylation, dehydrogenation and benzisoxazole scission. Paliperidone was mainly excreted in urine (80% of a radiolabelled dose), while only a small part was excreted in faeces (11%). Almost 60% of the dose was excreted as unchanged drug in urine. Renal clearance of unchanged paliperidone was on average 53 ml/min. About 50% of the renal clearance of unchanged paliperidone was by means of filtration, the other half occurred by active processes[2-7] .

**Clinical aspects**

The short-term efficacy of INVEGA (3 mg to 15 mg once daily) was established in three placebo-controlled and active-controlled 6-week, fixed-dose trials in non-elderly adult subjects (mean

age of 37) who met DSM-IV criteria for schizophrenia[10]. Studies were carried out in North America, Eastern Europe, Western Europe, and Asia. The doses studied among these three trials included 3 mg/day, 6 mg/day, 9 mg/day, 12 mg/day, and 15 mg/day. Dosing was in the morning without regard to meals[10-12].

Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS), a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. Efficacy was also evaluated using the Personal and Social Performance (PSP) scale. 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[5]. In all 3 studies (n = 1665), INVEGA was superior to placebo on the PANSS at all doses. Mean effects at all doses were fairly similar, although the higher doses in all studies were numerically superior. INVEGA was also superior to placebo on the PSP in those trials.

In a longer-term trial, adult outpatients meeting DSM-IV criteria for schizophrenia who had clinically responded were entered into a 6-week open-label stabilization phase where they received INVEGA (doses ranging from 3 mg to 15 mg once daily). After the stabilization phase, patients were randomized in a double-blind manner to either continue on INVEGA at their achieved stable dose, or to placebo, until they experienced a relapse of schizophrenia symptoms. Relapse was pre-defined as significant increase in PANSS (or pre-defined PANSS subscales), hospitalization, clinically significant suicidal or homicidal ideation, or deliberate injury to self or others. An interim analysis of the data showed a significantly longer time to relapse in patients treated with INVEGA compared

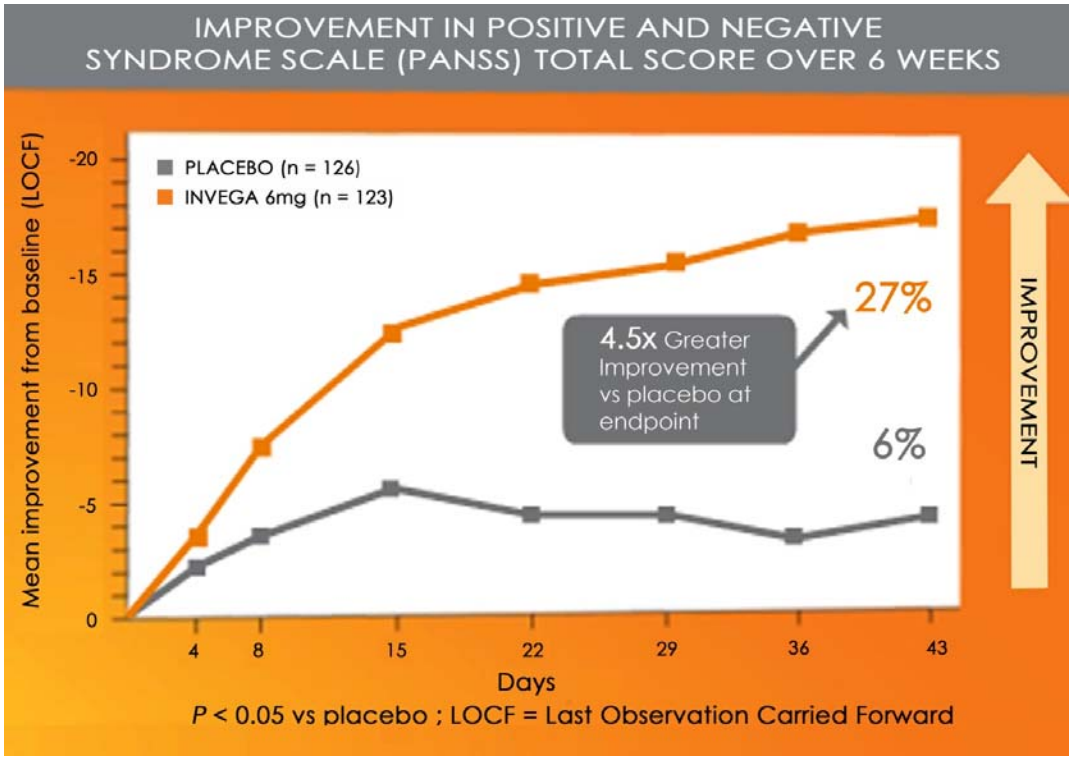


**Fig. 1**

to placebo, and the trial was stopped early because maintenance of efficacy was demonstrated[10-12].

In a 6-week, double-blind, placebo-controlled study (Kane study—trial 303) involving 628 patients with acute schizophrenia where the patients received once-daily paliperidone (6 mg, 9 mg, or 12 mg) or placebo, the paliperidone exhibited greater improvement than the placebo at the end point[4].

**Contraindications**

Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated paliperidone. Paliperidone is a metabolite of risperidone and is therefore contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone[7].

**Warnings and precautions**

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Paliperidone is not approved for the treatment of dementia-related psychosis[7].

**Drug interactions**

**Potential for paliperidone to affect other drugs**

Paliperidone should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists. Because of its potential for inducing orthostatic hypotension, an additive effect may be observed when paliperidone is administered with other therapeutic agents that have this potential. At therapeutic concentrations, paliperidone did not inhibit P-glycoprotein[6-9]. Paliperidone is therefore not expected to inhibit P-glycoprotein-mediated transport of other drugs in a clinically relevant manner.

**Potential for other drugs to affect paliperidone:**

Paliperidone is metabolized to a limited extent by CYP2D6. In an interaction study in healthy subjects in which a single 3 mg dose was administered concomitantly with 20 mg per day of paroxetine (a potent CYP2D6 inhibitor), paliperidone exposures were on average 16% (90% CI: 4, 30) higher in CYP2D6 extensive metabolizers. Higher doses of paroxetine have not been studied. The clinical relevance is unknown[6].

**Adverse reactions[7]**

- Increased mortality in elderly patients with dementia-related psychosis.
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis.
- Neuroleptic malignant syndrome.
- Tardive dyskinesia.
- Hyperglycemia and diabetes mellitus.
- Hyperprolactinemia.
- Potential for Gastrointestinal Obstruction.
- Orthostatic hypotension and syncope.
- Nervous system disorders
- Thrombotic thrombocytopenic purpura (TTP)
- Disruption of body temperature regulation
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies
- Diseases or conditions that could affect metabolism or hemodynamic responses

## CONCLUSION

Paliperidone is an atypical psychotropic agent belonging to the chemical class of benzisoxazole derivatives. Chemically, it is the major metabolite of the widely used atypical antipsychotic drug,resperidone. Paliperidone is indicated for acute and maintenance treatment of schizophrenia. There is wide scope for the research in pharmacy to work on the delivery aspects of Paliperidone by oral route and parenteral route

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