# FERZAPIN

**Instructions for the medicinal product**

**Trade name:** Ferzapin.
**International Nonproprietary Name:** Olanzapine.
**Dosage form:** Uncoated tablets.
**Composition:**
*Ferzapin 5 mg:* Each uncoated tablet contains:
Olanzapine USP 5 mg.
*Ferzapin 10 mg:* Each uncoated tablet contains:
Olanzapine USP 10 mg.
**Pharmacotherapeutic group:** Antipsychotic (neuroleptic).
**ATC code:** N05AH03.
**Pharmacological Action:**
*Pharmacodynamic :*
Olanzapine is an antipsychotic, antimanic, and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.
In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki <100nM) for serotonin 5HT2A/2C, 5HT3, 5HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors M1-M5; α1 adrenergic; and histamine H1receptors. Olanzapine demonstrated a greater in vitro affinity for serotonin 5HT2 than dopamine D2 receptors and greater 5HT2 than D2 activity in in vivo models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an 'anxiolytic' test.
In a single oral dose (10mg) Positron Emission Tomography (PET) study in healthy volunteers, olanzapine produced a higher 5HT2A than dopamine D2 receptor occupancy. In addition, a Single Photon Emission Computed Tomography (SPECT) imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D2 occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.
*Pharmacokinetics:*
*Absorption* - olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food. Absolute oral bioavailability relative to intravenous administration has not been determined.
*Distribution* - the plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and $\alpha_1$-acid-glycoprotein.
*Biotransformation* - olanzapine is metabolised in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites; both exhibited significantly less in vivo pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent, Olanzapine.
*Elimination* - after oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.
In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hours) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia >65 years of age, dosing from 5 to 20mg/day was not associated with any distinguishing profile of adverse events.
In female versus male subjects, the mean elimination half-life was somewhat prolonged (36.7 versus 32.3 hours) and the clearance was reduced (18.9 versus 27.3 l/hr). However, olanzapine (5-20mg) demonstrated a comparable safety profile in female (n = 467) as in male patients (n = 869).
*Renal impairment* - in renally impaired patients (creatinine clearance <10ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hours) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57% of radiolabelled olanzapine appeared in urine, principally as metabolites.
*Smokers* - in smoking subjects with mild hepatic dysfunction, mean elimination half-life (39.3 hours) was prolonged and clearance (18.0 l/hr) was reduced analogous to non- smoking healthy subjects (48.8 hours and 14.1 l/hr, respectively).
In non-smoking versus smoking subjects (males and females), the mean elimination half-life was prolonged (38.6 versus 30.4 hours) and the clearance was reduced (18.6 versus 27.7 l/hr).
The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals.
**Indications for use:**
- Treatment of schizophrenia;
- Effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response;
- Treatment of moderate to severe manic episode;
- Prevention of recurrence in patients with bipolar disorder.

**Contraindication:**
- Hypersensitivity to the active substance or to any of the excipients;
- Patients with known risk for narrow-angle glaucoma;
- Lactation;
- Children age to 18 years (due to a lack of data on safety and efficacy).

*Pregnancy and lactation:*
Nevertheless, because human experience is limited, olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Should be advised not to breast-feed an infant if they are taking Ferzapin.
**Dosage and directions for use:**
*Adults:*
*Schizophrenia:* The recommended starting dose for Ferzapin is 10mg/day.
*Manic episode:* The starting dose is 15mg as a single daily dose in monotherapy or 10mg daily in combination therapy.
*Preventing recurrence in bipolar disorder:* The recommended starting dose is 10mg/day. For patients who have been receiving Ferzapin for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, Ferzapin treatment should be continued (with dose optimization as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.
During treatment for schizophrenia, manic episode, and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours. Ferzapin can be given without regard for meals, as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing Ferzapin.
*Patients with renal and/or hepatic impairment:*
A lower starting dose (5 mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5 mg and only increased with caution.
**Side-effects:**
*Blood and the lymphatic system:* often - eosinophilia, rarely - leukopenia, very rarely - thrombocytopenia, neutropenia.
*Metabolism and nutrition:* very common - weight gain, often - increased appetite unknown frequency - the development or exacerbation of diabetes, diabetic ketoacidosis, diabetic coma, including deaths.
*Nervous system:* very common - sleepiness, often - dizziness, akathisia, parkinsonism, dyskinesia, gait disturbance (in patients with dementia of Alzheimer's type), rarely - extrapyramidal disorders (mainly at high doses), very rarely - sweating, insomnia , tremor, anxiety, nausea, unknown frequency - neuroleptic malignant syndrome (NMS), dystonia (including oculogyric crisis), tardive dyskinesia.
*Cardiovascular system:* often - orthostatic hypotension, rarely - bradycardia, prolongation QT; unknown frequency - ventricular tachycardia / ventricular fibrillation, sudden death, pulmonary embolism, deep vein thrombosis.
*Digestive system:* often - dry mouth, constipation (m-anticholinergic effect), very rarely - hepatitis (including hepatocellular, cholestatic or mixed), pancreatitis.
*Skin and subcutaneous tissue:* rare - photosensitivity reaction, rarely - a skin rash, very rare - alopecia.
*Musculoskeletal and connective tissue:* very rarely - rhabdomyolysis.
*Renal and urinary:* uncommon - incontinence, very rare - priapism, urinary retention.
*Investigations:* common - elevated plasma prolactin levels, uncommom - high creatine phosphokinase,increased total bilirubin, not known - increased alkaline phosphatase.
*General:* often - asthenia, fatigue, peripheral edema, not known frequency - hypothermia syndrome "cancel" (excessive sweating, insomnia, tremor, anxiety, nausea, vomiting).
*Special populations:* in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo. Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.
In patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently
In patients with bipolar mania, taking Ferzapin in combination with lithium or valproic acid: very common - weight gain, dry mouth, increased appetite, tremor, and often - a speech disorder.
**Overdose:**
*Signs and Symptoms:* Very common symptoms in overdose ( >10% incidence) include tachycardia, agitation/ aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.
Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (<2% of overdose cases), and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450mg, but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.
*Treatment:* There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (ie, gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.
Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity, since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.
**Drug Interaction:**
The co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine.
Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.
Inducers of CYP1A2- Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.
Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The co-administration of alcohol (i.e., ethanol) with olanzapine potentiated the orthostatic hypotension observed with olanzapine.
Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine.
Fluoxetine (60 mg single dose or 60 mg daily dose for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance.
Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics.
Inducers of CYP1A2 or Glucuronyl Transferase: Omeprazole and rifampin may cause an increase in olanzapine clearance.
The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.
CNS Acting Drugs: Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.
Antihypertensive Agents: Olanzapine, because of its potential for inducing hypotension, may enhance the effects of certain antihypertensive agents.
Levodopa and Dopamme Agonists: Olanzapme may antagonize the effects or levodopa and dopamme agonists.
Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium
Olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.
Effect of Olanzapine on Drug Metabolizing Enzymes: In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.
Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.
Olanzapine did not influence the pharmacokinetics of diazepam or its active metabolite N-desmethyldiazepam. However, diazepam co-administered with olanzapine increased the orthostatic hypotension observed with either drug given alone.Multiple doses of olanzapine did not influence the kinetics of biperiden.
Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.
**Cautions:**
Ferzapin is not approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident.
NMS is a potentially life-threatening condition associated with antipsychotic medicinal product. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.
Hyperglycaemia and/or development or exacerbation of diabetes, occasionally associated with ketoacidosis or coma, has been reported rarely, including some fatal cases. Patients treated with any antipsychotic agents, including olanzapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials.Patients treated with any antipsychotic agents, including olanzapine, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines.
While olanzapine demonstrated anticholinergic activity in vitro, experience during the clinical trials revealed a low incidence of related events. However, as clinical experience with olanzapine in patients with concomitant illness is limited, caution is advised when prescribing for patients with prostatic hypertrophy, or paralytic ileus and related conditions.
Transient, asymptomatic elevations of hepatic aminotransferases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised and follow-up organized in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicines. In cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.
Caution should be exercised in patients with low leucocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly.
Caution should be exercised when olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.
Temporal association of olanzapine treatment and venous thromboembolism has very rarely (< 0.01%) been reported. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g., immobilisation of patients, should be identified and preventive measures undertaken.
Caution should be used when it is taken in combination with other centrally acting medicines and alcohol. As it exhibits in vitro dopamine antagonism, olanzapine may antagonise the effects of direct and indirect dopamine agonists. Ferzapin should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold.
If signs or symptoms of tardive dyskinesia appear in a patient on Ferzapin, a dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.
**Presentation:**
*Ferzapin 5 or 10 mg:* 3x10 PVC Blister in a monocarton, with package insert.
**Storage :**
Keep in dry place, protected from light at a temperature below 25°C. Keep out of reach of children.
**Shelf Life:**
Labeled. Do not use after expiry date.
**Distribution Condition:**
Prescribed medicine.

Manufactured for:
SPEY MEDICAL
**London, United Kingdom**
Manufactured by:
Akums Drugs & Pharmaceuticals Ltd.
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