



Restricted Circulation

PACKAGING RESEARCH & DEVELOPMENT

ARTWORK / PRINTPROOF APPROVAL FORM
(Front Page)

320 mm

Patient Characteristics	Half - Life (hours)	Plasma Clearance (L/hr)
Nonsmoking	38.6	18.6
Smoking	30.4	27.7
Female	36.7	18.9
Male	32.3	27.3
Elderly (65 and older)	51.8	17.5
Nonelderly	33.8	18.2

through smoking status, gender, and, to a lesser extent, age may affect olanzapine clearance and half-life, the magnitude of the impact of these single factors is small in comparison to the overall variability between individuals.

Special populations

Geriatrics: The mean elimination half-life of olanzapine was about 1.5 times greater in elderly (>65 years) than in non-elderly subjects (≤ 65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity.

Gender: Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Race: In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in olanzapine pharmacokinetics among the three populations. Cytochrome P450 isoform CYP2D6 status does not affect the metabolism of olanzapine.

Renal insufficiency: No differences in the single-dose pharmacokinetics of oral olanzapine were noted in subjects with clinically significant cirrhosis (who were mostly smokers) when compared to healthy subjects (all non-smokers). Multiple-dose studies in patients with hepatic impairment, however, have not been performed.

Renal Insufficiency: There was no significant difference in mean elimination half-life or olanzapine plasma clearance between subjects with severely impaired renal function compared to individuals with normal renal function. Approximately 57% of radio-labelled olanzapine is excreted in urine, principally as metabolites.

INDICATIONS

Olanzapine is indicated for the treatment of schizophrenia.

Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Olanzapine is indicated for short-term treatment of acute manic episode associated with Bipolar I Disorder.

Olanzapine is indicated for preventing recurrence of manic, mixed or depressive episodes in Bipolar I Disorder.

RECOMMENDED DOSAGE

Adults:

Schizophrenia: The recommended starting dose for Olanzapine 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 Olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, Olanzapine treatment should be continued (with dose optimisation 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.

Olanzapine can be given without regard for meals, as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing Olanzapine.

Special populations

Children:

Olanzapine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in short term studies of adolescent patients than in studies of adult patients

Elderly patients:

A lower starting dose (5mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant.

Patients with Renal and/or hepatic impairment:

A lower starting dose (5mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh class A or B), the starting dose should be 5mg and only increased with caution.

Gender:

The starting dose and dose range need not be routinely altered for female patients relative to male patients.

Smokers

The starting dose and dose range need not be routinely altered for non-smokers relative to smoking patients. The metabolism of Olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of Olanzapine dose may be considered if necessary. When more than one factor is present which might result in slower metabolism (female gender, geriatric age, nonsmoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated should be conservative in such patients.

ROUTE OF ADMINISTRATION:

Oral

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients. Patients with known risk of narrow-angle glaucoma.

WARNINGS AND PRECAUTIONS

During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period.

Dementia-related psychosis and/or behavioural disturbances

Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident.

Parkinson's disease

The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended.

Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially life-threatening condition associated with antipsychotic medicinal products. 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 creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.

Hyperglycaemia and diabetes

Hyperglycaemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given this confounder, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Lipid alterations

Undesirable alterations in lipids have been observed. Lipid alterations should be managed as clinically appropriate, particularly in dyslipidaemic patients and in patients with risk factors for the development of lipid disorders. Patients treated with any antipsychotic medicines, including olanzapine film-coated tablets, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines, e.g. at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter.

Anticholinergic activity

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.

Hepatic function

Transient, asymptomatic elevations of hepatic aminotransferases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised and follow-up organised 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.

Neutropenia

Caution should be exercised in patients with low leukocyte 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 hypers eosinophilic conditions or with myelodysplastic disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly.

Discontinuation of treatment

Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported rarely when olanzapine is stopped abruptly.

QT interval

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.

Thromboembolism

Temporal association of olanzapine treatment and venous thromboembolism has been reported uncommonly. A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. 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.

General CNS activity

Given the primary CNS effects of olanzapine, 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 antagonize the effects of direct and indirect dopamine agonists.

Seizures

Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur uncommonly in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures was reported.

Tardive Dyskinesia

Olanzapine was associated with a statistically significant lower incidence of treatment emergent dyskinesia. However the risk of tardive dyskinesia increases with long term exposure, and therefore if signs or symptoms of tardive dyskinesia appear in a patient on Olanzapine, a dose reduction or discontinuation should be considered. These symptoms can potentially deteriorate or even arise after discontinuation of treatment.

Postural hypotension

Postural hypotension was infrequently observed in elderly. It is recommended that blood pressure is measured periodically in patients over 65 years.

Sudden cardiac death

In post-marketing reports with olanzapine, the event of sudden cardiac death has been reported in patients with olanzapine.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. Discontinue olanzapine if DRESS is suspected.

Paediatric population

Olanzapine is not indicated for use in the treatment of children and adolescents.

Effects on ability to drive and use machines

Olanzapine may cause somnolence and dizziness; patients should be cautioned about operating machinery, including motor vehicles.

INTERACTIONS WITH OTHER MEDICAMENTS:

Paediatric population

Interaction studies have only been performed in adults.

Potential interactions affecting olanzapine

Since olanzapine is metabolised by CYP1A2, substances that can specifically induce or inhibit this isoenzyme may affect the pharmacokinetics of olanzapine.

Induction of CYP1A2

The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary.

