Olinstab®

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Olanzapine Tablets USP 5/10 mg

OLINSTAB® 5
Composition:
Each Film Coated Tablet Contains:

Olanzapine	USP	5 mg
Excipients		q.s

Colour: Titanium Dioxide BP

OLINSTAB® 10
Composition:
Each Film Coated Tablet Contains:

Olanzapine	USP	10 mg
Excipients		q.s

Colour: Quinoline Yellow

PHARMACODYNAMIC:
Pharmacotherapeutic Group: Atypical Antipsychotic
Pharmacodynamics Properties:
Pharmacotherapeutic Group: Psycholeptics, Diazepines, Oxazepines, Thiazepines and Oxepines,
ATC code: N05A H03.
Pharmacodynamics Effects
Olanzapine is an antipsychotic, antimanic, and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.
Olanzapine exhibited a range of receptor affinities (Ki <100nM) for serotonin $5HT_{2A/2C}$, $5HT_3$, $5HT_6$; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors M_1-M_5; α_1 adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin $5HT_2$ than dopamine D_2 receptors and greater $5HT_2$ than D_2 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.
Paediatric Population
Controlled efficacy data in adolescents (ages 13 to 17 years) are limited to short term studies in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin were greater in adolescents than in adults.

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 α_1-acid-glycoprotein.
Biotransformation
Olanzapine is metabolized 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.
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 radio labelled olanzapine appeared in urine, principally as metabolites.
Smoking
In non-smoking versus smoking 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.
Paediatric population
Adolescents (ages 13 to 17 years): The pharmacokinetics of olanzapine are similar between adolescents and adults. In clinical studies, the average olanzapine exposure was approximately 27% higher in adolescents. Demographic differences between the adolescents and adults include a lower average body weight and fewer adolescents were smokers. Such factors possibly contribute to the higher average exposure observed in adolescents.

INDICATION:
Adults
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 the treatment of moderate to severe manic episode.
In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder.

POSOLOGY AND METHOD OF ADMINISTRATION:
Adults
Schizophrenia: The recommended starting dose for olanzapine is 10 mg/day.
Manic episode: The starting dose is 15 mg as a single daily dose in monotherapy or 10 mg daily in combination therapy.
Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg/day.
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 5-20 mg/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.

Special Populations
Elderly
A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant.
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.
Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. 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, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.
Paediatric population
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.

Method of Administration:
Oral use.

SPECIAL WARNING AND PRECAUTION FOR USE:
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. Olanzapine was started at 2.5 mg/day and titrated to a maximum of 15 mg/day based on investigator judgement.
Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal products. 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 high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.
Hyperglycemia and Diabetes
Patients treated with any antipsychotic medicines, should be observed for signs and symptoms of Hyperglycemia (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, e.g., at baseline, 4, 8 and 12 weeks after starting olanzapine treatment and quarterly thereafter.
Lipid Alterations
Patients treated with any antipsychotic medicines should be monitored regularly for lipids in accordance with utilized antipsychotic guidelines, e.g., at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter.
Anticholinergic Activity:
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.
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 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.
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 hypereosinophilic conditions or with myeloproliferative 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 ($\geq 0.01\%$ and $< 0.1\%$) when olanzapine is stopped abruptly.
Thromboembolism
Temporal association of olanzapine treatment and venous thromboembolism has been reported uncommonly ($\geq 0.1\%$ and $< 1\%$). 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 were reported.
Tardive Dyskinesia
In comparator studies of one year or less duration, 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 temporally deteriorate or even arise after discontinuation of treatment.
Postural Hypotension
Postural hypotension was infrequently observed in the elderly in olanzapine clinical trials. 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. In a retrospective observational cohort study, the risk of presumed sudden cardiac death in patients treated with olanzapine was approximately twice the risk in patients not using antipsychotics. In the study, the risk of olanzapine was comparable to the risk of atypical antipsychotics included in a pooled analysis.
Paediatric Population
Olanzapine is not indicated for use in the treatment of children and adolescents. Studies in patients aged 13-17 years showed various adverse reactions, including weight gain, changes in metabolic parameters and increases in prolactin levels.

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

DRUG INTERACTIONS:
Interaction studies have only been performed in adults.
Potential interactions affecting olanzapine
Since olanzapine is metabolized 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.
Inhibition of CYP1A2
Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine C_{max} following fluvoxamine was 54% in female non-smokers and 77% in male smokers. The mean increase in olanzapine AUC was 52% and 108%, respectively. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.
Decreased bioavailability
Activated charcoal reduces the bioavailability of oral olanzapine by 50 to 60% and should be taken at least 2 hours before or after olanzapine.
Fluoxetine (a CYP2D6 inhibitor), single doses of antacid (aluminium, magnesium) or cimetidine have not been found to significantly affect the pharmacokinetics of olanzapine.
Potential for olanzapine to affect other medicinal products
Olanzapine may antagonise the effects of direct and indirect dopamine agonists.
Olanzapine does not inhibit the main CYP450 isoenzymes in vitro (e.g., 1A2, 2D6, 2C9, 2C19, 3A4). Thus, no particular interaction is expected, as verified through in vivo studies, where no inhibition of metabolism of the following active substances was found: tricyclic antidepressant (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2), or diazepam (CYP3A4 and 2C19).
Olanzapine showed no interaction when co-administered with lithium or biperiden.
Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant olanzapine.
General CNS activity
Caution should be exercised in patients who consume alcohol or receive medicinal products that can cause central nervous system depression.
The concomitant use of olanzapine with anti-Parkinsonian medicinal products in patients with Parkinson's disease and dementia is not recommended.
QTc interval
Caution should be used if olanzapine is being administered concomitantly with medicinal products known to increase QTc interval.

PREGNACY AND LACTATION:
Pregnancy
Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with olanzapine. Nevertheless, because human experience is limited, olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.
New born infants exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.
Breast-feeding
Olanzapine was excreted in breast milk. Mean infant exposure (mg/kg) at steady-state was estimated to be 1.8% of the maternal olanzapine dose (mg/kg). Patients should be advised not to breast-feed an infant if they are taking olanzapine.
Fertility
Effects on fertility are unknown.

SIDE EFFECTS
Common Side Effects (may affect up to 1 in 10 people) include
- changes in the levels of some blood cells, circulating fats and early in treatment, temporary increases in liver enzymes.
- increases in the level of sugars in the blood and urine.
- increases in levels of uric acid and creatine
- phosphokinase in the blood
- feeling more hungry.
- dizziness.
- restlessness.
- tremor.
- unusual movements (dyskinesias)
- constipation.
- dry mouth.
- rash.
- loss of strength.
- extreme tiredness.
- water retention leading to swelling of the hands, ankles or feet,
- fever
- joint pain and sexual dysfunctions such as decreased libido in males and females or erectile dysfunction in males.

Uncommon side effects: (may affect up to 1 in 100 people) include
- Hypersensitivity (e.g. swelling in the mouth and throat, itching, rash)
- Diabetes or the worsening of diabetes, occasionally associated with ketoacidosis (ketones in the blood and urine) or coma;
- Seizures, usually associated with a history of
- seizures (epilepsy);
- Muscle stiffness or spasms including eye movements);
- Restless legs syndrome
- Problems with speech
- stuttering
- slow heart rate.
- sensitivity to sunlight.
- Bleeding from the nose;
- Abdominal distension;
- drooling;
- Memory loss or forgetfulness
- urinary incontinence, lack of ability to urinate.
- hair loss.
- absence or decrease in menstrual periods.
- changes in breasts in males and females such as an abnormal production of breast milk or abnormal growth.

Rare side effects (may affect up to 1 in 1000 people)
- Lowering of normal body temperature
- Abnormal rhythms of the heart
- Sudden unexplained death
- Inflammation of the pancreas causing severe
- Stomach pain, fever and sickness
- Liver disease appearing as yellowing of the skin and white parts of the eyes
- Muscle disease presenting as unexplained aches and pains
- Prolonged and/or painful erection.

EFFECT ON ABILITY TO DRIVE OR TO USE MACHINES:
Olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

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 450 mg, but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.
Management
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e., 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.

SHELF LIFE:
3 Years

PACKAGING:
10 tablets are packed in aluminium strip & such 3 strips are packed in printed carton along with pack insert.

STORAGE CONDITION:
Stored at a temperature not exceeding 30°C. Protect from light and moisture.
Keep the medicine out of reach of children.

Marketed by:

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