Olanzax®

Olanzapine

FORMS AND PRESENTATION

Olanzax® 5: Mouth dissolving tablets: Box of 30.

Olanzax® 10: Mouth dissolving tablets: Box of 30.

COMPOSITION:

Olanzax® 5: Each mouth dissolving tablet contains: Olanzapine 5 mg.

Olanzax® 10: Each mouth dissolving tablet contains: Olanzapine 10 mg. Excipients: Microcrystalline cellulose, Magnesium Stearate, Fructose, Mannitol, Crospovidone and Colloidal Silicon Dioxide.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code: N05AH03.

Pharmacodynamic effects

Olanzapine is an antipsychotic, antimanic and mood stabilizing agent that demonstrates a broad pharmacologic profile across several receptor systems.

Olanzapine exhibits a range of receptor affinities (Ki < 100 nM) for serotonin 5 $HT_{2A/2C}$, 5 HT_3, 5 HT_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 behavioral studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile.

Olanzapine demonstrates greater *in vitro* affinity for serotonin 5 HT_2 than dopamine D_2 receptors and greater 5 HT_2 than D_2 activity *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.

Olanzapine produces a higher 5 HT_{2A} than dopamine D_2 receptor occupancy. In addition, olanzapine-responsive patients had lower striatal D_2 occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

Pharmacokinetic Properties

Olanzapine mouth dissolving tablets are bioequivalent to olanzapine tablets, with a similar rate and extent of absorption and may be used as an alternative to olanzapine tablets.

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-acidglycoprotein.

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 patients varied based on age and gender.

In healthy elderly (65 and over) versus non-elderly patients, the mean elimination half-life was prolonged and the clearance was reduced. The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In patients with schizophrenia 65 years of age, dosing from 5 to 20 mg/day was not associated with any distinguishing profile of adverse events.

In female versus male patients the mean elimination half-life was somewhat prolonged and the clearance was reduced. However, olanzapine demonstrated a comparable safety profile in female as in male patients.

Renal impairment

In renally impaired patients (creatinine clearance < 10 ml/min), there was no significant difference in mean elimination half-life or clearance compared to healthy patients. Approximately 57% of radiolabeled olanzapine appeared in urine, principally as metabolites.

Hepatic impairment

Patients with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster elimination half-time compared to patients with no hepatic dysfunction.

Smoking

In non-smoking versus smoking patients (males and females) the mean elimination half-life was prolonged, and the clearance was reduced.

Paediatric population

Adolescents (ages 13 to 17 years): The pharmacokinetics of olanzapine are similar between adolescents and adults. The average olanzapine exposure was approximately 27% higher in adolescents.

INDICATIONS

Adults

Olanzax® is indicated for the treatment of schizophrenia.

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

Olanzax® is indicated for the treatment of moderate to severe manic episode.

In patients whose manic episode has responded to Olanzax® treatment, Olanzax® is indicated for the prevention of recurrence in patients with bipolar disorder.

CONTRAINDICATIONS

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

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 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.

Parkinson's disease

The use of Olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended. In clinical trials, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo, and Olanzapine was not more effective than placebo in the treatment of psychotic symptoms.

Neuroleptic Malignant Syndrome (NMS)

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 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.

Hyperglycaemia and diabetes

Hyperglycaemia and/or development or exacerbation of diabetes, occasionally associated with ketoacidosis or coma, has been reported uncommonly, including some fatal cases. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilized antipsychotic guidelines, e.g. measuring of blood glucose at baseline, 12 weeks after starting Olanzapine treatment and annually thereafter. Patients treated with any antipsychotic medicines, 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, e.g. at baseline, 4, 8 and 12 weeks after starting Olanzapine treatment and quarterly thereafter.

Lipid alterations

Undesirable alterations in lipids have been observed in Olanzapine-treated patients. Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic medicines, including Olanzapine, 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 transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised in patients at risk. In the event of elevated ALT and/or AST during treatment, follow-up should be organised and dose reduction should be considered. In cases where hepatitis has been diagnosed, Olanzapine treatment should be discontinued.

Neutropenia

Caution should be exercised in patients with low leucocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia or bone marrow depression/toxicity 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 very rarely (<0.01%) when Olanzapine is stopped abruptly.

QT interval

In clinical trials, clinically meaningful QTc prolongations were uncommon in patients treated with Olanzapine. However, 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 antagonise 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 rarely in patients when treated with Olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

Tardive dyskinesia

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. It is recommended that blood pressure is measured periodically in patients over 65 years.

Sudden cardiac death

In postmarketing 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.

PREGNANCY AND LACTATION

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with Olanzapine. Olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Newborn 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, 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.

DRUG INTERACTIONS

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.

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.

ADVERSE EFFECTS

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the data available).

Adults

Blood and lymphatic system disorders: Eosinophilia, leukopenia, neutropenia (common); thrombocytopenia (rare).

Immune system disorders: Hypersensitivity (uncommon).

Metabolism and nutrition disorders: Weight gain (very common); elevated cholesterol levels, elevated glucose levels, elevated triglyceride levels, glucosuria, increased appetite (common); development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (uncommon); hypothermia (rare).

Nervous system disorders: Somnolence (very common); dizziness, akathisia, parkinsonism, dyskinesia (common); seizures where in most cases a history of seizures or risk factors for seizures were reported, dystonia (including oculogyration), tardive dyskinesia, amnesia, dysarthria, stuttering, restless legs syndrome (uncommon); neuroleptic malignant syndrome, discontinuation symptoms (rare).

Cardiac disorders: Bradycardia, QTc prolongation (uncommon); ventricular tachycardia/fibrillation, sudden death (rare).

Vascular disorders: orthostatic hypotension (very common); thromboembolism (including pulmonary embolism and deep vein thrombosis) (uncommon).

Respiratory, thoracic and mediastinal disorders: Epistaxis (uncommon).

Gastrointestinal disorders: Mild, transient anticholinergic effects including constipation and dry mouth (common); abdominal distension, salivary hypersecretion (uncommon); pancreatitis (not known).

Hepatobiliary disorders: transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (common); hepatitis (including hepatocellular, cholestatic or mixed liver injury) (rare).

Skin and subcutaneous tissue disorders: rash (common); photosensitivity reaction, alopecia (uncommon); Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (not known).

Musculoskeletal and connective tissue disorders: Arthralgia (common); rhabdomyolysis (rare).

Renal and urinary disorders: urinary incontinence, urinary retention, urinary hesitation (uncommon).

Pregnancy, puerperium and perinatal conditions: Drug withdrawal syndrome neonatal (not known).

Reproductive system and breast disorders: Erectile dysfunction in males, decreased libido in males and females (common); amenorrhea, breast enlargement, galactorrhea in females, gynaecomastia/breast enlargement in males (uncommon); priapism (rare).

General disorders and administration site conditions: Asthenia, fatigue, oedema, pyrexia (common).

Investigations: Increased alkaline phosphatase, high creatine phosphokinase, high gamma glutamyltransferase, high uric acid (very common); Increased total bilirubin (common).

Paediatric population

Olanzapine is not indicated for the treatment of children and adolescent patients below 18 years, although available data in adolescents have been compared with those from the adult population.

Metabolism and nutrition disorders: Weight gain, elevated triglycerides levels, increased appetite (very common); elevated cholesterol levels (common).

Nervous system disorders: Sedation (including hypersomnia, lethargy, somnolence) (very common).

Gastrointestinal disorders: Dry mouth (common).

Hepatobiliary disorders: Elevations of hepatic aminotransferases (ALT/AST) (very common).

Investigations: Decreased total bilirubin, increased GGT, elevated plasma prolactin levels (very common).

DOSAGE AND ADMINISTRATION

Adults

Schizophrenia: the recommended starting dose for Olanzax® 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.

For patients who have been receiving Olanzax® for treatment of manic episodes, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, Olanzax® treatment should be continued (with dose optimization as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

During treatment for schizophrenia, manic episodes, 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.

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

Olanzax® should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the mouth dissolving tablet from the mouth is difficult. Since the mouth dissolving tablet is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or other suitable beverage (orange juice, apple juice, milk, or coffee) immediately before administration.

Olanzax® mouth dissolving tablets are bioequivalent to olanzapine coated tablets, with a similar rate and extent of absorption. It has the same dosage and frequency of administration as olanzapine coated tablets. Olanzax® mouth dissolving tablets may be used as an alternative to olanzapine coated tablets.

Children and adolescents

Olanzax® 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

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. Monitoring is recommended, and an increase of Olanzax® dose may be considered if necessary.

When more than one factor is present which might result in slower metabolism, consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.

OVERDOSAGE

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 of Overdose: 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.

STORAGE CONDITIONS

Store below 30˚C.

Keep in original pack in intact conditions.

Date of revision: July 2025.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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