Olanzax®

Olanzapine

FORMS AND PRESENTATION

Olanzax® 2.5: Mouth dissolving tablets: Box of 30.
Olanzax® 5: Mouth dissolving tablets: Box of 30.
Olanzax® 7.5: Mouth dissolving tablets: Box of 30.
Olanzax® 10: Mouth dissolving tablets: Box of 30.
Olanzax® 15: Mouth dissolving tablets: Box of 30.
Olanzax® 20: Mouth dissolving tablets: Box of 30.

COMPOSITION:

Olanzax® 2.5: Each mouth dissolving tablet contains: Olanzapine 2.5 mg. Excipients: microcrystalline cellulose, aspartame, magnesium stearate, crospovidone, powderome orange premium, colloidal anhydrous silica.
Olanzax® 5: Each mouth dissolving tablet contains: Olanzapine 5 mg. Excipients: microcrystalline cellulose, aspartame, magnesium stearate, crospovidone, powderome orange premium, lake sunset yellow.
Olanzax® 7.5: Each mouth dissolving tablet contains: Olanzapine 7.5 mg. Excipients: microcrystalline cellulose, aspartame, magnesium stearate, crospovidone, powderome orange premium.
Olanzax® 10: Each mouth dissolving tablet contains: Olanzapine 10 mg. Excipients: microcrystalline cellulose, croscarmellose sodium, starch, lake sunset yellow, povidone, aspartame, magnesium stearate, crospovidone, colloidal anhydrous silica, powderome orange premium.
Olanzax® 15: Each mouth dissolving tablet contains: Olanzapine 15 mg. Excipients: microcrystalline cellulose, croscarmellose sodium, starch, povidone, aspartame, magnesium stearate, crospovidone, colloidal anhydrous silica, powderome orange premium.
Olanzax® 20: Each mouth dissolving tablet contains: Olanzapine 20 mg. Excipients: microcrystalline cellulose, croscarmellose sodium, starch, lake sunset yellow, povidone, aspartame, magnesium stearate, crospovidone, colloidal anhydrous silica, powderome orange premium.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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 (K_i; <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.
In a single oral dose (10 mg) Positron Emission Tomography (PET) study in healthy volunteers, Olanzapine produced a higher $5HT_{2A}$ than dopamine D2 receptor occupancy. In addition, a SPECT (Single Photon Emission Computed Tomography) 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.
In a multinational, double-blind, comparative study of schizophrenia, schizoaffective and related disorders, which included 1,481 patients with varying degrees of associated depressive symptoms (baseline mean of 16.6 on the Montgomery-Asberg Depression Rating Scale), a prospective secondary analysis of baseline to endpoint mood score change demonstrated a statistically significant improvement (P = 0.001) favouring Olanzapine (-6.0) versus haloperidol (-3.1).
In patients with a manic or mixed episode of bipolar disorder, Olanzapine demonstrated superior efficacy to placebo and valproate semisodium in reduction of manic symptoms over 3 weeks. Olanzapine also demonstrated comparable efficacy results to haloperidol in terms of the proportion of patients in symptomatic remission from mania and depression at 6 and 12 weeks. In a co-therapy study of patients treated with lithium or valproate for a minimum of 2 weeks, the addition of Olanzapine 10 mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

Pharmacokinetic Properties

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.
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. After oral administration, the mean terminal elimination half-life of Olanzapine in healthy subjects varied on the basis of age and gender.
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.
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.
The plasma protein binding of Olanzapine was about 93% over the concentration range of about 7 to about 1,000ng/ml. Olanzapine is bound predominantly to albumin and α_1-acid-glycoprotein.

INDICATIONS

<u>*Adults*</u>

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.

<u>*Dementia-related psychosis and/or behavioural disturbances*</u>

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.

<u>*Parkinson's disease*</u>

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.

<u>*Neuroleptic Malignant Syndrome (NMS)*</u>

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. 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.

<u>*Hyperglycaemia and diabetes*</u>

Hyperglycaemia and/or development or exacerbation of diabetes, occasionally associated with ketoacidosis or coma, has been reported rarely, 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 utilised antipsychotic guidelines.

<u>*Lipid alterations*</u>

Undesirable alterations in lipids have been observed in Olanzapine-treated patients in placebo-controlled clinical trials. Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders.

<u>*Anticholinergic activity*</u>

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.

<u>*Hepatic function*</u>

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.

<u>*Neutropenia*</u>

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.

<u>*Discontinuation of treatment*</u>

Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely (<0.01%) when Olanzapine is stopped abruptly.

<u>*QT interval*</u>

In clinical trials, clinically meaningful QTc prolongations were uncommon in patients treated with Olanzapine. However, as with other antipsychotics, caution should be exercised when Olanzapine is prescribed with medicines known to increase QTc interval.

<u>*Thromboembolism*</u>

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.

<u>*General CNS activity*</u>

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.

<u>*Seizures*</u>

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.

<u>*Tardive dyskinesia*</u>

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.

PI075/3

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.

Use in children and adolescents under 18 years of age

Olanzapine is not indicated for use in the treatment of children and adolescents. Studies in patients aged 13-17 years showed various adverse reactions.

Phenylalanine

Olanzax® tablet contains aspartame, which is a source of phenylalanine. May be harmful for people with phenylketonuria.

PREGNANCY AND LACTATION

There are no adequate and well-controlled studies in pregnant women. Because human experience is limited, Olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Spontaneous reports have been very rarely received on tremor, hypertonia, lethargy and sleepiness, in infants born to mothers who had used Olanzapine during the 3rd trimester.

In a study in breast-feeding, healthy women, Olanzapine was excreted in breast milk. 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

The most frequently (seen in ≥1% of patients) reported adverse effects associated with the use of Olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels, glucosuria, increased appetite, dizziness, akathisia, parkinsonism, dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic transaminases, rash, asthenia, fatigue and oedema.

The following are adverse effects and laboratory investigations observed from spontaneous reporting and in clinical trials. Within each frequency grouping, adverse effects are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the data available).

Blood and lymphatic system disorders: Common: eosinophilia. Uncommon: leucopenia, neutropenia. Not known: thrombocytopenia.

Immune system disorders: Not known: allergic reaction.

Metabolism and nutrition disorders: Very common: weight gain. Common: elevated cholesterol levels, elevated glucose levels, elevated triglyceride levels, glucosuria, increased appetite. Not known: development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases, hypothermia.

Nervous system disorders: Very common: somnolence. Common: dizziness, akathisia, parkinsonism, dyskinesia. Not known: seizures where in most cases a history of seizures or risk factors for seizures were reported, neuroleptic malignant syndrome, dystonia (including oculogyration), tardive dyskinesia, discontinuation symptoms.

Cardiac disorders: Uncommon: bradycardia, QTc prolongation. Not known: ventricular tachycardia/fibrillation, sudden death.

Vascular disorders: Common: orthostatic hypotension. Not known: thromboembolism (including pulmonary embolism and deep vein thrombosis).

Gastrointestinal disorders: Common: mild, transient anticholinergic effects including constipation and dry mouth. Not known: pancreatitis.

Hepatobiliary disorders: Common: transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment. Not known: hepatitis (including hepatocellular, cholestatic or mixed liver injury).

Skin and subcutaneous tissue disorders: Common: rash. Uncommon: photosensitivity reaction, alopecia.

Musculoskeletal and connective tissue disorders: Not known: rhabdomyolysis.

Renal and urinary disorders: Uncommon: urinary incontinence. Not known: urinary hesitation.

Reproductive system and breast disorders: Not known: priapism.

General disorders and administration site conditions: Common: asthenia, fatigue, oedema.

Investigations: Very common: elevated plasma prolactin levels. Uncommon: high creatine phosphokinase, increased total bilirubin. Not known: increased alkaline phosphatase.

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 episode, 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 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 5-20 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.

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.

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 smokers.

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: February 2014.

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

Council of Arab Health Ministers
Union of Arab Pharmacists

Benta SAL
Dbayeh- Lebanon

Prepared by: Nisrine Wehbeh **Date:** Feb 2014

Product Name: Olanzax **Type:** Package insert

Die Cut N°: N/A **Die Cut Dimension:** 190*280

Version N°: 3 **Market:** Lebanon-export countries

Specs: 40-50gsm unfolded **Code:** PI075

Reason for Revision: modification in storage condition

Delivered to Logistic Department:

Name: _____ **Date:** _____

Color Shade number:

Black

Checked & Approved by:

RA : _____ **Date:** _____

Production: _____ **Date:** _____

Marketing: _____ **Date:** _____

Quality Assurance: _____ **Date:** _____