15 cm

PREGNANCY AND LACTATION

There are no adequate and well-controlled studies in pregnant women. 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 fetus.

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. 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

UNDESIRABLE EFFECTS

Very common (>%10) undesirable effects associated with the use of olanzapine in clinical trials were somnolence and weight gain.

In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse events compared to placebo (See Warnings and precautions for use). Very common (>%10) undesirable effects 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 (%10-1).

In clinical trials 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 than with placebo.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of %4.1; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (>%10) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly (%1 to %10). During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥%7 from baseline body weight occurred in %17.4 of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥%7 from baseline body weight in %39.9 of patients.

The following table of undesirable effects is based on adverse event reporting and laboratory investigations from clinical trials.

Blood and lymphatic system disorders Common (%10–1): Eosinophilia.
Metabolism and nutrition disorders Very common (>%10): Weight gain[1]. Common (%10–1): Increased appetite. Elevated glucose levels (see note 2 below). Elevated triglyceride levels[3,4]. Elevated cholesterol levels[3,5]. Glycosuria.
Nervous system disorders Very common (> %10): Somnolence. Common (%10–1): Dizziness. Akathisia. Parkinsonism. Dyskinesia. (See also note 6 below).
Cardiac disorders Uncommon (1–0.1 %): Bradycardia with or without hypotension or syncope, QT prolongation (see Warnings and precautions for use).
Vascular disorders Common (%10–1): Orthostatic hypotension.
Gastrointestinal disorders Common (%10–1): Mild, transient anticholinergic effects including constipation and dry mouth.
Hepato-biliary disorders Common (%10–1): Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (See Warnings and precautions for use).
Skin and subcutaneous tissue disorders Uncommon (1–0.1 %): Photosensitivity reaction.
General disorders and administration site conditions Common (%10–1): Asthenia. Fatigue. Oedema.
Investigations Very common (>%10): Elevated plasma prolactin levels, but associated clinical manifestations (e.g., gynaecomastia, galactorrhoea, and breast enlargement) were rare. In most patients, levels returned to normal ranges without cessation of treatment. Uncommon (%1–0.1): High creatine phosphokinase.

1 Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Weight gain ≥%7 of baseline body weight was very common and ≥%15 of baseline body weight was common.

2 Observed for fasting normal levels at baseline (<5.56 mmol/l) which increased to high (≥7 mmol/l). Changes in fasting glucose from borderline at baseline (≥7> - 5.56 mmol/l) to high (≥7 mmol/l) were very common.

3 Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline.

4 Observed for fasting normal levels at baseline (<1.69 mmol/l) which increased to high (≥2.26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥2.26> - 1.69 mmol/l) to high (≥2.26 mmol/l) were very common.

5 Observed for fasting normal levels at baseline (<5.17 mmol/l) which increased to high (≥6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥6.2> - 5.17 mmol/l) to high (≥6.2 mmol/l) were very common.

6 In clinical trials, the incidence of parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

The following table of undesirable effects is based on post-marketing spontaneous reports.

Blood and lymphatic system disorders Rare (%0.1–0.01): Leukopenia. Very rare (<%0.01): Thrombocytopenia. Neutropenia.
Immune system disorders Very rare (<%0.01): Allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritis or urticaria).
Metabolism and nutrition disorders Rare (%0.1–0.01): Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been spontaneously reported rarely, including some fatal cases (See Warnings and precautions for use). Very rare (<%0.01): Hypertriglyceridaemia, hypercholesterolaemia and hypothermia.
Nervous system disorders Rare (%0.1–0.01): Seizures have been reported to occur rarely in patients treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported. Very rare (<%0.01): Cases reported as Neuroleptic Malignant Syndrome (NMS) have been received in association with olanzapine (See Warnings and precautions for use). Parkinsonism, dystonia (including oculogyration) and tardive dyskinesia have been reported very rarely with olanzapine. Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely when olanzapine is stopped abruptly.
Cardiac disorders Very rare (<%0.01): QTc prolongation, ventricular tachycardia/fibrillation and sudden death (See Warnings and precautions for use).
Vascular disorders Very rare (<%0.01): Thromboembolism (including pulmonary embolism and deep vein thrombosis).
Gastrointestinal disorders Very rare (<%0.01): Pancreatitis.
Hepato-biliary disorders Rare (%0.1–0.01): Hepatitis (including hepatocellular, cholestatic or mixed liver injury).
Musculoskeletal and connective tissue and bone disorders Very rare (<%0.01): Rhabdomyolysis.
Skin and subcutaneous tissue disorders Rare (%0.1–0.01): Rash. Very rare (<%0.01): Alopecia.
Renal and urinary disorders Very rare (<%0.01): Urinary hesitation.
Reproductive system and breast disorders Very rare (<%0.01): Priapism.
Investigations Increased transaminases. Very rare (<%0.01): Increased alkaline phosphatase. Increased total bilirubin.

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 1500 mg.

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.

Preclinical safety data

Acute (single-dose) toxicity

Signs of oral toxicity in rodents were characteristic of potent neuroleptic compounds: hypoactivity, coma, tremors, clonic convulsions, salivation, and depressed weight gain. The median lethal doses were approximately 210 mg/kg (mice) and 175 mg/kg (rats). Dogs tolerated single oral doses up to 100 mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, labored respiration, miosis, and anorexia. In monkeys, single oral doses up to 100 mg/kg resulted in prostration and, at higher doses, semi-consciousness.

Repeated-dose toxicity

In studies up to 3 months duration in mice and up to 1 year in rats and dogs, the predominant effects were CNS depression, anticholinergic effects, and peripheral haematological disorders. Tolerance developed to the CNS depression. Growth parameters were decreased at high doses. Reversible effects consistent with elevated prolactin in rats included decreased weights of ovaries and uterus and morphologic changes in vaginal epithelium and in mammary gland.

Haematologic toxicity: Effects on hematology parameters were found in each species, including dose-related reductions in circulating leukocytes in mice and non-specific reductions of circulating leukocytes in rats; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia, or anemia developed in a few dogs treated with 8 or 10 mg/kg/day (total olanzapine exposure [area under the curve] is ~12 to ~15fold greater than that of a man given a ~12mg dose). In cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

Reproductive toxicity

Olanzapine had no teratogenic effects. Sedation affected mating performance of male rats. Estrous cycles were affected at doses of 1.1 mg/kg (3 times the maximum human dose) and reproduction parameters were influenced in rats given 3 mg/kg (9 times the maximum human dose). In the offspring of rats given olanzapine, delays in fetal development and transient decreases in offspring activity levels were seen.

Mutagenicity

Olanzapine was not mutagenic or clastogenic in a full range of standard tests, which included bacterial mutation tests and in vitro and in vivo mammalian tests.

Carcinogenicity

Based on the results of studies in mice and rats, it was concluded that olanzapine is not carcinogenic.

Incompatibilities

Not applicable.

Precautions for storage

Store below 30°C.

Nature and contents of container

Aluminum blister strips in cartons of 28 or 30 orodispersible tablets per carton.

Hospital packs are also available (500 and 1000).

Note: Not all pack sizes are available in all countries.

This is a medicament:

- A medicament is a product that 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.
- Keep out of reach of children.

Council of Arab Health Ministers
Union of Arab Pharmacists

Al Taqaddom Pharmaceutical Industries,
Amman - Jordan

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July, 2017
I-Olexa-LM0-R2/EE

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Dimensions: 15 x 24 cm Pantone 2607C

15 cm

Olexa®

olanzapine

Antipsychotic, antimanic and mood stabilizing agent.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Olexa 5 mg, 10 mg orodispersible tablet contains 5 mg, 10 mg olanzapine respectively.

Excipients:

Mannitol Ph. Eur. (Pearlitol SD- 200), Low Substituted Hydroxy Propyl Cellulose (LHPC LH11-) IH, Aspartam Ph. Eur. (NutraSweet), Strawberry Flavor IH 52311 AP 0551, Silica colloidal anhydrous Ph. Eur. (Aerosil 200), Magnesium stearate Ph. Eur. (Hyqual).

PHARMACEUTICAL FORM

Orodispersible tablet

Olexa 5 mg, 10 mg Orodispersible Tablets are a yellow, round, flat face tablet, with a characteristic flavor which is placed in the mouth or alternatively is dispersed in water or other suitable beverage.

INDICATIONS

Olanzapine is indicated for the acute and maintenance treatment of schizophrenia and other psychoses where positive symptoms (e.g., delusions, hallucinations, disordered thinking, hostility, and suspiciousness) and/or negative symptoms (e.g., flattened affect, emotional and social withdrawal, poverty of speech) are prominent. Olanzapine also alleviates the secondary affective symptoms commonly associated with schizophrenia and related disorders.

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

- 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. 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 20-5 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. Olanzapine can be given without regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

Olexa Orodispersible Tablet should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible 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.

Olanzapine orodispersible tablet is 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. Olanzapine orodispersible tablets may be used as an alternative to olanzapine coated tablets. There is no experience in children.

- Elderly patients: A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant (See warnings and precautions for use).
- 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.
- 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.

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.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS FOR USE

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see Undesirable effects). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable particularly in diabetic patients and in patients with risk factors for the development of diabetes mellitus for which regular glucose control is recommended.

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

Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely (<%0.01) when olanzapine is stopped abruptly. Gradual dose reduction should be considered when discontinuing olanzapine.

Concomitant illnesses: 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.

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 (See Undesirable effects), and olanzapine was not more effective than placebo in the treatment of psychotic symptoms. In these trials, patients were initially required to be stable on the lowest effective dose of anti-parkinsonian medications (dopamine agonist) and to remain on the same anti-Parkinsonian medications and dosages throughout the study. Olanzapine was started at 2.5 mg/day and titrated to a maximum of 15 mg/day based on investigator judgment.

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. In placebo-controlled clinical trials (12-6 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a ~2fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (%3.5 vs. %1.5, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include: age >65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient ischemic attack), including fatalities, were reported. There was a ~3fold increase in CVAE in patients treated with olanzapine compared to patients treated with placebo (%1.3 vs. %0.4, respectively). All olanzapine- and placebo-treated patients who experienced a cerebrovascular event had pre-existing risk factors. Age >75 years and vascular/mixed type dementia were identified as risk factors for CVAE in association with olanzapine treatment. The efficacy of olanzapine was not established in these trials.

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. Transient, asymptomatic elevations of hepatic transaminases, alanine transferase (ALT), aspartate transferase (AST) have been seen commonly, especially in early treatment. Caution should be exercised 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 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 (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

As with other neuroleptic medicines, 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 (See Undesirable effects).

There are limited data on co-medication with lithium and valproate. There are no clinical data available on olanzapine and carbamazepine co-therapy, however a pharmacokinetic study has been conducted (See Interactions).

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially life-threatening condition associated with antipsychotic medication. 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.

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: 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.

Given the primary central nervous system 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.

Postural hypotension was infrequently observed in the elderly in olanzapine clinical trials. As with other antipsychotics, it is recommended that blood pressure is measured periodically in patients over 65 years.

In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥500 milliseconds [msec] at any time post baseline in patients with baseline QTcF <500 msec) were uncommon (0.1 % to 1 %) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. However, as with other antipsychotics, 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, hypokalemia or hypomagnesaemia.

Temporal association of olanzapine treatment and venous thromboembolism has very rarely (<%0.01) been reported. 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.

Phenylalanine: Olexa orodispersible tablet contains aspartame, which is a source of phenylalanine, May be harmful for people with phenylketonuria.

Mannitol: Olexa orodispersible tablet contains mannitol.

INTERACTIONS

Caution should be exercised in patients who receive medicinal products that can cause central nervous system depression.

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 (See Posology and method of administration).

Inhibition of CYP1A2: Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine Cmax 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 (aluminum, 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., 1A2,2D2 ,6C9,2C19,3A4). 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.

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Dimensions: 15 x 24 cm Pantone 2607C