Olanzaget™

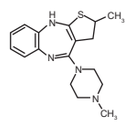
[Olanzapine + Fluoxetine]

اولینزاگیٹ

Capsules 3mg + 25mg & 6mg + 25mg

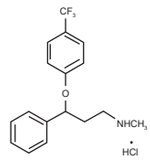
DESCRIPTION

Olanzaget combines an atypical antipsychotic and a selective serotonin reuptake inhibitor, Olanzapine and Fluoxetine hydrochloride. Olanzapine belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1piperazinyl)-10H-thieno[2,3-b] [1,5]benzodiazepine. Its molecular formula is $C_{17}H_{20}N_4S$ and the structural formula is:



Olanzapine

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI). The chemical designation is (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)oxy]propylamine hydrochloride. Its molecular formula is $C_{17}H_{18}F_3NO$•HCl and the structural formula is:



Fluoxetine Hydrochloride

QUALITATIVE AND QUANTITATIVE COMPOSITION

Olanzaget (Olanzapine + Fluoxetine) is available for oral administration as:

Olanzaget Capsules 3mg + 25mg
Each capsule contains:
Olanzapine USP…3mg
Fluoxetine HCl USP equivalent to Fluoxetine…25mg

Olanzaget Capsules 6mg + 25mg
Each capsule contains:
Olanzapine USP…6mg
Fluoxetine HCl USP equivalent to Fluoxetine…25mg

CLINICAL PHARMACOLOGY

Mechanism of Action

The combined effect of Olanzapine + Fluoxetine at the monoaminergic neural systems (serotonin, norepinephrine and dopamine) could be responsible for the pharmacological effect.

Olanzapine binds with high affinity to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$, dopamine D_{1-4}, histamine H_1 and adrenergic α_1 receptors. Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ and muscarinic M_{1-5}. Olanzapine binds weakly to GABAA, BZD and β-adrenergic receptors. Fluoxetine is an inhibitor of the serotonin transporter and is a weak inhibitor of the norepinephrine and dopamine transporters.

Pharmacokinetics

Absorption:

Following a single oral 12mg + 50mg dose of Olanzapine + Fluoxetine, peak plasma concentrations of Olanzapine + Fluoxetine occur at approximately 4 and 6 hours, respectively.

Olanzapine:

Olanzapine is well absorbed and reaches peak concentration approximately 6 hours following an oral dose. Food does not affect the rate or extent of Olanzapine absorption when Olanzapine is given alone. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation.

Fluoxetine:

Following a single oral 40mg dose, peak plasma concentrations of Fluoxetine from 15 to 55ng/mL are observed after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of Fluoxetine when given alone, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant.

Distribution:

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100ng/mL, binding primarily to albumin and α_1-acid glycoprotein. Over the concentration range from 200 to 1000ng/mL, approximately 94.5% of Fluoxetine is bound in vitro to human serum proteins, including albumin and α_1-glycoprotein.

Metabolism & Elimination:

Olanzapine displays linear pharmacokinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours and apparent plasma clearance ranges from 12 to 47 L/hr. Administration of Olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses.

Following a single oral dose of ^{14}C-labeled Olanzapine, 7% of the dose of Olanzapine was recovered in the urine as unchanged drug, indicating that Olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, Olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of Olanzapine and 4´-N-desmethyl Olanzapine, present at steady state at 31% of the concentration of Olanzapine. Both metabolites lack pharmacological activity at the concentrations observed. Direct glucuronidation and CYP450-mediated oxidation are the primary metabolic pathways for Olanzapine. In vitro studies suggest that CYP1A2, CYP2D6 and the flavin-containing monooxygenase system are involved in Olanzapine oxidation. CYP2D6-mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of Olanzapine is not reduced in subjects who are deficient in this enzyme.

Fluoxetine is a racemic mixture (50/50) of R-Fluoxetine and S-Fluoxetine enantiomers. Both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The S-Fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state. Fluoxetine is extensively metabolized in the liver to its only identified active metabolite, norfluoxetine, via the CYP2D6 pathway. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Special Populations

Elderly: Based on the individual pharmacokinetic profiles of Olanzapine + Fluoxetine, the pharmacokinetics of Olanzapine + Fluoxetine may be altered in geriatric patients. Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity.

Renal Impairment: The pharmacokinetic characteristics of Olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, Olanzapine is not removed by dialysis.

In depressed patients on dialysis, Fluoxetine administered as 20mg once daily for 2 months produced steady-state Fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of Fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.

Hepatic Impairment: Based on the individual pharmacokinetic profiles of Olanzapine + Fluoxetine, the pharmacokinetics of Olanzapine + Fluoxetine may be altered in patients with hepatic impairment. The lowest starting dose should be considered for patients with hepatic impairment.

Combined Effects: The combined effects of age, smoking and gender could lead to substantial pharmacokinetic differences in populations. The clearance of Olanzapine in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Olanzapine + Fluoxetine dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of the Olanzapine component.

THERAPEUTIC INDICATIONS

Olanzaget (Olanzapine + Fluoxetine) is indicated for the treatment of:

- Acute depressive episodes in Bipolar I Disorder.
- Treatment resistant depression (Major Depressive Disorder in patient who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode).

DOSAGE & ADMINISTRATION

Depressive Episodes Associated with Bipolar I Disorder

Adults

Administer Olanzaget (Olanzapine + Fluoxetine) once daily in the evening, generally beginning with the 6mg + 25mg capsule.

Make dosage adjustments, if indicated, according to efficacy and tolerability. Antidepressant efficacy was demonstrated with Olanzaget (Olanzapine + Fluoxetine) in a dose range of Olanzapine 6mg to 12mg and Fluoxetine 25mg to 50mg. Periodically reexamine the need for continued pharmacotherapy.

Children and Adolescents (10 to 17 years of age)

Administer Olanzaget (Olanzapine + Fluoxetine) once daily in the evening, generally beginning with the 3mg + 25mg capsule, without regard to meals, with a recommended target dose within the approved dosing range. Periodically reexamine the need for continued pharmacotherapy.

Treatment Resistant Depression

Administer Olanzaget (Olanzapine + Fluoxetine) once daily in the evening, generally beginning with the 6mg + 25mg capsule. Adjust dosage, if indicated, according to efficacy and tolerability.

Antidepressant efficacy was demonstrated with Olanzaget (Olanzapine + Fluoxetine) in a dose range of Olanzapine 6mg to 18mg and Fluoxetine 25mg to 50mg. Periodically reexamine the need for continued pharmacotherapy.

Special Populations

Start Olanzaget (Olanzapine + Fluoxetine) at 3mg + 25mg or 6mg + 25mg in patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of Olanzaget (Olanzapine + Fluoxetine) (female gender, geriatric age, nonsmoking status) or those patients who may be pharmacodynamically sensitive to Olanzapine. Titrate slowly and adjust dosage as needed in patients who exhibit a combination of factors that may slow metabolism.

Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with Olanzaget (Olanzapine + Fluoxetine). Conversely, at least 5 weeks should be allowed after stopping Olanzaget (Olanzapine + Fluoxetine) before starting an MAOI intended to treat psychiatric disorders.

ADVERSE REACTIONS:

Most common adverse reactions (≥5% and at least twice that for placebo) in adults:

Somnolence, sedation, hypersomnia, lethargy, weight increased, appetite increased, dry mouth, fatigue, edema, tremor, disturbance in attention and blurred vision.

Other adverse reaction reported by patient who are treated with Olanzapine + Fluoxetine are chills, neck rigidity, photosensitivity reaction, vasodilatation, diarrhea, gastritis, gastroenteritis, nausea and vomiting, peptic ulcer, gastrointestinal hemorrhage, intestinal obstruction, liver fatty deposit, pancreatitis, ecchymosis, anemia, thrombocytopenia, leukopenia, purpura, edema, weight loss, bilirubinemia, creatinine increased, gout, osteoporosis, amnesia, ataxia, buccoglossal syndrome, coma, depersonalization, dysarthria, emotional lability, euphoria, hypokinesia, movement disorder, myoclonus, hyperkinesia, libido increased, withdrawal syndrome, epistaxis, yawn, laryngismus, alopecia, dry skin, pruritus; exfoliative dermatitis, taste perversion, abnormality of accommodation, dry eyes, breast pain, menorrhagia, urinary frequency, urinary incontinence, amenorrhea, female lactation, hypomenorrhea, metrorrhagia, urinary retention, urinary urgency, urination impaired, breast engorgement, hyperglycemia, hyperlipidemia, flatulence, abdominal distension, asthenia, pain, pyrexia, sinusitis, arthralgia, musculoskeletal stiffness, lethargy, sestlessness, thinking abnormal, nervousness and erectile dysfunction.

Children and adolescents:

Somnolence, sedation, hypersomnia, weight increased, appetite increased, tremor, triglyceride increased, hepatic enzymes (Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test abnormal, gamma-glutamyltransferase increased and transaminases) increased, blood cholesterol increased, dyspepsia, anxiety, restlessness, suicidal ideation, back pain, accidental overdose & dysmenorrhea

Post marketing experience:

The adverse reactions identified during post-approval use of Olanzapine + Fluoxetine are rhabdomyolysis and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis)

"To report SUSPECTED ADVERSE REACTIOND to Getz Pharma's Pharmacovigilance Section, plese contact at dsafety@getzpharma.com or +92-21-38636363

CONTRAINDICATIONS

1. Use of Olanzapine + Fluoxetine is contraindicated in patients with hypersensitivity to Olanzapine, Fluoxetine or to any of the excipient of the product.
2. Use of Olanzapine + Fluoxetine is contraindicated with following products:
   a. Monoamine Oxidase Inhibitors (MAOIs):
      The use of MAOIs intended to treat psychiatric disorders with Olanzapine + Fluoxetine or within 5 weeks of stopping treatment with Olanzapine + Fluoxetine is contraindicated because of an increased risk of serotonin syndrome. The use of Olanzapine + Fluoxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated.
      Starting Olanzapine + Fluoxetine in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome.
   b. Other products
      - Pimozide
      - Thioridazine

PRECAUTIONS

Suicidal Thoughts and Behaviors: Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents and young adults. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening and emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the healthcare provider.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Olanzapine + Fluoxetine is not approved for the treatment of patients with dementia-related psychosis.

General

In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules and monitoring of clinical status.

Neuroleptic Malignant syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including Olanzapine. Manage with immediate discontinuation and close monitoring. If after recovering from NMS, a patient requires treatment with an antipsychotic, the patient should be carefully monitored, since recurrences of NMS have been reported.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DRESS has been reported with Olanzapine exposure. Discontinue Olanzapine + Fluoxetine if DRESS is suspected.

Metabolic Change
Metabolic changes may be associated with increased cardiovascular/cerebrovascular risk. Atypical antipsychotic drugs have been associated with metabolic changes including hyperglycemia, dyslipidemia and weight gain. Patients receiving Olanzapine + Fluoxetine should receive regular monitoring of weight, hyperglycemia and dyslipidemia.

Serotonin Syndrome
Serotonin syndrome has been reported with SSRIs and SNRIs, including Olanzapine + Fluoxetine, both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines and St. John's Wort). If such symptoms occur, discontinue Olanzapine + Fluoxetine and initiate supportive treatment. If concomitant use of Olanzapine + Fluoxetine with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Angle-Closure Glaucoma
Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants.

Allergic Reactions and Rash
Anaphylactoid reactions, including bronchospasm, angioedema and urticaria alone and in combination, have been reported. Pulmonary reactions, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. Upon the appearance of rash or of other possible allergic phenomena for which an alternative etiology cannot be identified, Olanzapine + Fluoxetine should be discontinued.

Activation of Mania/Hypomania
Prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for Bipolar Disorder.

Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. If signs and symptoms of tardive dyskinesia appear in a patient on Olanzapine + Fluoxetine, drug discontinuation should be considered. However, some patients may require treatment with Olanzapine + Fluoxetine despite the presence of the syndrome. The need for continued treatment should be reassessed periodically.

Orthostatic Hypotension
Olanzapine + Fluoxetine can be associated with bradycardia and syncope. Risk is increased during initial dose titration. Use caution in patients with cardiovascular disease or cerebrovascular disease and those conditions that could affect hemodynamic responses.

Falls
Olanzapine + Fluoxetine may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Leukopenia, Neutropenia and Agranulocytosis
Leukopenia, Neutropenia and Agranulocytosis has been reported with antipsychotics, including Olanzapine + Fluoxetine. Patients with a history of a clinically significant low white blood cell count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy. Consider discontinuing Olanzapine + Fluoxetine at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic drug use.

Seizures
Seizures have also been reported with both Olanzapine + Fluoxetine monotherapy. Olanzapine + Fluoxetine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.

Hyponatremia
Hyponetremia can occur in association with syndrome of inappropriate antidiuretic hormone (SIADH). Consider discontinuing Olanzapine + Fluoxetine, if symptomatic hyponatremia occurs (SIADH).

Potential for Cognitive and Motor Impairment
Olanzapine + Fluoxetine has potential to impair judgment, thinking and motor skills. Caution patients about operating machinery.

Body Temperature Dysregulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic drugs.

QT Prolongation
QT prolongation and ventricular arrhythmia including Torsade de Pointes have been reported with Fluoxetine. Use with caution in conditions that predispose to arrhythmias or increased Fluoxetine exposure. Use cautiously in patients with risk factors for QT prolongation.

Anticholinergic (antimuscarinic) Effects
Use with caution with other anticholinergic drugs and in patients with urinary retention, prostatic hypertrophy, constipation, history of paralytic ileus or related conditions

Hyperprolactinemia
Olanzapine + Fluoxetine elevates prolactin levels and the elevation persists during administration. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Discontinuation Adverse Reactions
Patients should be monitored when discontinuing treatment with Fluoxetine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.

Sexual Dysfunction
Use of SSRIs, including Fluoxetine, may cause symptoms of sexual dysfunction. Discuss potential management strategies to support patients in making informed decisions about treatment.

Pregnancy
SSRI use, particularly later in pregnancy, may increase the risk for persistent pulmonary hypertension and symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, irritability, tremor) in the neonate. Olanzapine may cause extrapyramidal symptoms and/or withdrawal symptoms in neonates with third trimester exposure. Olanzapine + Fluoxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Olanzapine, Fluoxetine and norfluoxetine is found to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Olanzapine + Fluoxetine and any potential adverse effects on the breastfed child from Olanzapine + Fluoxetine or the underlying maternal condition.

DRUG INTERACTIONS
CNS Acting Drugs
Caution is advised if the concomitant administration of Olanzapine + Fluoxtine and other CNS-active drugs is required.

NSAIDs, Aspirin, Warfarin
Concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SNRIs or SSRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Olanzapine + Fluoxtine is initiated or discontinued.

Benzodiazepines
Co-administration of diazepam with Olanzapine potentiated the orthostatic hypotension. When concurrently administered with Fluoxetine, the half-life of diazepam may be prolonged in some patients. Coadministration of alprazolam and Fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

Inducers of 1A2
Carbamazepine therapy (200mg BID) causes an approximate 50% increase in the clearance of Olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in Olanzapine clearance.

Inhibitors of CYP1A2
Fluvoxamine decreases the clearance of Olanzapine. This results in a mean increase in Olanzapine C_{max} following fluvoxamine administration of 54% in female nonsmokers and 77% in male smokers. The mean increase in Olanzapine AUC is 52% and 108%, respectively. Lower doses of the Olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

The Effect of Other Drugs on Olanzapine
Fluoxetine, an inhibitor of CYP2D6, decreases Olanzapine clearance a small amount. Agents that induce CYP1A2 or glucuronyl transferase enzymes, such as omeprazole and rifampin, may cause an increase in Olanzapine clearance.

Alcohol
The coadministration of ethanol with Olanzapine + Fluoxetine may potentiate sedation and orthostatic hypotension.

Tricyclic Antidepressants (TCAs)
The dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when Olanzapine + Fluoxetine is coadministered or has been recently discontinued.

Antihypertensive Agents
Because of the potential for Olanzapine to induce hypotension, Olanzapine + Fluoxetine may enhance the effects of certain antihypertensive agents.

Levodopa and Dopamine Agonists
Olanzapine may antagonize the effects of levodopa and dopamine agonists.

Clozapine
Elevation of blood levels of clozapine has been observed in patients receiving concomitant Fluoxetine.

Haloperidol
Elevation of blood levels of haloperidol has been observed in patients receiving concomitant Fluoxetine.

Phenytoin
Patients on stable doses of phenytoin have developed elevated plasma levels of phenytoin with clinical phenytoin toxicity following initiation of concomitant Fluoxetine.

Drugs Metabolized by CYP2D6
Fluoxetine inhibits the activity of CYP2D6 and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Coadministration of Fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals) and antiarrhythmics (e.g., propafenone, flecainide and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving Fluoxetine concurrently or has taken it in the previous 5 weeks. If Fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for a decreased dose of the original medication should be considered.

Lithium
There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with Fluoxetine. Lithium levels should be monitored in patients taking Olanzapine + Fluoxetine concomitantly with lithium.

Drugs Tightly Bound to Plasma Proteins
Because Fluoxetine is tightly bound to plasma protein, the administration of Fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound Fluoxetine by other tightly bound drugs.

Drugs that Prolong the QT Interval
Use Olanzapine + Fluoxetine with caution in combination with other drugs that cause QT prolongation. These include: specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, mesoridazine, droperidol); specific antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sparfloxacin); Class 1A antiarrhythmic medications (e.g., quinidine, procainamide); Class III antiarrhythmics (e.g., amiodarone, sotalol); and others (e.g., pentamidine, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, probucol or tacrolimus).

OVERDOSAGE
Symptoms
Somnolence (sedation), impaired consciousness (coma), impaired neurologic function (ataxia, confusion, convulsions, dysarthria), arrhythmias, lethargy, essential tremor, agitation, acute psychosis, hypotension, hypertension and aggression. Fatalities have been confounded by exposure to additional substances including alcohol, thioridazine, oxycodone and propoxyphene.

Management
In managing overdose, consider the possibility of multiple drug involvement. Establish and maintain an airway and ensure adequate ventilation. Commence cardiovascular monitoring immediately and include continuous electrocardiographic monitoring to detect possible arrhythmias. A specific precaution involves patients who are taking or have recently taken Olanzapine + Fluoxetine and may have ingested excessive quantities of a TCA (tricyclic antidepressant). In such cases, accumulation of the parent TCA and/or an active metabolite increases the possibility of serious sequelae and extends the time needed for close medical observation. Due to the large volume of distribution of Olanzapine + Fluoxetine, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidote for either Fluoxetine or Olanzapine overdose is known.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Olanzaget (Olanzapine + Fluoxetine) Capsules 3mg + 25mg are available in pack of 14's.
Olanzaget (Olanzapine + Fluoxetine) Capsules 6mg + 25mg are available in pack of 14's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz pharma (PVT) LIMITED
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