OLANZAPINE

EPINOZAL-OD 5

5 mg Orally Disintegrating Tablet
ANTIPSYCHOTIC

℞

FORMULATION:
Each tablet contains:
Olanzapine USP ..... 5 mg
Excipients ..... Q.S

PRODUCT DESCRIPTION:
Yellow coloured, round shaped, flat uncoated tablet having break line on one side and plain on other side.

MECHANISM OF ACTION:
Olanzapine is an atypical antipsychotic agent, is used to treat both negative and positive symptoms of schizophrenia, acute mania with bipolar disorder, agitation, and psychotic symptoms in dementia.

PHARMACODYNAMIC PROPERTIES
Therapeutic Class:
Olanzapine is an antipsychotic agent.

PHARMACODYNAMICS:
Olanzapine is an antipsychotic agent that demonstrates a broad pharmacologic profile across a number of receptor systems. In preclinical studies, olanzapine exhibited affinities for serotonin 5-HT2A/C, 5 HT3, 5 HT6; dopamine D1, D2, D3, D4, D5; muscarinic M1.5; adrenergic 1; and histamine H1, receptors. Animal behavioral studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated greater in vitro receptor affinity for serotonin 5HT2, as well as greater *in vivo* serotonin 5HT2 activity compared to dopamine D2 receptor affinity and activity. 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 two of two placebo and two of three comparator controlled trials with over 2,900 schizophrenic patients presenting with both positive and negative symptoms, olanzapine was associated with statistically significantly greater improvements in negative as well as positive symptoms.

PHARMACOKINETICS:
Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food. Plasma concentrations of olanzapine were linear and dose proportional in trials studying doses from 1 to 20 mg. Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N glucuronide, which in theory does not pass the blood-brain barrier. Cytochrome P450 isoforms CYP1A2 and CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites. Both metabolites exhibited significantly less in vivo pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine. After oral administration to healthy subjects, the mean terminal elimination half-life was 33 hours (21 to 54 hours for 5th to 95th percentile) and the mean olanzapine plasma clearance was 26 L/hr (12 to 47 L/hr for the 5th to 95th percentile). Olanzapine pharmacokinetics varied on the basis of smoking status, gender, and age. The following summarizes these effects. See Table 1.

Table 1.

Patient Characteristics	Half-Life (hours)	Plasma Clearance (L/hr.)
Nonsmoking	38.6	18.6
Smoking	30.4	27.7
Female	36.7	18.9
Male	32.3	27.3
Elderly (65 and older)	51.8	17.5
Nonelderly	33.8	18.2

Although smoking status, gender, and, to a lesser extent, age may affect olanzapine clearance and half-life, the magnitude of the impact of these single factors is small in comparison to the overall variability between individuals.

Adolescents (ages 13 to 17 years):
The pharmacokinetics of olanzapine are similar between adolescents and adults. In clinical studies, the average olanzapine exposure was approximately 27% higher in adolescents. Demographic differences between the adolescents and adults include a lower average body weight and fewer adolescents were smokers. Such factors likely contribute to the higher average exposure observed in adolescents. There was no significant difference in mean elimination half-life or olanzapine plasma clearance between subjects with severely impaired renal function compared to individuals with normal renal function. Approximately 57% of radio labeled olanzapine is excreted in urine, principally as metabolites. Subjects with mild hepatic dysfunction who smoked had reduced clearance comparable to nonsmoking subjects with no hepatic dysfunction. 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 1-acid-glycoprotein. In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in olanzapine pharmacokinetics among the three populations. Cytochrome P450 isoform CYP2D6 status does not affect the metabolism of olanzapine.

INDICATIONS:
Olanzapine is indicated for the treatment of schizophrenia.
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.

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

DOSAGE AND ADMINISTRATION:
Route of Administration: Oral
Adults:
Schizophrenia: The recommended starting dose for olanzapine is 10 mg/day.
Manic episode: The starting dose is 15 mg as a single daily dose in monotherapy or 10 mg daily in combination therapy.
Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg/day. 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 optimization 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.
Olanzapine 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.

ADVERSE EFFECTS:
The most frequently reported adverse reactions associated with the use of olanzapine 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.

DRUG INTERACTIONS:
Diazepam: The co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine.
Cimetidine and Antacids: Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.
Alcohol: Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The co administration of alcohol (i.e., ethanol) with olanzapine potentiated the orthostatic hypotension observed with olanzapine.
Potential for Olanzapine to Affect Other Medicinal Products: Olanzapine may antagonise the effects of direct and indirect dopamine agonists.
General CNS activity: The concomitant use of olanzapine with anti-Parkinsonian medicinal products in patients with Parkinson's disease and dementia is not recommended.

PREGNANCY AND LACTATION:
PREGNANCY:
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.
Lactation:
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.

PRECAUTION /WARNINGS:
- Elderly Patients with Dementia-Related Psychosis: Increased risk of death and increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack).
- Suicide: The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy; when using in combination with fluoxetine.
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring.
- Hyperglycemia: In some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking olanzapine. Patients taking olanzapine should be monitored for symptoms of hyperglycemia and undergo fasting blood glucose testing at the beginning of, and periodically during, treatment.
- Hyperlipidemia: Undesirable alterations in lipids have been observed. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically during, treatment.
- Weight Gain: Potential consequences of weight gain should be considered. Patients should receive regular monitoring of weight.
- Tardive Dyskinesia: Discontinue if clinically appropriate.
- Orthostatic Hypotension: Orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, may occur especially during initial dose titration.
- Seizures: Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.
- Potential for Cognitive and Motor Impairment: Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery.
- Hyperprolactinemia: May elevate prolactin levels.
- Laboratory Tests: Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment.

OVERDOSAGE AND TREATMENTS:
Signs and Symptoms:
Very common symptoms in overdose (> 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (<2% of overdose cases), and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg, but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.
Management:
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e., gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.

STORAGE CONDITION:
Store at temperatures not exceeding 30ºC.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction.

AVAILABILITY:
EPINOZAL-OD 5 - Alu/Alu Blister Pack of 10's (Box of 50's)
EPINOZAL-OD 5 - Alu/Alu Blister Pack of 10's (Box of 30's)

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