OLENZA TABLET

Composition:

OLENZA 5MG TABLET: Each tablet contains 5mg Olanzapine
OLENZA 10MG TABLET: Each tablet contains 10mg Olanzapine

Description:

OLENZA 5MG TABLET: A white to off white round shaped film coated tablet with score on one side.
OLENZA 10MG TABLET: A white to off white round shaped film coated tablet with score on one side.

Pharmacodynamics:

Pharmacotherapeutic group: Diazepines, oxazepines and thiazepines. ATC code: NO5A H03. Olanzapine is an antipsychotic agent that demonstrates a broad pharmacological profile across a number of receptor systems. It is a thienbenozodiazepine atypical antipsychotic. It has affinity for dopamine (D1, D2, and D4), histamine (H1), serotonin (5HT 2A/2C) and adrenergic (α1) receptors.

Pharmacokinetics:

Olanzapine is well absorbed from the gastrointestinal tract after oral administration but undergoes considerable first-pass metabolism. Peak plasma concentrations are achieved about 5-8 hours after oral administration and about 15 to 45 minutes after intramuscular administration. The absorption is not affected by food. 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 pre-dominant pharmacologic activity is from the parent olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine varied on the basis of age and gender. In healthy elderly mean $t_{1/2}$ is 51.8 hours. In non-elderly subjects the mean $t_{1/2}$ is 33.8 hours. In female versus male subjects the mean elimination $t_{½}$ was 36.7 versus 32.3 hours.
In renally impaired patients (creatinine clearance <10 ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hr) or drug clearance (21.2 versus 25.0 L/hr). A mass balance study showed that approximately 57 % of radiolabeled olanzapine appeared in urine, principally as metabolites.
The plasma clearance of olanzapine is lower in elderly versus young subjects, in female versus males, and in non-smoker versus smoker. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to overall variability between individuals.
The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to 1000 ng/ml. Olanzapine is bound predominately to albumin and a_1-acid-glycoprotein.

Indication:

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 continuing therapy in patients who have shown initial treatment response.

Olanzapine is indicated for short term treatment of acute manic episode associated with Bipolar 1 Disorder.
Olanzapine is indicated for preventing recurrence of manic, mixed or depressive episodes in Bipolar 1 Disorder

Recommended dose:
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 10 mg daily in combination therapy.
Preventing recurrence in bipolar disorder: The recommended starting dose is 10mg/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 moods 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 greater then 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
Children: Olanzapine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy.
Elderly patients: A lower starting dose (5mg/day) is not routinely indicated but should be considered for those 65 and above when clinical factors warrant.
Patients with renal and/or hepatic impairment: A lower starting dose (5mg) 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-smoking patients relative to smoking patients.
When more than one factor is present which might result in slower metabolism (female gender, generic age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.

Route of Administration:
Oral administration

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

Warning and precautions:
Hyperglycemia and Diabetes Mellitus
Hyperglycemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given this confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical

antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.
Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness.
Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.
During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period.

Dementia-related psychosis and/or behavioral disturbances
Olanzapine is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphasia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with without aspiration), or concomitant use bendazodiapines.

Parkinson's disease
The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended.

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal product. Rare cases reported as NMS have also been received in association with olanzapine. 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.

Lipid alterations
Undesirable alterations in lipids have been observed in olanzapine-treated patients. Lipid alterations should be managed as clinically appropriate, particularly in dsylipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated any antipsychotic agents, including olanzapine, should be monitored regularly for lipids in accordance with utilized antipsychotic guidelines.

Anticholinergic activity
While olanzapine demonstrated anticholinergic activity in vitro, caution is advised when prescribing for patients with prostatic hypertrophy, or paralytic ileus and related conditions.

Hepatic function
Transient, asymptomatic elevations of transaminases, ALT, 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 hepototoxic medicines. In the event of elevated ALT and/or AST during treatment, follow-up should be organized 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.

Neutropenia
Caution should be exercised in patient with low leukocyte and/or neutrophill 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.

Discontinued of treatment
Acute symptoms such as sweating, insomnia, tremor anxiety, nausea or vomiting have been reported very rarely when olanzapine is stopped abruptly.

QT interval
As with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patient with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Thromboembolism
Temporal association of olanzapine treatment and venous thromboembolism has very rarely been reported. A causal relationship between the occurrence of venous thromboembolism all possible risk factors of VTE e.g. immobilization of patients, should be identified and preventive measure undertaken.

General CNS activity
Given the primary CNS effects of olanzapine, caution should be used when it is taken in combination with other centrally acting medicines and alcohol. As it exhibits in vitro dopamine antagonism, olanzapine may antagonize the effects of direct and indirect dopamine agonists.

Seizures
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur rarely in patients when treated with olanzapine. In most of these cases, a history of seizure or risk factors for seizures were reported.

Tardive Dyskinesia.
The risk to tardive dyskinesia increase with long term exposure, and therefore if signs or symptoms of tardive dyskinesia appearing a patient on olanzapine, a dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinued of treatment.

Postural hypotension
As with other antipsyhotics, it is recommended that blood pressure is measure periodically in patient over 65 years.

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, including weight gain, changes in metabolic parameters and increased in prolactin levels. Long-term outcomes associated with these events have not been studied and remain unknown.

Lactose
Olanzapine tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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.

Drug Reaction with Eosinophilia and systemic symptoms (DRESS)
Drug reaction with Eosinophilia and systemic symptoms (DRESS) has been reported with olanzapine exposure. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. Discontinue olanzapine if DRESS is suspected.

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 CYP1 A2:
Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors eg, ciprofloxacin or ketoconazole. 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 50-60% and should be taken at least 2 hrs 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* (ie, 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.

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.
Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged

hospitalization. OLENZA should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

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.

Side effects:
Adults
The most frequently reported adverse reactions associated with the use of olanzapine were somnolence, weight gain, eosinophilia, elevated porlactic, chloresterol, 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 table lists the adverse reactions and laboratory investigations.

Very common	Common	Uncommon	Not known
Blood and the Iymphatic system disorders			
	Eosinophilia	Leucopenia Neutropenia	Thrombocytopenia
Immune system disorders			
			Allergic reaction
Weight gain	Elevated cholesterol levels Elevated glucose levels Elevated triglyceride levels Glucosuria Increased appetite		Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases Hypothermia.
Nervous system disorders			
Somnolence	Dizziness Akathisia Parkinsonism Dyskinesia		Seizure where in most cases a history of seizures or risk factors for seizures were reported Neuroleptic malignant syndrome Dystonia (including oculogyration) Tardive dsykinesia Discontinuation symptoms
Cardiac disorders			
		Bradycardia QT_c prolongation	Ventricular tachycardia/fibrillation sudden death

Vascular disorders			
	Orthostatic hypotension		Thromboembolism (including pulmonary embolism and deep vein thrombosis
Gastrointestinal disorders			
	Mild, transient anticholinergic effects including constipation and dry mouth		Pancreatitis
Hepato-biliary disorders			
	Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment		Hepatitis (including hepatocellular, cholestatic or mixed liver injury)
Skin and subcutaneous tissue disorders			
	Rash	Photosensitivity reaction Alopecia	
Musculoskeletal and connective tissue disorders			
			Rhabdomyolysis
Renal and urinary disorders			
			Urinary hesitation
Reproductive and breast disorders			
			Priapism
General disorders and administration site conditions			
	Asthena Fatigue Oedema		
Investigations			
Elevated plasma prolactin levels		High creatine phosphokinase Increased total bilirubin	Increased alkaline phosphatase

Nervous System Disorders :
Restless legs syndrome

Respiratory, Thoracic and Mediastinal Disorders :
Sleep apnoea*

*Atypical antipsychotic drugs, such as Olanzapine have been associated with cases of sleep apnoea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, OLENZA should be prescribed with caution.

Renal and Urinary Disorders :

Urinary retention

Long-.term exposure (at least 48 weeks.)

The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 4-6 months.

Additional information on special populations

In elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions. Very common adverse reactions 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.

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.

In patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥ 7% from baseline body weight occurred in 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 patients.

Children and adolescents

Olanzapine is not indicated for the treatment of children and adolescent patients below 18 years.

The following table summarizes the adverse reactions reported with a greater frequency in adolescent patients (aged 13-17 years) than in adult patients or adverse reactions only identified in adolescent patients.

Metabolism and nutrition disorders Very common: Weight gain, elevated triglyceride levels, increased appetite. Common: Elevated cholesterol levels
Nervous system disorders Very common: Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders Common: Dry mouth
Hepato-biliary disorders Very common: Elevations of hepatic transaminases (ALT/AST).
Investigations Very common: Decreased total bilirubin, increased GGT, elevated plasma prolactin levels.

Skin and subcutaneous tissue disorders:
Very rare: Drug reaction with Eosinophilia and systemic symptoms (DRESS)

Overdosage:
Signs and Symptoms
Very common symptoms in overdose 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, 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:
Store below 30°C

Presentation:
7 tablets in a strip. 4 strips in a box.

Product Registration Holder and Manufacturer:
Noripharma Sdn. Bhd. 200701034604 (792633-A)
Lot 5030, Jalan Teratai,
5 1/2 Mile off Jalan Meru,
41050 Klang,
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