PRODUCT NAME	:	Tolanz	COUNTRY : Malaysia		Supersedes A/W No.:	
ITEM / PACK	:	Insert	NO. OF COLORS: 1		REMARK :	
DESIGN STYLE	:	Front/Back	PANTONE SHADE NOS.:		SUBSTRATE :	
CODE	:	xxxxxxxx	Activities	Department	Name	Signature	Date
DIMENSIONS (MM)	:	180 x 290	Prepared By	Pkg.Dev			
ART WORK SIZE	:	S/S	Reviewed By	Pkg.Dev			
DATE	:	09-08-2019	Approved By	Quality			

This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.

The information revised as per NPRA Directive dated 23/10/2018 [Ref: (26) dlm.BPFK/PPP/07/25 Jld. 2]

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

TOLANZ TABLET 5 MG
TOLANZ TABLET 10 MG

(Olanzapine Tablets)

NAME AND STRENGTH OF ACTIVE SUBSTANCE(S)

Tolanz Tablet 5 mg

Each uncoated tablet contains
Olanzapine USP 5 mg

Tolanz Tablet 10 mg

Each uncoated tablet contains
Olanzapine USP 10 mg

DOSAGE FORM

Uncoated Tablets

PRODUCT DESCRIPTION

Tolanz Tablet 5 mg

Yellow colored, round, biconvex uncoated tablets debossed with "5" on one side and "67" on other side.

Tolanz Tablet 10 mg

Yellow colored, round, biconvex uncoated tablets debossed with "10" on one side and "169" on other side.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Olanzapine is an antipsychotic agent that demonstrates a broad pharmacologic profile across a number of receptor systems. Olanzapine exhibited a range of receptor affinities (Ki; < 100 nM) for serotonin 5 HT2A/2C, 5 HT3, 5HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic. It is reported that 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.

Olanzapine produced a higher 5-HT2 A than dopamine D2 receptor occupancy. In addition, olanzapine-responsive patients had lower striatal D2 occupancy than some other antipsychotic and risperidone-responsive patients, while being comparable to clozapineresponsive patients.

It is reported that 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.

Olanzapine is metabolized 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 Ndesmethyl and 2-hydroxymethyl metabolites. It is reported that both exhibited significantly less in vivo pharmacological activity than olanzapine. The predominant pharmacologic activity is from the parent olanzapine.

INDICATION

Adults

Olanzapine is indicated for the treatment of schizophrenia.

Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Olanzapine is indicated for short-term treatment of acute manic episode associated with Bipolar I Disorder.

Olanzapine is indicated for preventing recurrence of manic, mixed or depressive episodes in Bipolar I Disorder.

CONTRAINDICATION

Hypersensitivity to the active substance or to any of the excipients.

Patients with known risk of narrow-angle glaucoma.

WARNINGS AND PRECAUTIONS

During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period.

Dementia-related psychosis and/or behavioural disturbances

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. There was a 2-fold increase in the incidence of death reported in olanzapine-treated patients. 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 independent of these risk factors.

Cerebrovascular adverse events (CVAE e.g., stroke, transient ischaemic attack), including fatalities, were also reported with use of olanzapine. All olanzapine patients who experienced a cerebrovascular event had pre-existing risk factors. Age> 75 years and vascular/mixed type dementia were reported as risk factors for CVAE in association with olanzapine treatment.

Parkinson's disease

The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended. Worsening of Parkinsonian symptomatology and hallucinations were reported with use of olanzapine.

Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially life-threatening condition associated with antipsychotic medicinal products. Rare cases reported as NMS have also been reported 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 creatine 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.

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia, 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 antipsychotic 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 these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-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 hyperglycaemia including polydipsia, polyuria; polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti diabetic treatment despite discontinuation of the suspect drug.

Lipid alterations

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

Anticholinergic activity

Olanzapine had anticholinergic activity. 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.

Hepatic function

Transient, asymptomatic elevations of hepatic aminotransferases, ALT, AST have been reported commonly, especially in early treatment.

Caution should be exercised and follow-up organised 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 cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

Neutropenia

Caution should be exercised in patients with low leucocyte 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.

Discontinuation of treatment

Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported 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 patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Thromboembolism

Temporal association of olanzapine treatment and venous thromboembolism has been reported with use of olanzapine. A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been reported. 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.

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. Olanzapine may antagonise 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 seizures or risk factors for seizures were reported.

Tardive dyskinesia

Olanzapine was reported a 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.

Postural hypotension

Postural hypotension was reported in the elderly in olanzapine. It is recommended that blood pressure is measured periodically in patients over 65 years.

Sudden cardiac death

The event of sudden cardiac death has been reported in patients with olanzapine. The risk of presumed sudden cardiac death in patients treated with olanzapine was reported approximately twice the risk in patients not using antipsychotics. The risk of olanzapine was reported comparable to the risk of atypical antipsychotics.

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 or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. Discontinue olanzapine if DRESS is suspected.

Paediatric population

Olanzapine is not indicated for use in the treatment of children and adolescents. Various adverse reactions, including weight gain, changes in metabolic parameters and increases in prolactin levels were reported in patients aged 13-17. Long-term outcomes associated with these events have not been reported and remain unknown.

Drug Interaction

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

Potential interactions affecting olanzapine: Since olanzapine is metabolized by CYP1A2, substances that can specifically induce or inhibit this isoenzyme may affect the pharmacokinetics of olanzapine.

Induction of CYP1A2: The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary.

Inhibition of CYP1A2: Fluvoxamine a specific CYP1A2 inhibitor has been shown to significantly inhibit the metabolism of olanzapine. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as 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 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 antagonize the effects of direct and indirect dopamine agonists. Olanzapine does not inhibit the main CYP450 isoenzymes in vitro (e.g. 1A2, 2D6, 2C9, 2C19.3A4). Thus no particular interaction is expected as verified through in vivo studies where no inhibition of metabolism of the following active substances was found: tricyclic antidepressant (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2) or diazepam (CYP3A4 and 2C19), Olanzapine showed no interaction when co-administered with lithium or biperiden.

Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant olanzapine.

General CNS activity

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

The concomitant use of olanzapine with anti-Parkinsonian medicinal products in patients with Parkinson's disease and dementia is not recommended.

QTc interval

Caution should be used if olanzapine is being administered concomitantly with medicinal products known to increase QTc interval

ADVERSE EFFECTS

Summary of the safety profile

Adults

The most frequent adverse reactions associated with the use of olanzapine are somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels, glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia, dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases, rash, asthenia, fatigue pyrexia, arthralgia, increased alkaline phosphatase, high gamma glutamyltransferase, high uric acid, high creatine phosphokinase and oedema.

Tabulated list of adverse reactions

In table below, adverse events are presented in order of decreasing seriousness.

Very common	Common	Uncommon	Rare	Not known
Blood and the lymphatic system disorders				
	Eosinophilia Leukopenia Neutropenia		Thrombocytopenia	
Immune system disorders				
		Hypersensitivity		
Metabolism and nutrition disorders				
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	Seizures where in most cases a history of seizures or risk factors for seizures were reported Dystonia (including oculogyration) Tardive dyskinesia Amnesia Dysarthria Restless legs syndrome	Neuroleptic malignant syndrome Discontinuation symptoms	
Cardiac disorders				
		Bradycardia QTc prolongation	Ventricular tachycardia/ fibrillation, sudden death	
Vascular disorders				
Orthostatic hypotension		Thromboembolism (including pulmonary embolism and deep vein thrombosis)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis 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, Tolanz Tablets should be prescribed with caution.		
Gastro-intestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension	Pancreatitis	
Hepato-biliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment		Hepatitis (including hepatocellular, cholestatic or mixed liver injury)	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction, Alopecia		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia		Rhabdomyolysis	
Renal and urinary disorders				
		Urinary incontinence, urinary retention Urinary hesitation		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal
Reproductive system and breast disorders				
	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhea in females Gynaecomastia/ breast enlargement in males	Priapism	
General disorders and administration site conditions				
	Asthenia, Fatigue, Oedema Pyrexia			

Investigations				
Elevated plasma prolactin levels	Increased alkaline phosphatase High creatine phosphokinase High Gamma Glutamyltransferase High Uric Acid	Increased total bilirubin		

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 reported increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 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 reported 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 reported commonly.

Patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly.

In patients with bipolar mania, valproate combination therapy with olanzapine reported an incidence of neutropenia; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate reported 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 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 reported with an increase body weight.

Paediatric population

Olanzapine is not indicated for the treatment of children and adolescent patients below 18 years. The following table summarises the adverse reactions reported with a greater frequency in adolescent patients (aged 13-17 years):

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 aminotransferases (ALT/AST)
Investigations Very common: Decreased total bilirubin, increased GGT, elevated plasma prolactin levels.

DOSAGE AND ADMINISTRATION

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 optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

During treatment for schizophrenia, manic episode, and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20 mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours.

Olanzapine can be given without regard for meals, as absorption is not affected by food.

Gradual tapering of the dose should be considered when discontinuing olanzapine.

Paediatric population

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. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in short-term studies of adolescent patients than in studies of adult patients

Elderly 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.

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.

Mode of Administration

Oral

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no adequate and wellcontrolled 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 foetus.

New born infants exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breastfeeding

Patients should be advised not to breastfeed an infant if they are taking olanzapine.

Fertility

Effects on fertility are unknown.

STORAGE CONDITIONS

Store below 30°C, Protect from light and moisture.
Keep out of reach of children.

PACKAGING AVAILABLE

Tolanz Tablets are packed in Alu-Alu blister of 10 tablets. Such blisters containing 10 tablets are packed into boxes of 10's, 30's, and 100's. Not all presentations may be available locally.

DATE OF REVISION OF PACKAGE INSERT

09/08/2019

Date of revision has been updated.

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

The information revised as per NPRA Directive dated 23/10/2018 [Ref: (26) dlm.BPFK/PPP/07/25 Jld. 2]