For the use of a Psychiatrist or a Hospital or a Laboratory only.

TOLAZ INJECTION
Olanzapine for Injection 10 mg (Lyophilized)

COMPOSITION
Each combipack contains:
A) Olanzapine for injection 10 mg:
Each vial contains:
Olanzapine I.P. 10 mg
Excipients q.s.
B) Sterile water for injection I.P. 2 ml
Each ampoule contains:
Sterile Water for Injection I.P. 2 ml

DOSAGE AND ADMINISTRATION
Agitation Associated with Schizophrenia and Bipolar I Mania
The recommended dose in Agitated Patients with Schizophrenia or Bipolar Mania is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant. If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated. Also, the safety of total daily doses greater than 30 mg, or 10mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose has not been established. Maximal dosing of intramuscular olanzapine (e.g., three doses of 10mg administered 2-4 hours apart) may be associated with significant orthostatic hypotension. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended. If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate.

Intramuscular Dosing in Special Populations - A dose of 5 mg per injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg per injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine

Administration of Olanzapine for injection
Olanzapine for injection should not be administered intravenously or subcutaneously. It should be injected slowly, deep into the muscle mass.

Direction:
Dissolve the contents of the vial using 2 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. Olanzapine Intra Muscular reconstituted with Sterile Water for Injection should be used immediately (within 1 hour) after reconstitution. Discard any unused portion.
The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

Dose (mg)	Volume of Injection (ml)	Dose (mg)	Volume of Injection (ml)
10	2.0		
7.5	1.5		
5	1.0		

2.5	0.5

Caution: - The reconstituted injection should not be used if it contains visible particulate matter.

Physical Incompatibility Information
Olanzapine for injection should be reconstituted only with Sterile Water for Injection.
Olanzapine for injection should not be combined in a syringe with diazepam injection
Because precipitation occurs when these products are mixed. Lorazepam injection should not be used to reconstitute olanzapine for injection as this combination results in a delayed reconstitution time. Olanzapine for injection should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

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 dose and dose range need not be routinely altered for female patients relative to Male patients.
Smokers: The 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 dose. Additional injections, when indicated, should be conservative in such patients.

INDICATIONS
Agitation Associated with Schizophrenia and Bipolar I Mania
Olanzapine for injection is indicated for the treatment of agitation associated with schizophrenia and bipolar I mania. The efficacy of olanzapine for injection for the treatment of agitation associated with schizophrenia and bipolar I mania has been established in short-term (24 hours) placebo-controlled trials in agitated inpatients with schizophrenia or Bipolar I Disorder (manic or mixed episodes).

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Special care must be taken to apply appropriate injection technique to avoid inadvertent intravascular or subcutaneous injection.

<u>Use in patients who are in an acutely agitated or severely psychotic state</u>
Olanzapine should not be used to treat patients with schizophrenia who are in an acutely agitated or severely psychotic state such that immediate symptom control is warranted.

<u>Post-Injection Delirium/Sedation Syndrome</u>
During pre-marketing clinical studies, reactions that presented with signs and symptoms consistent with olanzapine overdose were reported in patients following an injection of Olanzapine. These reactions occurred in <0.1% of injections and approximately 2% of patients. Most of these patients have developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria,

ataxia, aggression, dizziness, weakness, hypertension and convulsion. In most cases, initial signs and symptoms related to this reaction have appeared within 1 hour following injection, and in all cases full recovery was reported to have occurred within 24 - 72 hours after injection. Reactions occurred rarely (<1 in 1,000 injections) between 1 and 3 hours, and very rarely (<1 in 10,000 injections) after 3 hours. Patients should be advised about this potential risk and the need to be observed for 3 hours in a healthcare facility each time Olanzapine is administered. Post-marketing reports of post-injection syndrome since the marketing authorization of Olanzapine are generally consistent with the experience seen in clinical studies.

After each injection, patients should be observed in a healthcare facility by appropriately qualified personnel for at least 3 hours for signs and symptoms consistent with olanzapine overdose.

Immediately prior to leaving the healthcare facility, it should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose. If an overdose is suspected, close medical supervision and monitoring should continue until examination indicates that signs and symptoms have resolved. The 3-hour observation period should be extended as clinically appropriate for patients who exhibit any signs or symptoms consistent with olanzapine overdose.

For the remainder of the day after injection, patients should be advised to be vigilant for signs and symptoms of overdose secondary to post-injection adverse reactions, be able to obtain assistance if needed, and should not drive or operate machinery.

If parenteral benzodiazepines are essential for management of post-injection adverse reactions, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

Injection site-related adverse events

The most commonly reported injection site-related adverse reaction was pain. The majority of these reactions were reported to be of “mild” to “moderate” severity. In the event of an injection site-related adverse reaction occurring, appropriate measures to manage these events should be taken.

Dementia-related psychosis and/or behavioural disturbances

Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in oral 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 oral olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse reactions (CVA Events e.g., stroke, transient ischaemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in

patients treated with oral olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All oral 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.

Parkinson's disease

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, and oral 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 medicinal products (dopamine agonist) and to remain on the same anti-Parkinsonian medicinal products and dosages throughout the study. Oral olanzapine was started at 2.5 mg/day and titrated to a maximum of 15 mg/day based on investigator judgement.

Neuroleptic Malignant Syndrome (NMS)

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

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported uncommonly, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines, e.g., measuring of blood glucose at baseline, 12 weeks after starting olanzapine treatment and annually thereafter. Patients treated with any antipsychotic medicines, including Olanzapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly, e.g., at baseline, 4, 8 and 12 weeks after starting olanzapine treatment and quarterly thereafter.

Lipid alterations

Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials. 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 medicines, including Olanzapine, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines, e.g., at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter.

Anticholinergic activity

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.

Hepatic function

Transient, asymptomatic elevations of hepatic aminotransferases, ALT, AST have been seen 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 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.

Discontinuation of treatment

Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported rarely (≥0.01% and <0.1%) when oral olanzapine is stopped abruptly.

QT interval

In clinical trials with oral olanzapine, 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. In clinical trials with olanzapine powder for solution for injection or OLANZAPINE, olanzapine was not associated with a persistent increase in absolute QT or in QTc intervals. However, 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 uncommonly (≥ 0.1% and < 1%). 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.

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 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 uncommonly 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.

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

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.

Paediatric population
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 increases in prolactin levels.

Use in elderly (>75 years)
No information on the use of Olanzapine in patients > 75 years is available. Due to biochemical and physiological modification and reduction of muscular mass, this formulation is not recommended to be started in this sub-group of patients.

DRUG-INTERACTION
Interaction studies have only been performed in adults.

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 CYP1A2
Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine C_{max} 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 (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* (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.

FERTILITY, 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. 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.

Breast-feeding
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.

Fertility
Effects on fertility are unknown.

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
Summary of the safety profile
Adults
The most frequently (seen in ≥ 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were 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
The following table lists the adverse reactions and laboratory investigations observed from spontaneous reporting and in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the data available).

Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and the lymphatic system disorders				
	Eosinophilia Leukopenia[10] Neutropenia[10]		Thrombocytopenia[1][1]	
Immune system disorders				
		Hypersensitivity[11]		
Metabolism and nutrition disorders				
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4]	Development or exacerbation of diabetes occasionally associated with	Hypothermia[12]	

	Elevated triglyceride levels[2,5] Glucosuria Increased appetite	ketoacidosis or coma, including some fatal cases [11]		
Nervous system disorders				
Somnolence	Dizziness Akathisia[6] Parkinsonism[6] Dyskinesia[6]	Seizures where in most cases a history of seizures or risk factors for seizures were reported [11] Dystonia (including oculogyration) [11] Tardive dyskinesia[11] Amnesia [9] Dysarthria Restless Legs Syndrome	Neuroleptic malignant syndrome [12] Discontinuation symptoms[7, 12]	
Cardiac disorders				
		Bradycardia QTc prolongation	Ventricular tachycardia/ fibrillation, sudden death [11]	
Vascular disorders				
Orthostatic hypotension[10]		Thromboembolism (including pulmonary embolism and deep vein thrombosis)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9]	Pancreatitis[11]	
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment		Hepatitis (including hepatocellular, cholestatic or mixed liver injury) [11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction		Drug Reaction

		Alopecia		with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	
Renal and urinary disorders				
		Urinary incontinence, urinary retention Urinary hesitation[11]		
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[12]	
General disorders and administration site conditions				
	Asthenia Fatigue Oedema Pyrexia[10]			
Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase[10] High uric acid [10]	Increased total bilirubin		

[1]Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Following short-term treatment (median duration 47 days), weight gain ≥ 7% of baseline body weight was very common (22.2%); ≥ 15% was common (4.2%); and ≥ 25% was uncommon (0.8%). Patients gaining ≥ 7%, ≥ 15% and ≥ 25% of their baseline body weight with long-term exposure (at least 48 weeks) were very common (64.4%, 31.7% and 12.3% respectively).

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

[3]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 (≥ 5.17 - < 6.2 mmol/l) to high (≥ 6.2 mmol/l) were very common.

[4]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 (≥ 5.56 - < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5]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 (≥ 1.69 mmol/l - < 2.26 mmol/l) to high (≥ 2.26 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.

[7]Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea and vomiting have been reported when olanzapine is stopped abruptly.

[8] In clinical trials of up to 12 weeks, plasma prolactin concentrations exceeded the upper limit of normal range in approximately 30% of olanzapine-treated patients with normal baseline prolactin value. In the majority of these patients the elevations were generally mild, and remained below two times the upper limit of normal range.

[9] Adverse event identified from clinical trials in the Olanzapine Integrated Database.

[10] As assessed by measured values from clinical trials in the Olanzapine Integrated Database.

[11] Adverse event identified from spontaneous post-marketing reporting with frequency determined utilising the Olanzapine Integrated Database.

[12] Adverse event identified from spontaneous post-marketing reporting with frequency estimated at the upper limit of the 95% confidence interval utilising the Olanzapine Integrated Database.

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 6 months.

Additional information on special populations

In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo. 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 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. 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.

Paediatric population

Olanzapine is not indicated for the treatment of children and adolescent patients below 18 years. Although no clinical studies designed to compare adolescents to adults have been conducted, data from the adolescent trials were compared to those of the adult trials.

The following table summarises the adverse reactions reported with a greater frequency in adolescent patients (aged 13-17 years) than in adult patients or adverse reactions only identified during short-term clinical trials in adolescent patients. Clinically significant weight gain (≥ 7%) appears to occur more frequently in the adolescent population compared to adults with comparable exposures. The magnitude of weight gain and the proportion of adolescent patients who had clinically significant weight gain were greater with long-term exposure (at least 24 weeks) than with short-term exposure.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10).

Metabolism and nutrition disorders *Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite. *Common:* Elevated cholesterol levels[15].
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth.
Hepatobiliary disorders *Very common:* Elevations of hepatic aminotransferases (ALT/AST).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16].

[13]Following short-term treatment (median duration 22 days), weight gain ≥ 7% of baseline body weight (kg) was very common (40.6%); ≥ 15% of baseline body weight was common (7.1%) and ≥ 25% was common (2.5%). With long-term exposure (at least 24 weeks), 89.4% gained ≥ 7%, 55.3% gained ≥ 15% and 29.1% gained ≥ 25% of their baseline body weight.

[14]Observed for fasting normal levels at baseline (< 1.016 mmol/l) which increased to high (≥ 1.467 mmol/l) and changes in fasting triglycerides from borderline at baseline (≥ 1.016 mmol/l - < 1.467 mmol/l) to high (≥ 1.467 mmol/l).

[15]Changes in total fasting cholesterol levels from normal at baseline (< 4.39 mmol/l) to high (≥ 5.17 mmol/l) were observed commonly. Changes in total fasting cholesterol levels from borderline at baseline (≥ 4.39 - < 5.17 mmol/l) to high (≥ 5.17 mmol/l) were very common.

[16]Elevated plasma prolactin levels were reported in 47.4% of adolescent patients.

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 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%.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code N05A H03.

Pharmacodynamic effects

Olanzapine is an antipsychotic, antimanic, and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

In preclinical studies, olanzapine exhibited a range of receptor affinities (K_i <100nM) for serotonin $5HT_{2A/2C}$, $5HT_3$, $5HT_6$; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors M_1-M_5; α_1 adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin $5HT_2$ than dopamine D_2 receptors and greater $5HT_2$ than D_2 activity in *in vivo* models. 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 a single oral dose (10 mg) Positron Emission Tomography (PET) study in healthy volunteers, olanzapine produced a higher $5HT_{2A}$ than dopamine D_2 receptor occupancy. In addition, a Single Photon Emission Computed Tomography (SPECT) imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D_2 occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

Clinical efficacy

The effectiveness of olanzapine in the treatment and maintenance treatment of schizophrenia is consistent with the established effectiveness of the oral formulation of olanzapine.
A total of 1469 patients with schizophrenia were included in 2 pivotal trials:
The first, an 8-week, placebo-controlled trial conducted in adult patients (n=404) who were experiencing acute psychotic symptoms. Patients were randomised to receive injections of olanzapine 405 mg every 4 weeks, 300 mg every 2 weeks, 210 mg every 2 weeks, or placebo every 2 weeks. No oral antipsychotic supplementation was allowed. Total Positive and Negative Symptom Scores (PANSS) showed significant improvement from baseline (baseline mean Total PANSS Score 101) to endpoint (mean changes -22.57, -26.32, -22.49 respectively) with each dose of olanzapine (405 mg every 4 weeks, 300 mg every 2 weeks, and 210 mg every 2 weeks) as compared to placebo (mean change -8.51). Visit wise mean change from baseline to endpoint in PANSS Total Score indicated that by Day 3, patients in the 300 mg/2 weeks and 405 mg/4 weeks treatment groups had statistically significantly greater reductions in PANSS Total Score compared to placebo (-8.6, -8.2, and -5.2, respectively). All 3 olanzapine treatment groups showed statistically significantly greater improvement than placebo beginning by end of Week 1. These results support efficacy for olanzapine over 8 weeks of treatment and a drug effect that was observed as early as 1 week after starting treatment with olanzapine.

The second, a long-term study in clinically stable patients (n=1065) (baseline mean Total PANSS Score 54.33 to 57.75), who were initially treated with oral olanzapine for 4 to 8 weeks and then switched to continue on oral olanzapine or to olanzapine for 24 weeks. No oral antipsychotic supplementation was allowed. Olanzapine treatment groups of 150 mg and 300 mg given every 2 weeks (doses pooled for analysis) and 405 mg given every 4 weeks were non-inferior to the combined doses of 10, 15 and 20 mg of oral olanzapine (doses pooled for analysis) as measured by rates of exacerbation of symptoms of schizophrenia (respective exacerbation rates, 10%, 10%, 7%). Exacerbation was measured by worsening of items on the PANSS derived BPRS Positive Scale and hospitalisation due to worsening of positive psychotic symptoms. The combined 150 mg and 300 mg/2-week treatment group was non-

inferior to the 405 mg/4 week treatment group (exacerbation rates 10% for each group) at 24 weeks after randomization.

Paediatric population
Olanzapine has not been studied in the paediatric population. Controlled efficacy data in adolescents (ages 13 to 17 years) are limited to short term oral olanzapine studies in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Oral olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with oral olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin were greater in adolescents than in adults. There are no controlled data on maintenance of effect or long term safety. Information on long term safety is primarily limited to open-label, uncontrolled data.

Pharmacokinetic properties
Absorption
Olanzapine is metabolised in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide. 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 predominant pharmacologic activity is from the parent, olanzapine.

After a single IM injection with olanzapine, the slow dissolution of the olanzapine in muscle tissue begins immediately and provides a slow continuous release of olanzapine for more than four weeks. The release becomes diminishingly smaller within eight to twelve weeks. Antipsychotic supplementation is not required at the initiation of olanzapine treatment.
The combination of the release profile and the dosage regimen (IM injection every two or four weeks) result in sustained olanzapine plasma concentrations. Plasma concentrations remain measurable for several months after each olanzapine injection. The half-life of olanzapine after olanzapine is 30 days compared to 30 hours following oral administration. The absorption and elimination are complete approximately six to eight months after the last injection.

Distribution
Oral olanzapine is rapidly distributed. The plasma protein binding of olanzapine is about 93% over the concentration range of 7 to about 1000 ng/mL. In plasma, olanzapine is bound to albumin and α_1-acid glycoprotein.

After repeated IM injections with 150 to 300 mg olanzapine every two weeks, the 10^{th} to 90^{th} percentile of steady-state plasma concentrations of olanzapine were between 4.2 and 73.2 ng/ml. The plasma concentrations of olanzapine observed across the dose range of 150mg every 4 weeks to 300mg every 2 weeks illustrate increased systemic olanzapine exposure with increased olanzapine doses. During the initial three months of treatment with olanzapine, accumulation of olanzapine was observed but there was no additional accumulation during long-term use (12 months) in patients who were injected with up to 300 mg every two weeks.

Elimination
Olanzapine plasma clearance after oral olanzapine is lower in females (18.9 l/hr) versus males (27.3 l/hr), and in non-smokers (18.6 l/hr) versus smokers (27.7 l/hr). Similar pharmacokinetic differences between males and females and smokers and non-smokers were observed in

olanzapine clinical trials. However, the magnitude of the impact of gender, or smoking on olanzapine clearance is small in comparison to the overall variability between individuals.

Elderly
No specific investigations have been conducted in the elderly with olanzapine. Olanzapine is not recommended for treatment in the elderly population (65 years and over) unless a well-tolerated and effective dosage regimen using oral olanzapine has been established. In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hours) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia >65 years of age, dosing from 5 to 20 mg/day was not associated with any distinguishing profile of adverse events.

Renal impairment
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 hours) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57% of radiolabelled olanzapine appeared in urine, principally as metabolites. Although patients with renal impairment were not studied with olanzapine, it is recommended that a well-tolerated and effective dosage regimen using oral olanzapine is established in patients with renal impairment before treatment with olanzapine is initiated.

Smokers
In smoking subjects with mild hepatic dysfunction, mean elimination half-life (39.3 hours) of orally administered olanzapine was prolonged and clearance (18.0 l/hr) was reduced analogous to non-smoking healthy subjects (48.8 hours and 14.1 l/hr, respectively). Although patients with hepatic impairment were not studied with olanzapine E, it is recommended that a well-tolerated and effective dosage regimen using oral olanzapine is established in patients with hepatic impairment before treatment with olanzapine is initiated.
In a study of oral olanzapine given to Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations.

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, laboured 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 haematology 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 anaemia developed in a few dogs treated with 8 or 10 mg/kg/day (total olanzapine exposure [area under the curve] is 12- to 15-fold greater than that of a man given a 12 mg 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.

Oestrous 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 foetal 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.

EXPIRY DATE
Do not use later than the date of expiry

DIRECTIONS
For IM use only after reconstitution.
To be reconstituted with Sterile Water for Injection I.P. (2 ml) just before use (Provided with this pack). Reconstituted injection is to be used within 1 hour, if stored at room temperature.

STORAGE AND HANDLING INSTRUCTIONS
Store at a temperature not exceeding 30°C, protected from light.
Do not freeze.
Keep all medicines out of reach of children.

PRESENTATION
Tolaz Injection is available as combipack of 10 mg in 5ml vial with 2ml ampoule of sterile water for injection as diluent.

MARKETED BY
torrent PHARMA
TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/TOLAZ INJECTION 10mg/MAY-17/02/PI