SUMMARY OF PRODUCT CHARACTERISTIC

1. Name of the Medicinal Product
Olmac 5/10

2. Qualitative and Quantitative Composition
Each tablet contains:
Olanzapine USP …… 5mg/10mg

For Excipients, see point 6.1

3. Pharmaceutical Form
Film-coated tablet

Olmac 5: White to off white coloured, round shaped, biconvex, film coated tablets having 'CL 42' debossed on one side and plain on other side.

Olmac 10: White to off white coloured, round shaped, biconvex, film coated tablets having 'CL 40' debossed on one side and plain on the other side

4. Clinical Particulars
4.1 Therapeutic indications
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 the treatment of moderate to severe manic episode.
- In patients whose manic episode has responded to Olanzapine treatment, Olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder

4.2 Posology and method of administration
Adults:
Schizophrenia: The recommended starting dose for Olanzapine is 10mg/day.
Manic episode: The starting dose is 15mg as a single daily dose in monotherapy or 10mg 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 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 5-20mg/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.

Special populations
Elderly patients:
A lower starting dose (5mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant.

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 5mg and only increased with caution.

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. The metabolism of Olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of Olanzapine dose may be considered if necessary.
When more than one factor is present which might result in slower metabolism (female gender, geriatric age, nonsmoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.

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 may occur in short-term studies of adolescent patients than in studies of adult patients.

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

4.4 Special warnings and precautions for use
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 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.
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 than in placebo-treated patients independent of these risk factors. Cerebrovascular adverse events (CVAE e.g., stroke, transient ischemic attack), including fatalities, were reported.

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 may occur.

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 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 creatinine 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 rarely, 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.

Lipid alterations
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 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 can occur 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 may occur 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 very rarely (<0.01%) 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 uncommonly. Patients with schizophrenia often may 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 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 may be associated with a statistical 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
As with other antipsychotics, it is recommended that blood pressure is measured periodically in patients over 65 years.

Sudden cardiac death
The event of sudden cardiac death may occur in patients with Olanzapine Treatment.

Paediatric population
Olanzapine is not indicated for use in the treatment of children and adolescents.

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

4.5 Interaction with other medicinal products and other forms of interaction
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, may show 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. 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.

4.6 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.

Lactation:
Patients should be advised not to breast-feed an infant if they are taking Olanzapine.

4.7 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.

4.8 Undesirable effects
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 (≥ 1/10,000to < 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[11]	
Immune system disorders				
		Hypersensitivity[11]		
Metabolism and nutrition disorders				
Weight gain1	Elevated cholesterol levels2,3	Development or exacerbation of	Hypothermia[12]	

	Elevated glucose levels4 Elevated triglyceride levels2,5 Glucosuria Increased appetite	diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4)[11]		
Nervous system disorders				
Somnolence	Dizziness Akathisia6 Parkinsonism6 Dyskinesia6	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 Stuttering[11] Restless legs syndrome[11]	Neuroleptic malignant syndrome (see section 4.4) [12] Discontinuation symptoms[7,12]	
Cardiac disorders				
		Bradycardia QTc prolongation (see section 4.4)	Ventricular tachycardia/fibrillation, sudden death (see section 4.4) [11]	
Vascular disorders				
Orthostatic hypotension[10]		Thromboembolism (including pulmonary embolism and deep vein thrombosis) **(see section 4.4)**.		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9] Salivary hypersecretion[11]	Pancreatitis[11]	
Hepato-biliary disorders				
	Transient, asymptomatic		Hepatitis (including hepatocellular,	

	elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4)		cholestatic or mixed liver injury) [11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		Drug Reaction 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 (see section 4.6)
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]	Increased total bilirubin		

	High Gamma Glutamyltransferase [10] High Uric Acid [10]			

[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 can not 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 ssociated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo (see section 4.4). 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.
Hepato-biliary disorders *Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16] .

[13]Following short-term treatment (median

Paediatric population
The following table summarises the adverse reactions reported with a greater frequency in adolescent patients (aged 13- 17 years) than in adult patients. 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.
Hepato-biliary disorders *Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16] .

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorization holder, or, if available, via the national reporting system (see details below);

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions*

4.9 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 450mg, but survival has also been reported following acute overdose of approximately 2g 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.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Olanzapine is an antipsychotic, antimanic, and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems. The mechanism of action of Olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism. The mechanism of action of Olanzapine in the treatment of acute manic or mixed episodes associated with bipolar I disorder is unknown.
Olanzapine binds with high affinity to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$ (Ki=4, 11, and 5 nM, respectively), dopamine D1-4 (Ki=11-31 nM), histamine H1 (Ki=7 nM), and adrenergic α1 receptors (Ki=19 nM).

Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT3 (Ki=57 nM) and muscarinic M1-5 (Ki=73, 96, 132, 32, and 48 nM, respectively).

Olanzapine binds weakly to GABAA, BZD, and β-adrenergic receptors (Ki > 10 μM).

5.2 Pharmacokinetic properties

Absorption
Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food. Absolute oral bioavailability relative to intravenous administration has not been determined.

Distribution
The plasma protein binding of Olanzapine was about 93% over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α1-acidglycoprotein.

Biotransformation
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 predominant pharmacologic activity is from the parent Olanzapine.

Elimination
After oral administration, the mean terminal elimination half-life of Olanzapine in healthy subjects varied on the basis of age and gender. In healthy elderly versus non-elderly subjects, the mean elimination half-life was prolonged and the clearance was reduced.
In female versus male subjects, the mean elimination half-life was somewhat prolonged and the clearance was reduced.

5.3 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, labored respiration, miosis, and anorexia. In monkeys, single oral doses up to 100 mg/kg resulted in prostration and, at higher doses, semiconsciousness.

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. Estrous 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 fetal 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.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystlline cellulose, Low substituted hydroxypropyl cellulose, Crospovidone, Magnesium Stearate, Opadry White AMB OY-B-28920, Purified Water

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C in a dry place. Protect from light and moisture.

6.5 Nature and contents of container

For 5mg:

Alu Alu Blister pack of 10 Tablets

For 10mg:

HDPE container pack of 30Tablets
Alu Alu Blister pack of 10 Tablets

6.6 Special Precaution for disposal

None.

7. Supplier

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8. Date of Revision of the Text:

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