

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Calmood 5 mg film coated tablets.

2. Qualitative and quantitative composition

Each film-coated tablet contains
Olanzapine 5 mg.

Excipients with known effect:
Lactose 75.5 mg.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablets

Round, blue, coated tablets.

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 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.

Special populations

Elderly

A lower starting dose (5 mg/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 (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.

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, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients. In cases where dose increments of 2.5 mg are considered necessary, CALMOOD coated tablets should be used.

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. 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. 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 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 olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient ischaemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in patients treated with olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All 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 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. 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 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 CALMOOD, 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 CALMOOD, 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 ($\geq 0.01\%$ and $< 0.1\%$) when olanzapine is stopped abruptly.

QT interval

In clinical trials, 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. 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 ($\geq 0.1\%$ 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.

Lactose

CALMOOD 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

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.

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.

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.

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

Summary of the safety profile Adults

The most frequently (seen in $\geq 1\%$ 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 inclinal trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the data available).

Syste m Orga n Class	Ve ry Co m mo n	Comm on	Uncom mon	Rare	Not Known
Blood and lymp hatic syste m disor ders	—	—	Eosinop hilia	Leukope nia ¹⁰ , neutrop enia ¹⁰	Thrombo cytopenia ¹¹
Imm une syste m	—	—	—	Hyperse nsitivity ¹	—

disorders					
Metabolism and nutrition disorders	Increased appetite	Weight gain ¹	Elevated cholesterol levels ^{2, 3} ; elevated glucose levels ⁴ ; elevated triglyceride levels ^{2, 5} ; glucosuria	—	Development or exacerbation of diabetes, occasionally associated with ketoacidosis or coma, including some fatal cases ¹¹ ; hypothermia ¹²
Nervous system disorders	Somnolence	Dizziness	Akathisia ⁶ , Parkinsonism ⁶ , dyskinesia ⁶	Neuroleptic malignant syndrome ¹² ; seizures, in most cases associated with a history of seizures or seizure risk factors ¹¹ ; dystonia including oculogyration ¹¹ ; tardive dyskinesia ¹¹ ; amnesia ⁹ ; dysarthria; stuttering ¹¹ ; restless legs syndrome ¹¹	—

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	Salivary hypersecretion ¹¹	Pancreatitis ¹¹
Hepatobiliary disorders	—	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially	—	—	Hepatitis, including hepatocellular, cholestatic or mixed liver injury ¹¹

		ally during early treatm ent			
Skin and subcu taneo us tissu e disor ders	—	Rash	Photose nsitivity reaction	Alopecia	Drug reaction with eosinophi lia and systemic symptom s (DRESS)
Musc ulosk eletal and conn ectiv e tissu e disor ders	—	—	Arthralgi a ⁹	—	Rhabdom yolysis ¹¹
Renal and urina ry disor ders	—	Urinar y incont inence , urinar y retenti on	—	Urinary hesitatio n ¹¹	—
Pregn ancy, puerp eriu m and perin atal condi tions	—	—	—	—	Neonatal drug withdraw al syndrom e
Repr oduct ive syste m and breas t disor ders	—	Erectil e dysfun ction in males; decrea sed libido in males and female s	Amenorr hoea, breast enlarge ment, galactorr hoea in females; gynaeco mastia/ breast enlarge ment in males	—	Priapism ^{1 2}

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-glutamyl transferase ¹⁰ ; high uric acid ¹⁰	Increased total bilirubin

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; QTc = corrected QT interval.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

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 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code: N05AH03.

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 ($K_i < 100$ nM) for serotonin 5 HT_{2A/2C}, 5 HT₃, 5 HT₆; dopamine D₁, D₂, D₃, D₄, D₅; cholinergic muscarinic receptors M₁-M₅; α_1 adrenergic; and histamine H₁ 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 5 HT₂ than dopamine D₂ receptors and greater 5 HT₂ than D₂ activity 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 5 HT_{2A} than dopamine D₂ receptor occupancy. In addition, a Single Photon Emission Computed Tomography (SPECT) imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D₂ occupancy than some other antipsychotic- and risperidone responsive patients, while being comparable to clozapine-responsive patients.

Clinical efficacy

In two of two placebo and two of three comparator-controlled trials with over 2,900 schizophrenic patients presenting with both positive and negative symptoms, olanzapine was associated with statistically significantly greater improvements in negative as well as positive symptoms. In a multinational, double-blind, comparative study of

schizophrenia, schizoaffective, and related disorders which included 1,481 patients with varying degrees of associated depressive symptoms (baseline mean of 16.6 on the Montgomery-Asberg Depression Rating Scale), a prospective secondary analysis of baseline to endpoint mood score change demonstrated a statistically significant improvement ($p=0.001$) favouring olanzapine (-6.0) versus haloperidol (-3.1). In patients with a manic or mixed episode of bipolar disorder, olanzapine demonstrated superior efficacy to placebo and valproate semisodium (divalproex) in reduction of manic symptoms over 3 weeks. Olanzapine also demonstrated comparable efficacy results to haloperidol in terms of the proportion of patients in symptomatic remission from mania and depression at 6 and 12 weeks. In a co-therapy study of patients treated with lithium or valproate for a minimum of 2 weeks, the addition of olanzapine 10 mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

In a 12-month recurrence prevention study in manic episode patients who achieved remission on olanzapine and were then randomised to olanzapine or placebo, olanzapine demonstrated statistically significant superiority over placebo on the primary endpoint of bipolar recurrence. Olanzapine also showed a statistically significant advantage over placebo in terms of preventing either recurrence into mania or recurrence into depression.

In a second 12-month recurrence prevention study in manic episode patients who achieved remission with a combination of olanzapine and lithium and were then randomised to olanzapine or lithium alone, olanzapine was statistically non-inferior to lithium on the primary endpoint of bipolar recurrence (olanzapine 30.0%, lithium 38.3%; $p=0.055$).

In an 18-month co-therapy study in manic or mixed episode patients stabilised with olanzapine plus a mood stabiliser (lithium or valproate), long-term olanzapine cotherapy with lithium or valproate was not statistically significantly superior to lithium or valproate alone in delaying bipolar recurrence, defined according to syndromic (diagnostic) criteria.

Paediatric population

Controlled efficacy data in adolescents (ages 13 to 17 years) are limited to short term studies in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin (see sections 4.4 and 4.8) were greater in adolescents than in adults. There are no controlled data on maintenance of effect or long term safety (see sections 4.4 and 4.8). Information on long term safety is primarily limited to open-label, uncontrolled data.

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 α 1-acid-glycoprotein.

Biotransformation

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 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 (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hr) 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. In female versus male subjects the mean elimination half life was somewhat prolonged (36.7 versus 32.3 hr) and the clearance was reduced (18.9 versus 27.3 l/hr). However, olanzapine (5-20 mg) demonstrated a comparable safety profile in female (n=467) as in male patients (n=869).

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 hr) 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.

Hepatic impairment

A small study of the effect of impaired liver function in 6 subjects with clinically significant (Childs Pugh Classification A (n = 5) and B (n = 1)) cirrhosis revealed little effect on the pharmacokinetics of orally administered olanzapine (2.5 – 7.5 mg single dose): Subjects with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster elimination half-time compared to subjects with no hepatic dysfunction (n = 3). There were more smokers among subjects

with cirrhosis (4/6; 67 %) than among subjects with no hepatic dysfunction (0/3; 0 %).

Smoking

In non-smoking versus smoking subjects (males and females) the mean elimination half-life was prolonged (38.6 versus 30.4 hr) and the clearance was reduced (18.6 versus 27.7 l/hr). The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals. In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations.

Paediatric population

Adolescents (ages 13 to 17 years): The pharmacokinetics of olanzapine are similar between adolescents and adults. In clinical studies, the average olanzapine exposure was approximately 27% higher in adolescents. Demographic differences between the adolescents and adults include a lower average body weight and fewer adolescents were smokers. Such factors possibly contribute to the higher average exposure observed in adolescents.

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, 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 doserelated 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 [AUC] 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 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.

6. Pharmaceutical Particulars

6.1 List of Excipients

Lactose BP
Hydroxypropyl cellulose 5 cps
Crospovidone USP
Purified water
Sodium stearyl fumarate USP
Microcrystalline cellulose USP
SEAL COAT
Tabcoat TC
Isopropyl alcohol BP
FILM COAT
Opadry QX
Brilliant blue water soluble

6.2 Incompatibilities

None

6.3 Shelf-Life

24 Months

6.4 Special Precautions for storage

None

6.5 Nature and Content of container

Tablets, 14 Tablets, 20 Tablets, 28 Tablets, 30 Tablets, 56 Tablets, 100 Tablets and 112 Tablets packed in blisters in cartons with literature insert

6.6 Special precautions for disposal and other handling

None

7. Marketing Authorization Holder

Cosmos Limited

P.O. Box 41433

GPO 00100-Nairobi, Kenya

8. Marketing Authorization Number

H2025/CTD11439/24680

9. Date of first authorization/renewal of the authorization

10/07/2025

10. Date of revision of the text

24/08/2026