**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 2.5 mg coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 2.5 mg olanzapine.

Excipient with known effect: Each coated tablet contains 80.7 mg lactose monohydrate

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Coated tablet

White, round, biconvex, coated tablets with '2.5' debossing on one side and 'CL2' on the other.

## 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 (see section 5.1).

### 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 (see section 5.1).

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 regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

*Paediatric population*
Olanzapine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in short term studies of adolescent patients than in studies of adult patients (see sections 4.4, 4.8, 5.1 and 5.2).

*Elderly patients*
A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant (see section 4.4).

*Patients with renal and/or hepatic impairment*
A lower starting dose (5 mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5 mg and only increased with caution.

*Gender*
The starting dose and dose range need not be routinely altered for female patients relative to male patients.

*Smokers*
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers.

When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.

(See sections 4.5 and 5.2)

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk for 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 approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. 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 ischemic 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 (see section 4.8), 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 (see section 4.8). 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 agents, including Olanzapine Cipla, 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 (see section 4.8). 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 Cipla, 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 (see section 4.8).

*Discontinuation of treatment*
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported rarely ( ≥ 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, 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 (≥ 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 antagonize the effects of direct and indirect dopamine agonists.

*Seizures*
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur 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. As with other antipsychotics, 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. Long-term outcomes associated with these events have not been studied and remain unknown (see sections 4.8 and 5.1).

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

**4.5 Interaction with other medicinal products and other forms of interaction**

*Paediatric population*
Interaction studies have only been performed in adults.

*Potential interactions affecting olanzapine*
Since olanzapine is metabolised by CYP1A2, substances that selectively 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 (see section 4.2).

*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 (see section 4.4).

*QTc interval*
Caution should be used if olanzapine is being administered concomitantly with medicinal products known to increase QTc interval (see section 4.4).

## 4.6 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.

Neonates 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, hypotonis, 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.

## 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

*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 (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases (see section 4.4), 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 |
|---|---|---|---|
| **Blood and the lymphatic system disorders** | | | |
| | Eosinophilia<br>Leukopenia[10]<br>Neutropenia[10] | | Thrombocytopenia[11] |
| **Immune system disorders** | | | |
| | | Hypersensitivity[11] | |
| **Metabolism and nutrition disorders** | | | |
| Weight gain[1] | Elevated cholesterol levels[2,3]<br>Elevated glucose levels[4]<br>Elevated triglyceride levels[2,5]<br>Glucosuria<br>Increased appetite | Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4) [11] | Hypothermia[12] |
| **Nervous system disorders** | | | |
| Somnolence | Dizziness<br>Akathisia[6]<br>Parkinsonism[6]<br>Dyskinesia[6] | Seizures where in most cases a history of seizures or risk factors for seizures were reported [11]<br><br>Dystonia (including oculogyration) [11]<br>Tardive dyskinesia[11]<br><br>Amnesia [9]<br><br>Dysarthria | Neuroleptic malignant syndrome (see section 4.4)[12]<br><br>Discontinuation symptoms[7, 12] |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| | | Epistaxis[9] | |
| **Cardiac disorders** | | | |
| | | Bradycardia<br>$QT_c$ 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) | |
| **Gastrointestinal disorders** | | | |
| | Mild, transient anticholinergic effects including constipation and dry mouth | Abdominal distension[9] | Pancreatitis[11] |
| **Hepato-biliary disorders** | | | |
| | Transient, asymptomatic elevations of hepatic aminotransferases | | Hepatitis (including hepatocellular, cholestatic or mixed liver injury)[11] |

| | | | |
|---|---|---|---|
| | (ALT, AST), especially in early treatment (see section 4.4) | | |
| **Skin and subcutaneous tissue disorders** | | | |
| | Rash | Photosensitivity reaction<br>Alopecia | |
| **Musculoskeletal and connective tissue disorders** | | | |
| | Arthralgia[9] | | Rhabdomyolysis[11] |
| **Renal and urinary disorders** | | | |
| | | Urinary incontinence, urinary retention<br>Urinary hesitation[11] | |
| | | | |
| | | | |
| **Reproductive system and breast disorders** | | | |
| | Erectile dysfunction in males<br>Decreased libido in males and females | Amenorrhea<br>Breast enlargement<br>Galactorrhea in females<br>Gynaecomastia/breast enlargement in males | Priapism[12] |
| **General disorders and administration site conditions** | | | |
| | Asthenia<br>Fatigue<br>Oedema<br>Pyrexia[10] | | |
| **Investigations** | | | |
| Elevated plasma prolactin levels[8] | Increased alkaline phosphatase[10]<br>High creatine phosphokinase[11]<br>High Gamma Glutamyltransferase[10]<br>High Uric Acid [10] | Increased total bilirubin | |
| | | | **Not known** |
| **Pregnancy, puerperium and perinatal conditions** | | | |
| | | | Drug withdrawal syndrome neonatal (see section 4.6) |



[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 (see also 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**<br>*Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite.<br>*Common:* Elevated cholesterol levels[15] |
| **Nervous system disorders**<br>*Very common:* Sedation (including: hypersomnia, lethargy, somnolence). |
| **Gastrointestinal disorders**<br>*Common:* Dry mouth |
| **Hepato-biliary disorders**<br>*Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4). |
| **Investigations**<br>*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.

## 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: diazepines, oxazepines and thiazepines., 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 ($K_i$ < 100 nM) for serotonin 5 $HT_{2A/2C}$, 5 $HT_3$, 5 $HT_6$; dopamine $D_1$, $D_2$, $D_3$, $D_4$, $D_5$; cholinergic muscarinic receptors $M_1$-$M_5$; $\alpha_1$ 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 5 $HT_2$ than $D_2$ 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 $D_2$ 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*
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 co-therapy 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*
The experience in adolescents (ages 13 to 17 years) is limited to short term efficacy data 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 data on maintenance of effect and limited data on long term safety (see sections 4.4 and 4.8).

## 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 $\alpha_1$-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.

*Smokers*
In smoking subjects with mild hepatic dysfunction, mean elimination half-life (38.8 hr) was prolonged and clearance (18.0 l/hr) was reduced analogous to non-smoking healthy subjects (48.8 hr and 14.1 l/hr, respectively).

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 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 [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

*Tablet core*
Lactose monohydrate,
Maize starch
Hydroxypropyl cellulose
Magnesium stearate

*Tablet coat*
Opadry II White containing:
Hypromellose (E464)
Titanium dioxide (E171)
Lactose monohydrate
Polyethylene glycol 3000
Glycerol triacetate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store in the original package.

Store below 30°C.

### 6.5 Nature and contents of container

Cold-formed aluminium blisters in cartons of 28 or 56 tablets per carton.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Cipla (EU) Limited
Hillbrow House
Hillbrow Road
Esher
Surrey
KT10 9NW
UK

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/426/001 – Olanzapine Cipla – 2.5 mg – coated tablets – 28 tablets per box

EU/1/07/426/002 – Olanzapine Cipla – 2.5 mg – coated tablets – 56 tablets per box

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 November 2007

Date of latest renewal: 01 October 2012

## 10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/.

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 5 mg coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 5 mg olanzapine.

Excipient with known effect: Each coated tablet contains 161.3 mg lactose monohydrate

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Coated tablet

White, round, biconvex, coated tablets with 'OLZ 5' debossing on one side and 'NEO' on the other.

## 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 (see section 5.1).

### 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 (see section 5.1).

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 regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

*Paediatric population*
Olanzapine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in short term studies of adolescent patients than in studies of adult patients (see sections 4.4, 4.8, 5.1 and 5.2).

*Elderly patients*
A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant (see section 4.4).

*Patients with renal and/or hepatic impairment*
A lower starting dose (5 mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5 mg and only increased with caution.

*Gender*
The starting dose and dose range need not be routinely altered for female patients relative to male patients.

*Smokers*
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers.

When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.

(See sections 4.5 and 5.2)

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk for 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 approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. 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 ischemic 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 (see section 4.8), 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 (see section 4.8). 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 agents, including Olanzapine Cipla, 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 (see section 4.8). 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 Cipla, 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 (see section 4.8).

*Discontinuation of treatment*
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported rarely ( ≥ 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, 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 (≥ 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 antagonize the effects of direct and indirect dopamine agonists.

*Seizures*
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur 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. As with other antipsychotics, 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. Long-term outcomes associated with these events have not been studied and remain unknown (see sections 4.8 and 5.1).

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

## 4.5 Interaction with other medicinal products and other forms of interaction

*Paediatric population*
Interaction studies have only been performed in adults.

*Potential interactions affecting olanzapine*
Since olanzapine is metabolised by CYP1A2, substances that selectively 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 (see section 4.2).

*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 (see section 4.4).

*QTc interval*
Caution should be used if olanzapine is being administered concomitantly with medicinal products known to increase QTc interval (see section 4.4).

## 4.6 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.

Neonates 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, hypotonis, 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.

## 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

*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 (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases (see section 4.4), 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 |
|---|---|---|---|
| **Blood and the lymphatic system disorders** | | | |
| | Eosinophilia<br>Leukopenia[10]<br>Neutropenia[10] | | Thrombocytopenia[11] |
| **Immune system disorders** | | | |
| | | Hypersensitivity[11] | |
| **Metabolism and nutrition disorders** | | | |
| Weight gain[1] | Elevated cholesterol levels[2,3]<br>Elevated glucose levels[4]<br>Elevated triglyceride levels[2,5]<br>Glucosuria<br>Increased appetite | Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4) [11] | Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4)<br>Hypothermia[12] |
| **Nervous system disorders** | | | |
| Somnolence | Dizziness<br>Akathisia[6]<br>Parkinsonism[6]<br>Dyskinesia[6] | Seizures where in most cases a history of seizures or risk factors for seizures were reported [11]<br>Dystonia (including oculogyration)[11]<br>Tardive dyskinesia[11]<br><br>Amnesia [9]<br><br>Dysarthria | Neuroleptic malignant syndrome (see section 4.4)[12]<br><br>Discontinuation symptoms[7, 12] |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| | | Epistaxis[9] | |
| **Cardiac disorders** | | | |
| | | Bradycardia<br>$QT_c$ 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) | |
| **Gastrointestinal disorders** | | | |
| | Mild, transient anticholinergic effects including constipation and dry mouth | Abdominal distension[9] | Pancreatitis[11] |
| **Hepato-biliary disorders** | | | |
| | Transient, asymptomatic elevations of hepatic aminotransferases | | Hepatitis (including hepatocellular, cholestatic or mixed liver injury)[11] |

| | | | |
|---|---|---|---|
| | (ALT, AST), especially in early treatment (see section 4.4) | | |
| **Skin and subcutaneous tissue disorders** | | | |
| | Rash | Photosensitivity reaction<br>Alopecia | |
| **Musculoskeletal and connective tissue disorders** | | | |
| | Arthralgia[9] | | Rhabdomyolysis |
| **Renal and urinary disorders** | | | |
| | | Urinary incontinence, urinary retention<br>Urinary hesitation[11] | |
| | | | |
| | | | |
| **Reproductive system and breast disorders** | | | |
| | Erectile dysfunction in males<br>Decreased libido in males and females | Amenorrhea<br>Breast enlargement<br>Galactorrhea in females<br>Gynaecomastia/breast enlargement in males | Priapism[12] |
| **General disorders and administration site conditions** | | | |
| | Asthenia<br>Fatigue<br>Oedema<br>Pyrexia[10] | | |
| **Investigations** | | | |
| Elevated plasma prolactin levels[8] | Increased alkaline phosphatase[10]<br>High creatine phosphokinase[11]<br>High Gamma Glutamyltransferase [10]<br>High Uric Acid [10] | Increased total bilirubin | |
| | | | **Not known** |
| **Pregnancy, puerperium and perinatal conditions** | | | |
| | | | Drug withdrawal syndrome neonatal (see section 4.6) |



[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 (see also 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**<br>*Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite.<br>*Common:* Elevated cholesterol levels[15] |
| **Nervous system disorders**<br>*Very common:* Sedation (including: hypersomnia, lethargy, somnolence). |
| **Gastrointestinal disorders**<br>*Common:* Dry mouth |
| **Hepato-biliary disorders**<br>*Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4). |
| **Investigations**<br>*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.**

## 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: diazepines, oxazepines and thiazepines., 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 ($K_i$ < 100 nM) for serotonin 5 $HT_{2A/2C}$, 5 $HT_3$, 5 $HT_6$; dopamine $D_1$, $D_2$, $D_3$, $D_4$, $D_5$; cholinergic muscarinic receptors $M_1$-$M_5$; $\alpha_1$ 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 5 $HT_2$ than $D_2$ 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 $D_2$ 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*
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 co-therapy 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*
The experience in adolescents (ages 13 to 17 years) is limited to short term efficacy data 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 data on maintenance of effect and limited data on long term safety (see sections 4.4 and 4.8).

## 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 $\alpha_1$-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.

*Smokers*
In smoking subjects with mild hepatic dysfunction, mean elimination half-life (38.8 hr) was prolonged and clearance (18.0 l/hr) was reduced analogous to non-smoking healthy subjects (48.8 hr and 14.1 l/hr, respectively).

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 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 [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

*Tablet core*
Lactose monohydrate,
Maize starch
Hydroxypropyl cellulose
Magnesium stearate

*Tablet coat*
Opadry II White containing:
Hypromellose (E464)
Titanium dioxide (E171)
Lactose monohydrate
Polyethylene glycol 3000
Glycerol triacetate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store in the original package.

Store below 30°C.

### 6.5 Nature and contents of container

Cold-formed aluminium blisters in cartons of 28 or 56 tablets per carton.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Cipla (EU) Limited
Hillbrow House
Hillbrow Road
Esher
Surrey
KT10 9NW
UK

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/426/003 – Olanzapine Cipla – 5 mg – coated tablets – 28 tablets per box

EU/1/07/426/004 – Olanzapine Cipla – 5 mg – coated tablets – 56 tablets per box

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 November 2007

Date of latest renewal: 01 October 2012

## 10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/.

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 7.5 mg coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 7.5 mg olanzapine.

Excipient with known effect: Each coated tablet contains 242 mg lactose monohydrate

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Coated tablet

White, round, biconvex, coated tablets with 'OLZ 7.5' debossing on one side and 'NEO' on the other.



## 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 (see section 5.1).

### 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 (see section 5.1).

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 regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

*Paediatric population*
Olanzapine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in short term studies of adolescent patients than in studies of adult patients (see sections 4.4, 4.8, 5.1 and 5.2).

*Elderly patients*
A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant (see section 4.4).

*Patients with renal and/or hepatic impairment*
A lower starting dose (5 mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5 mg and only increased with caution.

*Gender*
The starting dose and dose range need not be routinely altered for female patients relative to male patients.

*Smokers*
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers.

When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.

(See sections 4.5 and 5.2)

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk for 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 approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. 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 ischemic 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 (see section 4.8), 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 (see section 4.8). 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 agents, including Olanzapine Cipla, 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 (see section 4.8). 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 Cipla, 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 (see section 4.8).

*Discontinuation of treatment*
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported rarely (≥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, 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 (≥ 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 antagonize the effects of direct and indirect dopamine agonists.

*Seizures*
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur 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. As with other antipsychotics, 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. Long-term outcomes associated with these events have not been studied and remain unknown (see sections 4.8 and 5.1).

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



## 4.5 Interaction with other medicinal products and other forms of interaction

*Paediatric population*
Interaction studies have only been performed in adults.

*Potential interactions affecting olanzapine*
Since olanzapine is metabolised by CYP1A2, substances that selectively 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 (see section 4.2).

*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 (see section 4.4).

*QTc interval*
Caution should be used if olanzapine is being administered concomitantly with medicinal products known to increase QTc interval (see section 4.4).

## 4.6 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.

Neonates 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, hypotonis, 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.

## 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

*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 (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases (see section 4.4), 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 |
|---|---|---|---|
| **Blood and the lymphatic system disorders** | | | |
| | Eosinophilia<br>Leukopenia[10]<br>Neutropenia[10] | | Thrombocytopenia[11] |
| **Immune system disorders** | | | |
| | | Hypersensitivity[11] | |
| **Metabolism and nutrition disorders** | | | |
| Weight gain[1] | Elevated cholesterol levels[2,3]<br>Elevated glucose levels[4]<br>Elevated triglyceride levels[2,5]<br>Glucosuria<br>Increased appetite | Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4) [11] | Hypothermia[12] |
| **Nervous system disorders** | | | |
| Somnolence | Dizziness<br>Akathisia[6]<br>Parkinsonism[6]<br>Dyskinesia[6] | Seizures where in most cases a history of seizures or risk factors for seizures were reported [11]<br><br>Dystonia (including oculogyration)[11]<br>Tardive dyskinesia[11]<br><br>Amnesia [9]<br><br>Dysarthria | Neuroleptic malignant syndrome (see section 4.4)<br>Discontinuation symptoms[7, 12] |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| | | Epistaxis[9] | |
| **Cardiac disorders** | | | |
| | | Bradycardia<br>$QT_c$ 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) | |
| **Gastrointestinal disorders** | | | |
| | Mild, transient anticholinergic effects including constipation and dry mouth | Abdominal distension[9] | Pancreatitis[11] |
| **Hepato-biliary disorders** | | | |
| | Transient, asymptomatic elevations of hepatic aminotransferases | | Hepatitis (including hepatocellular, cholestatic or mixed liver injury)[11] |

| | | | |
|---|---|---|---|
| | (ALT, AST), especially in early treatment (see section 4.4) | | |
| **Skin and subcutaneous tissue disorders** | | | |
| | Rash | Photosensitivity reaction<br>Alopecia | |
| **Musculoskeletal and connective tissue disorders** | | | |
| | Arthralgia[9] | | Rhabdomyolysis[11] |
| **Renal and urinary disorders** | | | |
| | | Urinary incontinence, urinary retention<br>Urinary hesitation[11] | Urinary hesitation |
| | | | |
| | | | |
| **Reproductive system and breast disorders** | | | |
| | Erectile dysfunction in males<br>Decreased libido in males and females | Amenorrhea<br>Breast enlargement<br>Galactorrhea in females<br>Gynaecomastia/breast enlargement in males | Priapism[12] |
| **General disorders and administration site conditions** | | | |
| | Asthenia<br>Fatigue<br>Oedema<br>Pyrexia[10] | | |
| **Investigations** | | | |
| Elevated plasma prolactin levels[8] | Increased alkaline phosphatase[10]<br>High creatine phosphokinase[11]<br>High Gamma Glutamyltransferase [10]<br>High Uric Acid [10] | Increased total bilirubin | |
| | | | **Not known** |
| **Pregnancy, puerperium and perinatal conditions** | | | |
| | | | Drug withdrawal syndrome neonatal (see section 4.6) |

[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 (see also 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**<br>*Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite.<br>*Common:* Elevated cholesterol levels[15] |
| **Nervous system disorders**<br>*Very common:* Sedation (including: hypersomnia, lethargy, somnolence). |
| **Gastrointestinal disorders**<br>*Common:* Dry mouth |
| **Hepato-biliary disorders**<br>*Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4). |
| **Investigations**<br>*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.

## 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: diazepines, oxazepines and thiazepines., 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 ($K_i$ < 100 nM) for serotonin 5 $HT_{2A/2C}$, 5 $HT_3$, 5 $HT_6$; dopamine $D_1$, $D_2$, $D_3$, $D_4$, $D_5$; cholinergic muscarinic receptors $M_1$-$M_5$; $\alpha_1$ 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 5 $HT_2$ than $D_2$ 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 $D_2$ 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*
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 co-therapy 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*
The experience in adolescents (ages 13 to 17 years) is limited to short term efficacy data 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 data on maintenance of effect and limited data on long term safety (see sections 4.4 and 4.8).



## 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 $\alpha_1$-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.

*Smokers*
In smoking subjects with mild hepatic dysfunction, mean elimination half-life (39.3 hr) was prolonged and clearance (18.0 l/hr) was reduced analogous to non-smoking healthy subjects (48.8 hr and 14.1 l/hr, respectively).

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 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 [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

*Tablet core*
Lactose monohydrate,
Maize starch
Hydroxypropyl cellulose
Magnesium stearate

*Tablet coat*
Opadry II White containing:
Hypromellose (E464)
Titanium dioxide (E171)
Lactose monohydrate
Polyethylene glycol 3000
Glycerol triacetate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store in the original package.

Store below 30°C.

### 6.5 Nature and contents of container

Cold-formed aluminium blisters in cartons of 28 or 56 tablets per carton.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Cipla (EU) Limited
Hillbrow House
Hillbrow Road
Esher
Surrey
KT10 9NW
UK

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/426/005 – Olanzapine Cipla – 7.5 mg – coated tablets – 28 tablets per box

EU/1/07/426/006 – Olanzapine Cipla – 7.5 mg – coated tablets – 56 tablets per box

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 November 2007

Date of latest renewal: 01 October 2012

## 10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/.

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 10 mg coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 10 mg olanzapine.

Excipient with known effect: Each coated tablet contains 322.6 mg lactose monohydrate

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Coated tablet

White, round, biconvex, coated tablets with 'OLZ 10' debossing on one side and 'NEO' on the other.

## 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 (see section 5.1).

### 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 (see section 5.1).

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 regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

*Paediatric population*
Olanzapine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in short term studies of adolescent patients than in studies of adult patients (see sections 4.4, 4.8, 5.1 and 5.2).

*Elderly patients*
A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant (see section 4.4).

*Patients with renal and/or hepatic impairment*
A lower starting dose (5 mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5 mg and only increased with caution.

*Gender*
The starting dose and dose range need not be routinely altered for female patients relative to male patients.

*Smokers*
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers.

When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.

(See sections 4.5 and 5.2)

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk for 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 approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. 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 ischemic 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 (see section 4.8), 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 (see section 4.8). 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 agents, including Olanzapine Cipla, 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 (see section 4.8). 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 Cipla, 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 (see section 4.8).

*Discontinuation of treatment*
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported rarely (≥ 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, 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 (≥ 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 antagonize the effects of direct and indirect dopamine agonists.

*Seizures*
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur 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. As with other antipsychotics, 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. Long-term outcomes associated with these events have not been studied and remain unknown (see sections 4.8 and 5.1).

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



## 4.5 Interaction with other medicinal products and other forms of interaction

*Paediatric population*
Interaction studies have only been performed in adults.

*Potential interactions affecting olanzapine*
Since olanzapine is metabolised by CYP1A2, substances that selectively 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 (see section 4.2).

*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 (see section 4.4).

*QTc interval*
Caution should be used if olanzapine is being administered concomitantly with medicinal products known to increase QTc interval (see section 4.4).

## 4.6 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.

Neonates 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, hypotonis, 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.

## 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

*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 (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases (see section 4.4), 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 |
|---|---|---|---|
| **Blood and the lymphatic system disorders** | | | |
| | Eosinophilia<br>Leukopenia[10]<br>Neutropenia[10] | | Thrombocytopenia[11] |
| **Immune system disorders** | | | |
| | | Hypersensitivity[11] | |
| **Metabolism and nutrition disorders** | | | |
| Weight gain[1] | Elevated cholesterol levels[2,3]<br>Elevated glucose levels[4]<br>Elevated triglyceride levels[2,5]<br>Glucosuria<br>Increased appetite | Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4) [11] | Hypothermia[12] |
| **Nervous system disorders** | | | |
| Somnolence | Dizziness<br>Akathisia[6]<br>Parkinsonism[6]<br>Dyskinesia[6] | Seizures where in most cases a history of seizures or risk factors for seizures were reported[11]<br><br>Dystonia (including oculogyration)[11]<br>Tardive dyskinesia[11]<br><br>Amnesia [9]<br><br>Dysarthria | Neuroleptic malignant syndrome (see section 4.4)[12]<br><br>Discontinuation symptoms[7, 12] |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| | | Epistaxis[9] | |
| **Cardiac disorders** | | | |
| | | Bradycardia<br>$QT_c$ 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) | |
| **Gastrointestinal disorders** | | | |
| | Mild, transient anticholinergic effects including constipation and dry mouth | Abdominal distension[9] | Pancreatitis[11] |
| **Hepato-biliary disorders** | | | |
| | Transient, asymptomatic elevations of hepatic aminotransferases | | Hepatitis (including hepatocellular, cholestatic or mixed liver injury)[11] |

| Very common | Common | Uncommon | Rare |
|---|---|---|---|
| | (ALT, AST), especially in early treatment (see section 4.4) | | |
| **Skin and subcutaneous tissue disorders** | | | |
| | Rash | Photosensitivity reaction<br>Alopecia | |
| **Musculoskeletal and connective tissue disorders** | | | |
| | Arthralgia[9] | | Rhabdomyolysis[11] |
| **Renal and urinary disorders** | | | |
| | | Urinary incontinence, urinary retention<br>Urinary hesitation[11] | |
| | | | |
| | | | |
| **Reproductive system and breast disorders** | | | |
| | Erectile dysfunction in males<br>Decreased libido in males and females | Amenorrhea<br>Breast enlargement<br>Galactorrhea in females<br>Gynaecomastia/breast enlargement in males | Priapism[12] |
| **General disorders and administration site conditions** | | | |
| | Asthenia<br>Fatigue<br>Oedema<br>Pyrexia[10] | | |
| **Investigations** | | | |
| Elevated plasma prolactin levels[8] | Increased alkaline phosphatase[2]<br>High creatine phosphokinase[11]<br>High Gamma Glutamyltransferase [10]<br>High Uric Acid [10] | Increased total bilirubin | |
| | | | **Not known** |
| **Pregnancy, puerperium and perinatal conditions** | | | |
| | | | Drug withdrawal syndrome neonatal (see section 4.6) |

[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 (see also 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**<br>*Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite.<br>*Common:* Elevated cholesterol levels[15] |
| **Nervous system disorders**<br>*Very common:* Sedation (including: hypersomnia, lethargy, somnolence). |
| **Gastrointestinal disorders**<br>*Common:* Dry mouth |
| **Hepato-biliary disorders**<br>*Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4). |
| **Investigations**<br>*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.

## 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: diazepines, oxazepines and thiazepines., 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 ($K_i$ < 100 nM) for serotonin 5 $HT_{2A/2C}$, 5 $HT_3$, 5 $HT_6$; dopamine $D_1$, $D_2$, $D_3$, $D_4$, $D_5$; cholinergic muscarinic receptors $M_1$-$M_5$; $\alpha_1$ 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 5 $HT_2$ than $D_2$ 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 $D_2$ 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*

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 co-therapy 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*
The experience in adolescents (ages 13 to 17 years) is limited to short term efficacy data 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 data on maintenance of effect and limited data on long term safety (see sections 4.4 and 4.8).



## 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 $\alpha_1$-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=886).

*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.

*Smokers*
In smoking subjects with mild hepatic dysfunction, mean elimination half-life (39.3 hr) was prolonged and clearance (18.0 l/hr) was reduced analogous to non-smoking healthy subjects (48.8 hr and 14.1 l/hr, respectively).

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 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 [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

*Tablet core*
Lactose monohydrate,
Maize starch
Hydroxypropyl cellulose
Magnesium stearate

*Tablet coat*
Opadry II White containing:
Hypromellose (E464)
Titanium dioxide (E171)
Lactose monohydrate
Polyethylene glycol 3000
Glycerol triacetate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store in the original package.

Store below 30°C.

### 6.5 Nature and contents of container

Cold-formed aluminium blisters in cartons of 7, 28 or 56 tablets per carton.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

No special requirements.



## 7. MARKETING AUTHORISATION HOLDER

Cipla (EU) Limited
Hillbrow House
Hillbrow Road
Esher
Surrey
KT10 9NW
UK

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/426/007 – Olanzapine Cipla – 10 mg – coated tablets – 7 tablets per box

EU/1/07/426/008 – Olanzapine Cipla – 10 mg – coated tablets – 28 tablets per box

EU/1/07/426/009 – Olanzapine Cipla – 10 mg – coated tablets – 56 tablets per box

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 November 2007

Date of latest renewal: 01 October 2012

## 10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/.

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 15 mg coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 15 mg olanzapine.

Excipient with known effect: Each coated tablet contains 315 mg lactose monohydrate

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Coated tablet

Blue, elliptical, convex, coated tablets with 'NEO' 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 (see section 5.1).

### 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 (see section 5.1).

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 regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

*Paediatric population*
Olanzapine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in short term studies of adolescent patients than in studies of adult patients (see sections 4.4, 4.8, 5.1 and 5.2).

*Elderly patients*
A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant (see section 4.4).

*Patients with renal and/or hepatic impairment*
A lower starting dose (5 mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5 mg and only increased with caution.

*Gender*
The starting dose and dose range need not be routinely altered for female patients relative to male patients.

*Smokers*
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers.

When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.

(See sections 4.5 and 5.2)

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk for 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 approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. 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 ischemic 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 (see section 4.8), 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 (see section 4.8). 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 agents, including Olanzapine Cipla, 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 (see section 4.8). 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 Cipla, 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 (see section 4.8).

*Discontinuation of treatment*
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported rarely ( ≥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, 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 (≥ 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 antagonize the effects of direct and indirect dopamine agonists.

*Seizures*
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur 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. As with other antipsychotics, 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. Long-term outcomes associated with these events have not been studied and remain unknown (see sections 4.8 and 5.1).

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

**4.5 Interaction with other medicinal products and other forms of interaction**

*Paediatric population*
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 (see section 4.2).

*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 (see section 4.4).

*QTc interval*
Caution should be used if olanzapine is being administered concomitantly with medicinal products known to increase QTc interval (see section 4.4).



## 4.6 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.

Neonates 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, hypotonis, 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.

## 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

*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 (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases

(see section 4.4), 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 |
|---|---|---|---|
| **Blood and the lymphatic system disorders** | | | |
| | Eosinophilia<br>Leukopenia[10]<br>Neutropenia[10] | | Thrombocytopenia[11] |
| **Immune system disorders** | | | |
| | | Hypersensitivity[11] | Allergic reaction |
| **Metabolism and nutrition disorders** | | | |
| Weight gain[1] | Elevated cholesterol levels[2,3]<br>Elevated glucose levels[4]<br>Elevated triglyceride levels[2,5]<br>Glucosuria<br>Increased appetite | Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4) [11] | Hypothermia[12] |
| **Nervous system disorders** | | | |
| Somnolence | Dizziness<br>Akathisia[6]<br>Parkinsonism[6]<br>Dyskinesia[6] | Seizures where in most cases a history of seizures or risk factors for seizures were reported[11]<br><br>Dystonia (including oculogyration)[11]<br>Tardive dyskinesia[11]<br><br>Amnesia[9]<br><br>Dysarthria | Neuroleptic malignant syndrome (see section 4.4)[12]<br><br>Discontinuation symptoms[7, 12] |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| | | Epistaxis[9] | |
| **Cardiac disorders** | | | |
| | | Bradycardia<br>$QT_c$ 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) | |
| **Gastrointestinal disorders** | | | |
| | Mild, transient anticholinergic effects including constipation and dry mouth | Abdominal distension[9] | Pancreatitis[11] |
| **Hepato-biliary disorders** | | | |
| | Transient, asymptomatic elevations of hepatic aminotransferases | | Hepatitis (including hepatocellular, cholestatic or mixed liver injury)[11] |

| | | | |
|---|---|---|---|
| | (ALT, AST), especially in early treatment (see section 4.4) | | |
| **Skin and subcutaneous tissue disorders** | | | |
| | Rash | Photosensitivity reaction<br>Alopecia | |
| **Musculoskeletal and connective tissue disorders** | | | |
| | Arthralgia[9] | | Rhabdomyolysis[11] |
| **Renal and urinary disorders** | | | |
| | | Urinary incontinence, urinary retention<br>Urinary hesitation[11] | |
| | | | |
| | | | |
| **Reproductive system and breast disorders** | | | |
| | Erectile dysfunction in males<br>Decreased libido in males and females | Amenorrhea<br>Breast enlargement<br>Galactorrhea in females<br>Gynaecomastia/breast enlargement in males | Priapism[12] |
| **General disorders and administration site conditions** | | | |
| | Asthenia<br>Fatigue<br>Oedema<br>Pyrexia[10] | | |
| **Investigations** | | | |
| Elevated plasma prolactin levels[8] | Increased alkaline phosphatase[10]<br>High creatine phosphokinase[11]<br>High Gamma Glutamyltransferase [10]<br>High Uric Acid [10] | Increased total bilirubin | |
| | | | **Not known** |
| **Pregnancy, puerperium and perinatal conditions** | | | |
| | | | Drug withdrawal syndrome neonatal (see section 4.6) |

[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 (see also 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**<br>*Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite.<br>*Common:* Elevated cholesterol levels[15] |
| **Nervous system disorders**<br>*Very common:* Sedation (including: hypersomnia, lethargy, somnolence). |
| **Gastrointestinal disorders**<br>*Common:* Dry mouth |
| **Hepato-biliary disorders**<br>*Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4). |
| **Investigations**<br>*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.

### 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: diazepines, oxazepines and thiazepines., 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 ($K_i$ < 100 nM) for serotonin 5 $HT_{2A/2C}$, 5 $HT_3$, 5 $HT_6$; dopamine $D_1$, $D_2$, $D_3$, $D_4$, $D_5$; cholinergic muscarinic receptors $M_1$-$M_5$; $\alpha_1$ 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 5 $HT_2$ than $D_2$ 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 $D_2$ 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*
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 co-therapy 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*
The experience in adolescents (ages 13 to 17 years) is limited to short term efficacy data 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 data on maintenance of effect and limited data on long term safety (see sections 4.4 and 4.8).



## 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 $\alpha_1$-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.

*Smokers*
In smoking subjects with mild hepatic dysfunction, mean elimination half-life (39.3 hr) was prolonged and clearance (18.0 l/hr) was reduced analogous to non-smoking healthy subjects (48.8 hr and 14.1 l/hr, respectively).

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 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 [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

*Tablet core*
Lactose monohydrate,
Maize starch
Hydroxypropyl cellulose
Magnesium stearate

*Tablet coat*
Opadry Blue containing:
Hypromellose (E464)
Titanium dioxide (E171)
Polyethylene glycol 6000
Indigo carmine aluminium lake (E132)
Brilliant blue FCF aluminium lake (E133)
Iron oxide black (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

Store in the original package.

Store below 30°C.

### 6.5 Nature and contents of container

Cold-formed aluminium blisters in cartons of 28 or 56 tablets per carton.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

Cipla (EU) Limited
Hillbrow House
Hillbrow Road
Esher
Surrey
KT10 9NW
UK

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/426/010 – Olanzapine Cipla – 15 mg – coated tablets – 28 tablets per box

EU/1/07/426/011 – Olanzapine Cipla – 15 mg – coated tablets – 56 tablets per box

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 November 2007

Date of latest renewal: 01 October 2012

## 10. DATE OF REVISION OF THE TEXT

{MM/YYYY}



Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/.

**ANNEX II**

**A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Pharmadox Healthcare Limited
KW20A Kordin Industrial Park
Paola PLA 3000
Malta

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

*The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.*
In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified,especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

**A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON OF COATED TABLETS IN BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 2.5 mg coated tablets
olanzapine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 2.5 mg olanzapine

## 3. LIST OF EXCIPIENTS

Contains lactose monohydrate, see package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

28 coated tablets
56 coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.



## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original package.
Store below 30°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cipla (EU) Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, UK
Tel: +44 (0)1372 461407
Fax: +44 (0)1372 461401

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/426/001, 28 coated tablets
EU/1/07/426/002, 56 coated tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Olanzapine Cipla 2.5 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**COLD-FORMED ALUMINIUM BLISTER STRIPS**

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 2.5 mg coated tablets
olanzapine

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Cipla (EU) Ltd

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON OF COATED TABLETS IN BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 5 mg coated tablets
olanzapine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 5 mg olanzapine

## 3. LIST OF EXCIPIENTS

Contains lactose monohydrate, see package leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

28 coated tablets
56 coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children



## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original package.
Store below 30°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cipla (EU) Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, UK
Tel: +44 (0)1372 461407
Fax: +44 (0)1372 461401

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/426/003, 28 coated tablets
EU/1/07/426/004, 56 coated tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Olanzapine Cipla 5 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**COLD-FORMED ALUMINIUM BLISTER STRIPS**

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 5 mg coated tablets
olanzapine

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Cipla (EU) Ltd

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON OF COATED TABLETS IN BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 7.5 mg coated tablets
olanzapine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 7.5 mg olanzapine

## 3. LIST OF EXCIPIENTS

Contains lactose monohydrate, see package leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

28 coated tablets
56 coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children



## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original package.
Store below 30°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cipla (EU) Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, UK
Tel: +44 (0)1372 461407
Fax: +44 (0)1372 461401

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/426/005, 28 coated tablets
EU/1/07/426/006, 56 coated tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Olanzapine Cipla 7.5 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**COLD-FORMED ALUMINIUM BLISTER STRIPS**

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 7.5 mg coated tablets
olanzapine

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Cipla (EU) Ltd

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON OF COATED TABLETS IN BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 10 mg coated tablets
olanzapine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 10 mg olanzapine

## 3. LIST OF EXCIPIENTS

Contains lactose monohydrate, see package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

7 coated tablets
28 coated tablets
56 coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children



## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original package.
Store below 30°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cipla (EU) Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, UK
Tel: +44 (0)1372 461407
Fax: +44 (0)1372 461401

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/426/007, 7 coated tablets
EU/1/07/426/008, 28 coated tablets
EU/1/07/426/009, 56 coated tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Olanzapine Cipla 10 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**COLD-FORMED ALUMINIUM BLISTER STRIPS**

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 10 mg coated tablets
olanzapine

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Cipla (EU) Ltd

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON OF COATED TABLETS IN BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Cipla 15 mg coated tablets
olanzapine

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 15 mg olanzapine

## 3. LIST OF EXCIPIENTS

Contains lactose monohydrate, see package leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

28 coated tablets
56 coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children



## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original package.
Store below 30°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cipla (EU) Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, UK
Tel: +44 (0)1372 461407
Fax: +44 (0)1372 461401

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/426/010, 28 coated tablets
EU/1/07/426/011, 56 coated tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Olanzapine Cipla 15 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**COLD-FORMED ALUMINIUM BLISTER STRIPS**

**1. NAME OF THE MEDICINAL PRODUCT**

Olanzapine Cipla 15 mg coated tablets
olanzapine

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Cipla (EU) Ltd

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the user**

**OLANZAPINE CIPLA 2.5 mg coated tablets**
**OLANZAPINE CIPLA 5 mg coated tablets**
**OLANZAPINE CIPLA 7.5 mg coated tablets**
**OLANZAPINE CIPLA 10 mg coated tablets**
**OLANZAPINE CIPLA 15 mg coated tablets**
olanzapine

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet





## 1. What OLANZAPINE CIPLA is and what it is used for

OLANZAPINE CIPLA belongs to a group of medicines called antipsychotics and is used to treat the following conditions:
- Schizophrenia, a disease with symptoms such as hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness, and becoming withdrawn. People with this disease may also feel depressed, anxious or tense.
- Moderate to severe manic episodes, a condition with symptoms of excitement or euphoria.

OLANZAPINE CIPLA has been shown to prevent recurrence of these symptoms in patients with bipolar disorder whose manic episode has responded to olanzapine treatment.

## 2. What you need to know before you take OLANZAPINE CIPLA

**Do not take OLANZAPINE CIPLA**
- iIf you are allergic (hypersensitive) to olanzapine or any of the other ingredients of this medicine (listed in section 6). An allergic reaction may be recognised as a rash, itching, a swollen face, swollen lips or shortness of breath. If this has happened to you, tell your doctor.
- If you have been previously diagnosed with eye problems such as certain kinds of glaucoma (increased pressure in the eye)**.**

**Warnings and precautions**
Talk to your doctor or pharmacist before you take OLANZAPINE CIPLA.
- The use of OLANZAPINE CIPLA in elderly patients with dementia is not recommended as it may have serious side effects.

- Medicines of this type may cause unusual movements mainly of the face or tongue. If this happens after you have been given OLANZAPINE CIPLA tell your doctor.
- Very rarely, medicines of this type cause a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness. If this happens, contact your doctor at once.
- Weight gain has been seen in patients taking OLANZAPINE CIPLA. You and your doctor should check your weight regularly.
- High blood sugar and high levels of fat (triglycerides and cholesterol) have been seen in patients taking OLANZAPINE CIPLA. Your doctor should do blood tests to check blood sugar and certain fat levels before you start taking OLANZAPINE CIPLA and regularly during treatment.
- Tell the doctor if you or someone else in your family has a history of blood clots, as medicines like these have been associated with the formation of blood clots.

If you suffer from any of the following illnesses tell your doctor as soon as possible:

- Stroke or "mini" stroke (temporary symptoms of stroke)
- Parkinson's disease
- Prostate problems
- A blocked intestine (Paralytic ileus)
- Liver or kidney disease
- Blood disorders
- Heart disease
- Diabetes
- Seizures

If you suffer from dementia, you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

As a routine precaution, if you are over 65 years your blood pressure may be monitored by your doctor.

**Children and adolescents**
OLANZAPINE CIPLA is not for patients who are under 18 years.

**Other medicines and OLANZAPINE CIPLA**
Only take other medicines while you are on OLANZAPINE CIPLA if your doctor tells you that you can. You might feel drowsy if OLANZAPINE CIPLA is taken in combination with antidepressants or medicines taken for anxiety or to help you sleep (tranquillisers).

Tell your doctor if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor if you are taking:
- medicines for Parkinson's disease.
- carbamazepine (an anti-epileptic and mood stabiliser), fluvoxamine (an antidepressant) or ciprofloxacin (an antibiotic) - it may be necessary to change your OLANZAPINE CIPLA dose.

**OLANZAPINE CIPLA with alcohol**
Do not drink any alcohol if you have been given OLANZAPINE CIPLA as together with alcohol it may make you feel drowsy.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. You should not be given this medicine when breast-feeding, as small amounts of OLANZAPINE CIPLA can pass into breast milk.

The following symptoms may occur in newborn babies, of mothers that have used OLANZAPINE CIPLA in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

**Driving and using machines**
There is a risk of feeling drowsy when you are given OLANZAPINE CIPLA. If this happens do not drive or operate any tools or machines. Tell your doctor.

**OLANZAPINE CIPLA contains lactose.**
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

## 3. How to take OLANZAPINE CIPLA

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will tell you how many OLANZAPINE CIPLA tablets to take and how long you should continue to take them. The daily dose of OLANZAPINE CIPLA is between 5 and 20 mg. Consult your doctor if your symptoms return but do not stop taking OLANZAPINE CIPLA unless your doctor tells you to.

You should take your OLANZAPINE CIPLA tablets once a day following the advice of your doctor. Try to take your tablets at the same time each day. It does not matter whether you take them with or without food. OLANZAPINE CIPLA coated tablets are for oral use. You should swallow the OLANZAPINE CIPLA tablets whole with water.

**If you take more OLANZAPINE CIPLA than you should**
Patients who have taken more OLANZAPINE CIPLA than they should have experienced the following symptoms: rapid beating of the heart, agitation/aggressiveness, problems with speech, unusual movements (especially of the face or tongue) and reduced level of consciousness. Other symptoms may be: acute confusional, seizures (epilepsy), coma, a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness, slowing of the breathing rate, aspiration, high blood pressure or low blood pressure, abnormal rhythms of the heart. Contact your doctor or hospital straightaway if you experience any of the above symptoms. Show the doctor your pack of tablets.

**If you forget to take OLANZAPINE CIPLA**
Take your tablets as soon as you remember. Do not take two doses in one day.

**If you stop taking OLANZAPINE CIPLA**
Do not stop taking your tablets just because you feel better. It is important that you carry on taking OLANZAPINE CIPLA for as long as your doctor tells you.

If you suddenly stop taking OLANZAPINE CIPLA, symptoms such as sweating, unable to sleep, tremor, anxiety or nausea and vomiting might occur. Your doctor may suggest you to reduce the dose gradually before stopping treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you have:

- unusual movement (a common side effect that may affect up to 1 in 10 people) mainly of the face or tongue;
- blood clots in the veins (an uncommon side effect that may affect up to 1 in 100 people) especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately;
- a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness (the frequency of this side effect cannot be estimated from the available data).

Very common side effects (may affect more than 1 in 10 people) include weight gain; sleepiness; and increases in levels of prolactin in the blood. In the early stages of treatment, some people may feel dizzy or faint (with a slow heart rate), especially when getting up from a lying or sitting position. This will usually pass on its own but if it does not, tell your doctor.

Common side effects (may affect up to 1 in 10 people) include changes in the levels of some blood cells circulating fats and early in treatment, temporary increases in liver enzymes; increases in the level of sugars in the blood and urine; increases in levels of uric acid and creatine phosphokinase in the blood; feeling more hungry; dizziness; restlessness; tremor;; unusual movements (dyskinesias); constipation; dry mouth; rash; loss of strength; extreme tiredness; water retention leading to swelling of the hands, ankles or feet; fever; joint pain; and sexual dysfunctions such as decreased libido in males and females or erectile dysfunction in males..

Uncommon side effects (may affect up to 1 in 100 people) include hypersensitivity (e.g. swelling in the mouth and throat, itching, rash); diabetes or the worsening of diabetes, occasionally associated with ketoacidosis (ketones in the blood and urine) or coma; seizures, usually associated with a history of seizures (epilepsy); muscle stiffness or spasms (including eye movements); problems with speech; slow heart rate; sensitivity to sunlight; bleeding from the nose; abdominal distension; memory loss or forgetfulness;urinary incontinence; lack of ability to urinate; hair loss; absence or decrease in menstrual periods; and changes in breasts in males and females such as an abnormal production of breast milk or abnormal growth.

Rare side effects (may affect up to 1 in 1000 people) include lowering of normal body temperature; abnormal rhythms of the heart; sudden unexplained death; inflammation of the pancreas causing severe stomach pain, fever and sickness; liver disease appearing as yellowing of the skin and white parts of the eyes; muscle disease presenting as unexplained aches and pains; and prolonged and/or painful erection.

While taking olanzapine, elderly patients with dementia may suffer from stroke, pneumonia, urinary incontinence, falls, extreme tiredness, visual hallucinations, a rise in body temperature, redness of the skin and have trouble walking. Some fatal cases have been reported in this particular group of patients.

In patients with Parkinson's disease OLANZAPINE CIPLA may worsen the symptoms.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

## 5. How to store OLANZAPINE CIPLA COATED TABLETS

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after Exp.
Store in the original package. Store below 30ºC.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## 6. Contents of the pack and other information

**What Olanzapine Cipla contains**

- The active substance is olanzapine. Each Olanzapine Cipla coated tablet contains either 2.5 mg, 5 mg, 7.5 mg, 10 mg or 15 mg of the active substance.
- The other ingredients are:
- Tablet core: lactose monohydrate (See also end of section 2 – important information about some of the ingredients of Olanzapine Cipla), maize starch, hydroxypropyl cellulose, magnesium stearate.
- Tablet coat:
- 2.5 mg, 5 mg, 7.5 mg and 10 mg tablets: Opadry white containing hypromellose (E464), titanium dioxide (E171), lactose monohydrate, polyethylene glycol 3000 and glycerol triacetate
- 15 mg tablets: Opadry Blue containing hypromellose (E464), titanium dioxide (E171), polyethylene glycol 6000, indigo carmine aluminium lake (E132), brilliant blue FCF aluminium lake (E133) and iron oxide black (E172)

**What OLANZAPINE CIPLA looks like and contents of the pack**
Olanzapine Cipla 2.5 mg coated tablets are white, round, biconvex coated tablets with '2.5' debossed on one side and 'OLZ' on the other.

Olanzapine Cipla 5 mg coated tablets are white, round, biconvex, coated tablets with 'OLZ 5' debossed on one side and 'NEO' on the other.

Olanzapine Cipla 7.5 mg coated tablets are white, round, biconvex, coated tablets with 'OLZ 7.5' debossed on one side and 'NEO' on the other.

Olanzapine Cipla 10 mg coated tablets are white, round, biconvex, coated tablets with 'OLZ 10' debossed on one side and 'NEO' on the other.

Olanzapine Cipla 15 mg coated tablets are blue, elliptical, convex, coated tablets with 'NEO' debossed on one side and plain on the other side.

Olanzapine Cipla 2.5 mg, 5 mg, 7.5 mg and 15 mg coated tablets are available in 28 and 56 blister packs.

Olanzapine Cipla 10 mg coated tablets are available in 7, 28 and 56 blister packs.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder:** Cipla (EU) Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, UK
Tel: +44 (0)1372 461407
Fax: +44 (0)1372 461401

**Manufacturer:**
Pharmadox Healthcare Limited, KW20A Kordin Industrial Park, Paola, PLA 3000, Malta
Tel: +356 21 808662
Fax: +356 21 808663

**This leaflet was last revised in {month YYYY}**

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: http://www.ema.europa.eu/.