ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg olanzapine.

Excipient with known effect: Each film-coated tablet contains 63.17 mg lactose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

White, round, biconvex film-coated tablets engraved 'APO' on one side and 'OLA' over '2.5' 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.

Special populations

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

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

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. The metabolism of olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.5).

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)

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk of narrow-angle glaucoma.

4.4 Special warnings and precautions for use

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

Dementia-related psychosis and/or behavioural disturbances
Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient 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 medicines, including Olanzapine Apotex, 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 medicines, including Olanzapine Apotex, 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, alanine transferase (ALT), aspartate transferase (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, 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. 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 (see sections 4.8 and 5.1).

Lactose
Olanzapine Apotex film-coated 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

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.

Newborn infants exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, 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.

Fertility
Effects on fertility are unknown (see section 5.3 for preclinical information).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

4.8 Undesirable effects

Summary of the safety profile
Adults
The most frequently (seen in ≥ 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 available data).

Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and lymphatic system disorders				
	Eosinophilia Leukopenia[10] Neutropenia[10]		Thrombocytopenia[11]	
Immune system disorders				
		Hypersensitivity[11]		
Metabolism and nutrition disorders				
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5] Glucosuria 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 Akathisia[6] Parkinsonism[6] Dyskinesia[6]	Seizures where in most cases a history of seizures or risk factors for seizures were reported [11] Dystonia (including oculogyration) [11] Tardive dyskinesia[11] Amnesia [9] Dysarthria Stuttering[11] Restless legs syndrome[11]	Neuroleptic malignant syndrome (see section 4.4)[12] Discontinuation symptoms[7, 12]	
Cardiac disorders				
		Bradycardia 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)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9] Salivary hypersecretion[11]	Pancreatitis[11]	
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury)[11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	
Renal and urinary disorders				
		Urinary incontinence, urinary retention Urinary hesitation[11]		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders				
	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhea in females Gynaecomastia/breast enlargement in males	Priapism[12]	
General disorders and administration site conditions				
	Asthenia Fatigue			

	Oedema Pyrexia[10]			
Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase[10] High uric acid [10]	Increased total bilirubin		

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

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

[3] Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol/l) to high (≥ 6.2 mmol/l) were very common.

[4] Observed for fasting normal levels at baseline (< 5.56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 5.56 - < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5] Observed for fasting normal levels at baseline (< 1.69 mmol/l) which increased to high (≥ 2.26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥ 1.69 mmol/l - < 2.26 mmol/l) to high (≥ 2.26 mmol/l) were very common.

[6] In clinical trials, the incidence of Parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of Parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

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

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

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

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

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

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

Long-term exposure (at least 48 weeks)
The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Additional information on special populations
In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo (see section 4.4). Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.

In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1%; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥10%) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥7% from baseline body weight in 39.9% of patients.

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

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

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

Metabolism and nutrition disorders *Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite. *Common:* Elevated cholesterol levels[15]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth
Hepatobiliary disorders *Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16].

[13] Following short term treatment (median 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms
Very common symptoms in overdose (> 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

Management
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code 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; α_1 adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5 HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin 5 HT_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
Controlled efficacy data in adolescents (ages 13 to 17 years) are limited to short term studies in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin (see sections 4.4 and 4.8) were greater in adolescents than in adults. There are no controlled data on maintenance of effect or long term safety (see sections 4.4 and 4.8). Information on long term safety is primarily limited to open-label, uncontrolled data.

5.2 Pharmacokinetic properties

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

Distribution
The plasma protein binding of olanzapine was about 93% over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α_1-acid-glycoprotein.

Biotransformation
Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine.

Elimination
After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hrs) 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 hrs) 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 hrs) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57 % of radiolabelled olanzapine appeared in urine, principally as metabolites.

Hepatic impairment
A small study of the effect of impaired liver function in 6 subjects with clinically significant (Childs Pugh Classification A (n = 5) and B (n = 1)) cirrhosis revealed little effect on the pharmacokinetics of orally administered olanzapine (2.5 – 7.5 mg single dose): Subjects with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster elimination half-time compared to

subjects with no hepatic dysfunction (n = 3). There were more smokers among subjects with cirrhosis (4/6; 67 %) than among subjects with no hepatic dysfunction (0/3; 0 %).

Smoking
In non-smoking versus smoking subjects (males and females), the mean elimination half-life was prolonged (38.6 versus 30.4 hrs) 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
Microcrystalline cellulose
Maize starch
Magnesium stearate

Tablet coat
Hypromellose
Hydroxypropylcellulose
Macrogol 8000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister strips in cartons of 28 film-coated tablets per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10.06.2010

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg olanzapine.

Excipient with known effect: Each film-coated tablet contains 126.34 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White, round biconvex film-coated tablets engraved 'APO' on one side and 'OLA' over '5' 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.

Special populations

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

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

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. The metabolism of olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.5).

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)

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk of narrow-angle glaucoma.

4.4 Special warnings and precautions for use

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

Dementia-related psychosis and/or behavioural disturbances
Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient 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 medicines, including Olanzapine Apotex, 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 medicines, including Olanzapine Apotex, 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, alanine transferase (ALT), aspartate transferase (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 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, 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. 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 (see sections 4.8 and 5.1).

Lactose
Olanzapine Apotex film-coated 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

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.

Newborn infants exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, 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.

Fertility
Effects on fertility are unknown (see section 5.3 for preclinical information).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

4.8 Undesirable effects

Summary of the safety profile
Adults
The most frequently (seen in ≥ 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 available data).

Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders				
	Eosinophilia Leukopenia[10] Neutropenia[10]		Thrombocytopenia[11]	
Immune system disorders				
		Hypersensitivity[11]		
Metabolism and nutrition disorders				
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5] Glucosuria 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 Akathisia[6] Parkinsonism[6] Dyskinesia[6]	Seizures where in most cases a history of seizures or risk factors for seizures were reported [11] Dystonia (including oculogyration) [11] Tardive dyskinesia[11] Amnesia [9] Dysarthria Stuttering[11] Restless legs syndrome[11]	Neuroleptic malignant syndrome (see section 4.4)[12] Discontinuation symptoms[7, 12]	
Cardiac disorders				
		Bradycardia 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)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9] Salivary hypersecretion[11]	Pancreatitis[11]	
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury) [11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	
Renal and urinary disorders				
		Urinary incontinence, urinary retention Urinary hesitation[11]		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders				
	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhea in females Gynaecomastia/breast enlargement in males	Priapism[12]	
General disorders and administration site conditions				
	Asthenia Fatigue Oedema			

	Pyrexia[10]			
Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase[10] High uric acid [10]	Increased total bilirubin		

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

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

[3] Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol/l) to high (≥ 6.2 mmol/l) were very common.

[4] Observed for fasting normal levels at baseline (< 5.56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 5.56 - < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5] Observed for fasting normal levels at baseline (< 1.69 mmol/l) which increased to high (≥ 2.26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥ 1.69 mmol/l - < 2.26 mmol/l) to high (≥ 2.26 mmol/l) were very common.

[6] In clinical trials, the incidence of Parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of Parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

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

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

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

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

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

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

Long-term exposure (at least 48 weeks)
The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Additional information on special populations
In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo (see section 4.4). Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.

In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1%; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥10%) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥7% from baseline body weight in 39.9% of patients.

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

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

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

Metabolism and nutrition disorders *Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite. *Common:* Elevated cholesterol levels[15]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth
Hepatobiliary disorders *Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16].

[13] Following short term treatment (median 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms
Very common symptoms in overdose (> 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

Management
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code 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; α_1 adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5 HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin 5 HT_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
Controlled efficacy data in adolescents (ages 13 to 17 years) are limited to short term studies in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin (see sections 4.4 and 4.8) were greater in adolescents than in adults. There are no controlled data on maintenance of effect or long term safety (see sections 4.4 and 4.8). Information on long term safety is primarily limited to open-label, uncontrolled data.

5.2 Pharmacokinetic properties

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

Distribution
The plasma protein binding of olanzapine was about 93% over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α_1-acid-glycoprotein.

Biotransformation
Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine.

Elimination
After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hrs) 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 hrs) 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 hrs) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57 % of radiolabelled olanzapine appeared in urine, principally as metabolites.

Hepatic impairment
A small study of the effect of impaired liver function in 6 subjects with clinically significant (Childs Pugh Classification A (n = 5) and B (n = 1)) cirrhosis revealed little effect on the pharmacokinetics of orally administered olanzapine (2.5 – 7.5 mg single dose): Subjects with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster

elimination half-time compared to subjects with no hepatic dysfunction (n = 3). There were more smokers among subjects with cirrhosis (4/6; 67 %) than among subjects with no hepatic dysfunction (0/3; 0 %).

Smoking
In non-smoking versus smoking subjects (males and females), the mean elimination half-life was prolonged (38.6 versus 30.4 hrs) 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
Microcrystalline cellulose
Maize starch
Magnesium stearate

Tablet coat
Hypromellose
Hydroxypropylcellulose
Macrogol 8000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister strips in cartons of 28, 56 and 98 film-coated tablets per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/002-003
EU/1/10/635/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10.06.2010

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 7.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 7.5 mg olanzapine.

Excipient with known effect: Each film-coated tablet contains 189.50 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White, round biconvex film-coated tablets engraved 'APO' on one side and 'OLA' over '7.5' 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.

Special populations

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

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

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. The metabolism of olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.5).

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)

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk of narrow-angle glaucoma.

4.4 Special warnings and precautions for use

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

Dementia-related psychosis and/or behavioural disturbances
Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient 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 medicines, including Olanzapine Apotex, 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 medicines, including Olanzapine Apotex, 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, alanine transferase (ALT), aspartate transferase (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 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, 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. 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 (see sections 4.8 and 5.1).

Lactose
Olanzapine Apotex film-coated 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

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.

Newborn infants exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, 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.

Fertility
Effects on fertility are unknown (see section 5.3 for preclinical information).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

4.8 Undesirable effects

Summary of the safety profile
Adults
The most frequently (seen in ≥ 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 available data).

Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders				
	Eosinophilia Leukopenia[10] Neutropenia[10]		Thrombocytopenia[11]	
Immune system disorders				
		Hypersensitivity[11]		
Metabolism and nutrition disorders				
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5] Glucosuria 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 Akathisia[6] Parkinsonism[6] Dyskinesia[6]	Seizures where in most cases a history of seizures or risk factors for seizures were reported [11] Dystonia (including oculogyration) [11] Tardive dyskinesia[11] Amnesia [9] Dysarthria Stuttering[11] Restless legs syndrome[11]	Neuroleptic malignant syndrome (see section 4.4)[12] Discontinuation symptoms[7, 12]	
Cardiac disorders				
		Bradycardia 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)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9] Salivary hypersecretion[11]	Pancreatitis[11]	
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury) [11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	
Renal and urinary disorders				
		Urinary incontinence, urinary retention Urinary hesitation[11]		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders				
	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhea in females Gynaecomastia/breast enlargement in males	Priapism[12]	
General disorders and administration site conditions				
	Asthenia Fatigue Oedema			

	Pyrexia[10]			
Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase[10] High uric acid [10]	Increased total bilirubin		

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

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

[3] Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol/l) to high (≥ 6.2 mmol/l) were very common.

[4] Observed for fasting normal levels at baseline (< 5.56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 5.56 - < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5] Observed for fasting normal levels at baseline (< 1.69 mmol/l) which increased to high (≥ 2.26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥ 1.69 mmol/l - < 2.26 mmol/l) to high (≥ 2.26 mmol/l) were very common.

[6] In clinical trials, the incidence of Parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of Parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

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

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

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

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

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

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

Long-term exposure (at least 48 weeks)
The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Additional information on special populations
In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo (see section 4.4). Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.

In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1%; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥10%) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥7% from baseline body weight in 39.9% of patients.

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

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

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

Metabolism and nutrition disorders *Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite. *Common:* Elevated cholesterol levels[15]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth
Hepatobiliary disorders *Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16].

[13] Following short term treatment (median 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms
Very common symptoms in overdose (> 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

Management
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code 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; α_1 adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5 HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin 5 HT_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
Controlled efficacy data in adolescents (ages 13 to 17 years) are limited to short term studies in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin (see sections 4.4 and 4.8) were greater in adolescents than in adults. There are no controlled data on maintenance of effect or long term safety (see sections 4.4 and 4.8). Information on long term safety is primarily limited to open-label, uncontrolled data.

5.2 Pharmacokinetic properties

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

Distribution
The plasma protein binding of olanzapine was about 93% over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α_1-acid-glycoprotein.

Biotransformation
Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine.

Elimination
After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hrs) 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 hrs) 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 hrs) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57 % of radiolabelled olanzapine appeared in urine, principally as metabolites.

Hepatic impairment
A small study of the effect of impaired liver function in 6 subjects with clinically significant (Childs Pugh Classification A (n = 5) and B (n = 1)) cirrhosis revealed little effect on the

pharmacokinetics of orally administered olanzapine (2.5 – 7.5 mg single dose): Subjects with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster elimination half-time compared to subjects with no hepatic dysfunction (n = 3). There were more smokers among subjects with cirrhosis (4/6; 67 %) than among subjects with no hepatic dysfunction (0/3; 0 %).

Smoking
In non-smoking versus smoking subjects (males and females), the mean elimination half-life was prolonged (38.6 versus 30.4 hrs) 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
Microcrystalline cellulose
Maize starch
Magnesium stearate

Tablet coat
Hypromellose
Hydroxypropylcellulose
Macrogol 8000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister strips in cartons of 28 and 56 film-coated tablets per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/004-005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10.06.2010

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg olanzapine.

Excipient with known effect: Each film-coated tablet contains 252.70 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White, round biconvex film-coated tablets engraved 'APO' on one side and 'OLA' over '10' 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.

Special populations

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

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

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. The metabolism of olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.5).

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)

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk of narrow-angle glaucoma.

4.4 Special warnings and precautions for use

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

Dementia-related psychosis and/or behavioural disturbances
Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient 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 medicines, including Olanzapine Apotex, 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 medicines, including Olanzapine Apotex, 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, alanine transferase (ALT), aspartate transferase (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 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, 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. 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 (see sections 4.8 and 5.1).

Lactose
Olanzapine Apotex film-coated 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

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.

Newborn infants exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, 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.

Fertility
Effects on fertility are unknown (see section 5.3 for preclinical information).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

4.8 Undesirable effects

Summary of the safety profile
Adults
The most frequently (seen in ≥ 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 available data).

Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders				
	Eosinophilia Leukopenia[10] Neutropenia[10]		Thrombocytopenia[11]	
Immune system disorders				
		Hypersensitivity[11]		
Metabolism and nutrition disorders				
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5] Glucosuria 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 Akathisia[6] Parkinsonism[6] Dyskinesia[6]	Seizures where in most cases a history of seizures or risk factors for seizures were reported [11] Dystonia (including oculogyration) [11] Tardive dyskinesia[11] Amnesia [9] Dysarthria Stuttering[11] Restless legs syndrome[11]	Neuroleptic malignant syndrome (see section 4.4)[12] Discontinuation symptoms[7, 12]	
Cardiac disorders				
		Bradycardia 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)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9] Salivary hypersecretion[11]	Pancreatitis[11]	
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury) [11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	
Renal and urinary disorders				
		Urinary incontinence, urinary retention Urinary hesitation[11]		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders				
	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhea in females Gynaecomastia/breast enlargement in males	Priapism[12]	
General disorders and administration site conditions				
	Asthenia Fatigue Oedema			

	Pyrexia[10]			
Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase[10] High uric acid [10]	Increased total bilirubin		

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

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

[3] Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol/l) to high (≥ 6.2 mmol/l) were very common.

[4] Observed for fasting normal levels at baseline (< 5.56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 5.56 - < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5] Observed for fasting normal levels at baseline (< 1.69 mmol/l) which increased to high (≥ 2.26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥ 1.69 mmol/l - < 2.26 mmol/l) to high (≥ 2.26 mmol/l) were very common.

[6] In clinical trials, the incidence of Parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of Parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

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

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

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

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

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

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

Long-term exposure (at least 48 weeks)
The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Additional information on special populations
In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo (see section 4.4). Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.

In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1%; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥10%) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥7% from baseline body weight in 39.9% of patients.

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

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

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

Metabolism and nutrition disorders *Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite. *Common:* Elevated cholesterol levels[15]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth
Hepatobiliary disorders *Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16].

[13] Following short term treatment (median 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms
Very common symptoms in overdose (> 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

Management
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code 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; α_1 adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5 HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin 5 HT_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
Controlled efficacy data in adolescents (ages 13 to 17 years) are limited to short term studies in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin (see sections 4.4 and 4.8) were greater in adolescents than in adults. There are no controlled data on maintenance of effect or long term safety (see sections 4.4 and 4.8). Information on long term safety is primarily limited to open-label, uncontrolled data.

5.2 Pharmacokinetic properties

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

Distribution
The plasma protein binding of olanzapine was about 93% over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α_1-acid-glycoprotein.

Biotransformation
Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine.

Elimination
After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hrs) 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 hrs) 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 hrs) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57 % of radiolabelled olanzapine appeared in urine, principally as metabolites.

Hepatic impairment
A small study of the effect of impaired liver function in 6 subjects with clinically significant (Childs Pugh Classification A (n = 5) and B (n = 1)) cirrhosis revealed little effect on the pharmacokinetics of orally administered olanzapine (2.5 – 7.5 mg single dose): Subjects with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster

elimination half-time compared to subjects with no hepatic dysfunction (n = 3). There were more smokers among subjects with cirrhosis (4/6; 67 %) than among subjects with no hepatic dysfunction (0/3; 0 %).

Smoking
In non-smoking versus smoking subjects (males and females), the mean elimination half-life was prolonged (38.6 versus 30.4 hrs) 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
Microcrystalline cellulose
Maize starch
Magnesium stearate

Tablet coat
Hypromellose
Hydroxypropylcellulose
Macrogol 8000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister strips in cartons of 28, 56 and 98 film-coated tablets per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/006-007
EU/1/10/635/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10.06.2010

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 5 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 5 mg olanzapine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

Yellow round flat faced radial edge tablets engraved 'APO' on one side and 'OL' over '5' 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.

Olanzapine Apotex orodispersible tablet should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or other suitable beverage (orange juice, apple juice, milk or coffee) immediately before administration.

Olanzapine orodispersible tablet is bioequivalent to olanzapine film-coated tablets, with a similar rate and extent of absorption. It has the same dosage and frequency of administration as olanzapine film-coated tablets. Olanzapine orodispersible tablets may be used as an alternative to olanzapine film-coated tablets.

Special populations

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

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

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. The metabolism of olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.5).

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

In cases where dose increments of 2.5 mg are considered necessary, Olanzapine Apotex film-coated tablets should be used.

(See sections 4.5 and 5.2).

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk of narrow-angle glaucoma.

4.4 Special warnings and precautions for use

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

Dementia-related psychosis and/or behavioural disturbances

Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient 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 medicines, including Olanzapine Apotex, 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 medicines, including Olanzapine Apotex, 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, alanine transferase (ALT), aspartate transferase (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, 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. 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 (see sections 4.8 and 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

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

Newborn infants exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, 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.

Fertility
Effects on fertility are unknown (see section 5.3 for preclinical information).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

4.8 Undesirable effects

Summary of the safety profile

Adults

The most frequently (seen in ≥ 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 available data).

Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and lymphatic system disorders				
	Eosinophilia Leukopenia[10] Neutropenia[10]		Thrombocytopenia[11]	
Immune system disorders				
		Hypersensitivity[11]		
Metabolism and nutrition disorders				
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5] Glucosuria 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 Akathisia[6] Parkinsonism[6] Dyskinesia[6]	Seizures where in most cases a history of seizures or risk factors for seizures were reported [11] Dystonia (including oculogyration) [11] Tardive dyskinesia[11] Amnesia [9] Dysarthria Stuttering[11] Restless legs syndrome[11]	Neuroleptic malignant syndrome (see section 4.4)[12] Discontinuation symptoms[7, 12]	
Cardiac disorders				
		Bradycardia	Ventricular	

		QT_c prolongation (see section 4.4)	tachycardia/fibrillation, sudden death (see section 4.4)[11]	
Vascular disorders				
Orthostatic hypotension[10]		Thromboembolism (including pulmonary embolism and deep vein thrombosis) (see section 4.4)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9] Salivary hypersecretion[11]	Pancreatitis[11]	
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury) [11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	
Renal and urinary disorders				
		Urinary incontinence, urinary retention Urinary hesitation[11]		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders				
	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhea in females Gynaecomastia/breast enlargement in males	Priapism[12]	
General disorders and administration site conditions				

	Asthenia Fatigue Oedema Pyrexia[10]			
Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase[10] High uric acid [10]	Increased total bilirubin		

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

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

[3] Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol/l) to high (≥ 6.2 mmol/l) were very common.

[4] Observed for fasting normal levels at baseline (< 5.56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 5.56 - < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5] Observed for fasting normal levels at baseline (< 1.69 mmol/l) which increased to high (≥ 2.26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥ 1.69 mmol/l - < 2.26 mmol/l) to high (≥ 2.26 mmol/l) were very common.

[6] In clinical trials, the incidence of Parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of Parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

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

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

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

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

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

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

Long-term exposure (at least 48 weeks)
The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Additional information on special populations
In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo (see section 4.4). Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.

In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1%; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥10%) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥7% from baseline body weight in 39.9% of patients.

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

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

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

Metabolism and nutrition disorders *Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite. *Common:* Elevated cholesterol levels[15]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth
Hepatobiliary disorders

Very common: Elevations of hepatic aminotransferases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16].

[13] Following short term treatment (median 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms
Very common symptoms in overdose (≥ 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

Management
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code 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 M1-M5; α_1 adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5 HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin 5 HT_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
Controlled efficacy data in adolescents (ages 13 to 17 years) are limited to short term studies in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin (see sections 4.4 and 4.8) were greater in adolescents than in adults. There are no controlled data on maintenance of effect or long term safety (see sections 4.4 and 4.8). Information on long term safety is primarily limited to open-label, uncontrolled data.

5.2 Pharmacokinetic properties

Olanzapine orodispersible tablet is bioequivalent to olanzapine coated tablets, with a similar rate and extent of absorption. Olanzapine orodispersible tablets may be used as an alternative to olanzapine coated tablets.

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

Distribution
The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α_1-acid-glycoprotein.

Biotransformation
Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites; both exhibited significantly less in vivo pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent, olanzapine.

Elimination
After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hrs) 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 hrs) 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 hrs) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57% of radiolabelled olanzapine appeared in urine, principally as metabolites.

Hepatic impairment

A small study of the effect of impaired liver function in 6 subjects with clinically significant (Childs Pugh Classification A (n = 5) and B (n = 1)) cirrhosis revealed little effect on the pharmacokinetics of orally administered olanzapine (2.5 – 7.5 mg single dose): Subjects with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster elimination half-time compared to subjects with no hepatic dysfunction (n = 3). There were more smokers among subjects with cirrhosis (4/6; 67 %) than among subjects with no hepatic dysfunction (0/3; 0 %).

Smoking
In non-smoking versus smoking subjects (males and females), the mean elimination half-life was prolonged (38.6 versus 30.4 hrs) 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

Mannitol (E421)
Microcrystalline cellulose
Carmellose calcium
Sucralose
Magnesium stearate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister strips in cartons of 28, 56 and 98 orodispersible tablets per carton

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/008-009
EU/1/10/635/017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10.06.2010

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 10 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 10 mg olanzapine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

Yellow round flat faced radial edge tablets engraved 'APO' on one side and 'OL' over '10' 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.

Olanzapine Apotex orodispersible tablet should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or other suitable beverage (orange juice, apple juice, milk or coffee) immediately before administration.

Olanzapine orodispersible tablet is bioequivalent to olanzapine film-coated tablets, with a similar rate and extent of absorption. It has the same dosage and frequency of administration as olanzapine film-coated tablets. Olanzapine orodispersible tablets may be used as an alternative to olanzapine film-coated tablets.

Special populations

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

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

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. The metabolism of olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.5).

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

In cases where dose increments of 2.5 mg are considered necessary, Olanzapine Apotex film-coated tablets should be used.

(See sections 4.5 and 5.2).

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk of narrow-angle glaucoma.

4.4 Special warnings and precautions for use

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

Dementia-related psychosis and/or behavioural disturbances

Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient 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 medicines, including Olanzapine Apotex, 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 medicines, including Olanzapine Apotex, 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, alanine transferase (ALT), aspartate transferase (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 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, 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. 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 (see sections 4.8 and 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

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

Newborn infants exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, 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.

Fertility
Effects on fertility are unknown (see section 5.3 for preclinical information).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

4.8 Undesirable effects

Summary of the safety profile

Adults

The most frequently (seen in ≥ 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 available data).

Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and lymphatic system disorders				
	Eosinophilia Leukopenia[10] Neutropenia[10]		Thrombocytopenia[11]	
Immune system disorders				
		Hypersensitivity[11]		
Metabolism and nutrition disorders				
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5] Glucosuria 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 Akathisia[6] Parkinsonism[6] Dyskinesia[6]	Seizures where in most cases a history of seizures or risk factors for seizures were reported [11] Dystonia (including oculogyration) [11] Tardive dyskinesia[11] Amnesia [9] Dysarthria Stuttering[11] Restless legs syndrome[11]	Neuroleptic malignant syndrome (see section 4.4)[12] Discontinuation symptoms[7, 12]	
Cardiac disorders				
		Bradycardia	Ventricular	

		QT_c prolongation (see section 4.4)	tachycardia/fibrillation, sudden death (see section 4.4)[11]	
Vascular disorders				
Orthostatic hypotension[10]		Thromboembolism (including pulmonary embolism and deep vein thrombosis) (see section 4.4)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9] Salivary hypersecretion[11]	Pancreatitis[11]	
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury) [11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	
Renal and urinary disorders				
		Urinary incontinence, urinary retention Urinary hesitation[11]		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders				
	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhea in females Gynaecomastia/breast enlargement in males	Priapism[12]	
General disorders and administration site conditions				

	Asthenia Fatigue Oedema Pyrexia[10]			
Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase[10] High uric acid [10]	Increased total bilirubin		

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

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

[3] Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol/l) to high (≥ 6.2 mmol/l) were very common.

[4] Observed for fasting normal levels at baseline (< 5.56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 5.56 - < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5] Observed for fasting normal levels at baseline (< 1.69 mmol/l) which increased to high (≥ 2.26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥ 1.69 mmol/l - < 2.26 mmol/l) to high (≥ 2.26 mmol/l) were very common.

[6] In clinical trials, the incidence of Parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of Parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

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

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

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

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

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

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

Long-term exposure (at least 48 weeks)
The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Additional information on special populations
In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo (see section 4.4). Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.

In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1%; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥10%) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥7% from baseline body weight in 39.9% of patients.

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

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

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

Metabolism and nutrition disorders *Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite. *Common:* Elevated cholesterol levels[15]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth
Hepatobiliary disorders

Very common: Elevations of hepatic aminotransferases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16].

[13] Following short term treatment (median 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms
Very common symptoms in overdose (≥ 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

Management
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code 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 M1-M5; α_1 adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5 HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin 5 HT_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
Controlled efficacy data in adolescents (ages 13 to 17 years) are limited to short term studies in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin (see sections 4.4 and 4.8) were greater in adolescents than in adults. There are no controlled data on maintenance of effect or long term safety (see sections 4.4 and 4.8). Information on long term safety is primarily limited to open-label, uncontrolled data.

5.2 Pharmacokinetic properties

Olanzapine orodispersible tablet is bioequivalent to olanzapine coated tablets, with a similar rate and extent of absorption. Olanzapine orodispersible tablets may be used as an alternative to olanzapine coated tablets.

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

Distribution
The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α_1-acid-glycoprotein.

Biotransformation
Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites; both exhibited significantly less in vivo pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent, olanzapine.

Elimination
After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hrs) 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 hrs) 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 hrs) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57% of radiolabelled olanzapine appeared in urine, principally as metabolites.

Hepatic impairment
A small study of the effect of impaired liver function in 6 subjects with clinically significant (Childs Pugh Classification A (n = 5) and B (n = 1)) cirrhosis revealed little effect on the pharmacokinetics of

orally administered olanzapine (2.5 – 7.5 mg single dose): Subjects with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster elimination half-time compared to subjects with no hepatic dysfunction (n = 3). There were more smokers among subjects with cirrhosis (4/6; 67 %) than among subjects with no hepatic dysfunction (0/3; 0 %).

Smoking
In non-smoking versus smoking subjects (males and females), the mean elimination half-life was prolonged (38.6 versus 30.4 hrs) 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

Mannitol (E421)
Microcrystalline cellulose
Carmellose calcium
Sucralose
Magnesium stearate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister strips in cartons of 28, 56 and 98 orodispersible tablets per carton

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/010-011
EU/1/10/635/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10.06.2010

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 15 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 15 mg olanzapine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

Yellow round flat faced radial edge tablets engraved 'APO' on one side and 'OL' over '15' 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.

Olanzapine Apotex orodispersible tablet should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or other suitable beverage (orange juice, apple juice, milk or coffee) immediately before administration.

Olanzapine orodispersible tablet is bioequivalent to olanzapine film-coated tablets, with a similar rate and extent of absorption. It has the same dosage and frequency of administration as olanzapine film-coated tablets. Olanzapine orodispersible tablets may be used as an alternative to olanzapine film-coated tablets.

Special populations

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

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

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. The metabolism of olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.5).

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

In cases where dose increments of 2.5 mg are considered necessary, Olanzapine Apotex film-coated tablets should be used.

(See sections 4.5 and 5.2).

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk of narrow-angle glaucoma.

4.4 Special warnings and precautions for use

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

Dementia-related psychosis and/or behavioural disturbances

Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient 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 medicines, including Olanzapine Apotex, 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 medicines, including Olanzapine Apotex, 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, alanine transferase (ALT), aspartate transferase (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 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, 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. 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 (see sections 4.8 and 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

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

Newborn infants exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, 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.

Fertility
Effects on fertility are unknown (see section 5.3 for preclinical information).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

4.8 Undesirable effects

Summary of the safety profile

Adults

The most frequently (seen in ≥ 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 available data).

Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and lymphatic system disorders				
	Eosinophilia Leukopenia[10] Neutropenia[10]		Thrombocytopenia[11]	
Immune system disorders				
		Hypersensitivity[11]		
Metabolism and nutrition disorders				
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5] Glucosuria 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 Akathisia[6] Parkinsonism[6] Dyskinesia[6]	Seizures where in most cases a history of seizures or risk factors for seizures were reported [11] Dystonia (including oculogyration) [11] Tardive dyskinesia[11] Amnesia [9] Dysarthria Stuttering[11] Restless legs syndrome[11]	Neuroleptic malignant syndrome (see section 4.4)[12] Discontinuation symptoms[7, 12]	
Cardiac disorders				
		Bradycardia	Ventricular	

		QT_c prolongation (see section 4.4)	tachycardia/fibrillation, sudden death (see section 4.4)[11]	
Vascular disorders				
Orthostatic hypotension[10]		Thromboembolism (including pulmonary embolism and deep vein thrombosis) (see section 4.4)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9] Salivary hypersecretion[11]	Pancreatitis[11]	
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury) [11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	
Renal and urinary disorders				
		Urinary incontinence, urinary retention Urinary hesitation[11]		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders				
	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhea in females Gynaecomastia/breast enlargement in males	Priapism[12]	
General disorders and administration site conditions				

	Asthenia Fatigue Oedema Pyrexia[10]			
Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase[10] High uric acid [10]	Increased total bilirubin		

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

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

[3] Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol/l) to high (≥ 6.2 mmol/l) were very common.

[4] Observed for fasting normal levels at baseline (< 5.56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 5.56 - < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5] Observed for fasting normal levels at baseline (< 1.69 mmol/l) which increased to high (≥ 2.26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥ 1.69 mmol/l - < 2.26 mmol/l) to high (≥ 2.26 mmol/l) were very common.

[6] In clinical trials, the incidence of Parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of Parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

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

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

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

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

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

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

Long-term exposure (at least 48 weeks)
The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Additional information on special populations
In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo (see section 4.4). Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.

In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1%; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥10%) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥7% from baseline body weight in 39.9% of patients.

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

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

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

Metabolism and nutrition disorders *Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite. *Common:* Elevated cholesterol levels[15]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth
Hepatobiliary disorders

Very common: Elevations of hepatic aminotransferases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16].

[13] Following short term treatment (median 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms
Very common symptoms in overdose (≥ 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

Management
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code 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 M1-M5; α_1 adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5 HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin 5 HT_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
Controlled efficacy data in adolescents (ages 13 to 17 years) are limited to short term studies in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin (see sections 4.4 and 4.8) were greater in adolescents than in adults. There are no controlled data on maintenance of effect or long term safety (see sections 4.4 and 4.8). Information on long term safety is primarily limited to open-label, uncontrolled data.

5.2 Pharmacokinetic properties

Olanzapine orodispersible tablet is bioequivalent to olanzapine coated tablets, with a similar rate and extent of absorption. Olanzapine orodispersible tablets may be used as an alternative to olanzapine coated tablets.

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

Distribution
The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α_1-acid-glycoprotein.

Biotransformation
Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites; both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent, olanzapine.

Elimination
After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hrs) 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 hrs) 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 hrs) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57% of radiolabelled olanzapine appeared in urine, principally as metabolites.

Hepatic impairment
A small study of the effect of impaired liver function in 6 subjects with clinically significant (Childs Pugh Classification A (n = 5) and B (n = 1)) cirrhosis revealed little effect on the pharmacokinetics of

orally administered olanzapine (2.5 – 7.5 mg single dose): Subjects with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster elimination half-time compared to subjects with no hepatic dysfunction (n = 3). There were more smokers among subjects with cirrhosis (4/6; 67 %) than among subjects with no hepatic dysfunction (0/3; 0 %).

Smoking
In non-smoking versus smoking subjects (males and females), the mean elimination half-life was prolonged (38.6 versus 30.4 hrs) 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

Mannitol (E421)
Microcrystalline cellulose
Carmellose calcium
Sucralose
Magnesium stearate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister strips in cartons of 28 orodispersible tablets per carton

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10.06.2010

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 20 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 20 mg olanzapine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

Yellow round flat faced radial edge tablets engraved 'APO' on one side and 'OL' over '20' 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.

Olanzapine Apotex orodispersible tablet should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or other suitable beverage (orange juice, apple juice, milk or coffee) immediately before administration.

Olanzapine orodispersible tablet is bioequivalent to olanzapine film-coated tablets, with a similar rate and extent of absorption. It has the same dosage and frequency of administration as olanzapine film-coated tablets. Olanzapine orodispersible tablets may be used as an alternative to olanzapine film-coated tablets.

Special populations

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

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

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. The metabolism of olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.5).

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

In cases where dose increments of 2.5 mg are considered necessary, Olanzapine Apotex film-coated tablets should be used.

(See sections 4.5 and 5.2).

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk of narrow-angle glaucoma.

4.4 Special warnings and precautions for use

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

Dementia-related psychosis and/or behavioural disturbances

Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient 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 medicines, including Olanzapine Apotex, 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 medicines, including Olanzapine Apotex, 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, alanine transferase (ALT), aspartate transferase (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 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, 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. 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 (see sections 4.8 and 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

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

Newborn infants exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, 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.

Fertility
Effects on fertility are unknown (see section 5.3 for preclinical information).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

4.8 Undesirable effects

Summary of the safety profile
Adults
The most frequently (seen in ≥ 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 available data).

Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders				
	Eosinophilia Leukopenia[10] Neutropenia[10]		Thrombocytopenia[11]	
Immune system disorders				
		Hypersensitivity[11]		
Metabolism and nutrition disorders				
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5] Glucosuria 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 Akathisia[6] Parkinsonism[6] Dyskinesia[6]	Seizures where in most cases a history of seizures or risk factors for seizures were reported [11] Dystonia (including oculogyration) [11] Tardive dyskinesia[11] Amnesia [9] Dysarthria Stuttering[11] Restless legs syndrome[11]	Neuroleptic malignant syndrome (see section 4.4)[12] Discontinuation symptoms[7, 12]	
Cardiac disorders				
		Bradycardia 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)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9] Salivary hypersecretion[11]	Pancreatitis[11]	
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury)[11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	
Renal and urinary disorders				
		Urinary incontinence, urinary retention Urinary hesitation[11]		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders				
	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhea in females Gynaecomastia/breast enlargement in males	Priapism[12]	
General disorders and administration site conditions				
	Asthenia Fatigue Oedema Pyrexia[10]			

Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase[10] High uric acid [10]	Increased total bilirubin		

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

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

[3] Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol/l) to high (≥ 6.2 mmol/l) were very common.

[4] Observed for fasting normal levels at baseline (< 5.56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 5.56 - < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5] Observed for fasting normal levels at baseline (< 1.69 mmol/l) which increased to high (≥ 2.26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥ 1.69 mmol/l - < 2.26 mmol/l) to high (≥ 2.26 mmol/l) were very common.

[6] In clinical trials, the incidence of Parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of Parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

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

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

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

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

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

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

Long-term exposure (at least 48 weeks)
The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Additional information on special populations
In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo (see section 4.4). Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.

In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1%; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥10%) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥7% from baseline body weight in 39.9% of patients.

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

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

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

Metabolism and nutrition disorders *Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite. *Common:* Elevated cholesterol levels[15]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth
Hepatobiliary disorders *Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16].

[13] Following short term treatment (median 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms
Very common symptoms in overdose (> 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

Management
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code 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 M1-M5; α_1 adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5 HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin 5 HT_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

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

5.2 Pharmacokinetic properties

Olanzapine orodispersible tablet is bioequivalent to olanzapine coated tablets, with a similar rate and extent of absorption. Olanzapine orodispersible tablets may be used as an alternative to olanzapine coated tablets.

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

Distribution
The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α_1-acid-glycoprotein.

Biotransformation
Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites; both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent, olanzapine.

Elimination
After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hrs) 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 hrs) 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 hrs) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57% of radiolabelled olanzapine appeared in urine, principally as metabolites.

Hepatic impairment
A small study of the effect of impaired liver function in 6 subjects with clinically significant (Childs Pugh Classification A (n = 5) and B (n = 1)) cirrhosis revealed little effect on the pharmacokinetics of orally administered olanzapine (2.5 – 7.5 mg single dose): Subjects with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster elimination half-time compared to

subjects with no hepatic dysfunction (n = 3). There were more smokers among subjects with cirrhosis (4/6; 67 %) than among subjects with no hepatic dysfunction (0/3; 0 %).

Smoking
In non-smoking versus smoking subjects (males and females), the mean elimination half-life was prolonged (38.6 versus 30.4 hrs) 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

Mannitol (E421)
Microcrystalline cellulose
Carmellose calcium
Sucralose
Magnesium stearate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister strips in cartons of 28 and 56 orodispersible tablets per carton

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/013-014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10.06.2010

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER 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. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

APL Swift Services (Malta) Ltd.
HF26 Hal Far Industrial Estate,
Hal Far, Birzebbugia,
BBG 3000, Malta.

Generis Farmacêutica, S.A.
Rua João de Deus, 19
2700-487 Amadora
Portugal

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 (PSURs)**

The marketing authorisation holder (MAH) shall submit PSURs 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)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 2.5 mg film-coated tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg olanzapine.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-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

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

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/001

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Olanzapine Apotex 2.5 mg film-coated tablet

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 2.5 mg film-coated tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 5 mg film-coated tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg olanzapine.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
56 film-coated tablets
98 film-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

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

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/002-003
EU/1/10/635/015

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Olanzapine Apotex 5 mg film-coated tablet

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 5 mg film-coated tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 7.5 mg film-coated tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 7.5 mg olanzapine.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
56 film-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

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

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/004-005

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Olanzapine Apotex 7.5 mg film-coated tablet

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 7.5 mg film-coated tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 10 mg film-coated tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg olanzapine.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
56 film-coated tablets
98 film-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

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

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/006-007
EU/1/10/635/016

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Olanzapine Apotex 10 mg film-coated tablet

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 10 mg film-coated tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 5 mg orodispersible tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg olanzapine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 orodispersible tablets
56 orodispersible tablets
98 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.
Place the tablet in your mouth. It will quickly dissolve with your saliva and can be swallowed.

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

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

Apotex Europe B.V.
Baarnsche Dijk 1

3741 LN Baarn
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/008-009
EU/1/10/635/017

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Olanzapine Apotex 5 mg orodispersible tablet

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 5 mg orodispersible tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 10 mg orodispersible tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg olanzapine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 orodispersible tablets
56 orodispersible tablets
98 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.
Place the tablet in your mouth. It will quickly dissolve with your saliva and can be swallowed.

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

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

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn

The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/010-011
EU/1/10/635/018

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Olanzapine Apotex 10 mg orodispersible tablet

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 10 mg orodispersible tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 15 mg orodispersible tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 15 mg olanzapine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.
Place the tablet in your mouth. It will quickly dissolve with your saliva and can be swallowed.

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

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

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/012

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Olanzapine Apotex 15 mg orodispersible tablet

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 15 mg orodispersible tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 20 mg orodispersible tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg olanzapine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 orodispersible tablets
56 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.
Place the tablet in your mouth. It will quickly dissolve with your saliva and can be swallowed.

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

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

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/635/013-014

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Olanzapine Apotex 20 mg orodispersible tablet

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 20 mg orodispersible tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Olanzapine Apotex 2.5 mg film-coated tablets
Olanzapine Apotex 5 mg film-coated tablets
Olanzapine Apotex 7.5 mg film-coated tablets
Olanzapine Apotex 10 mg film-coated tablets

Olanzapine

Read all of this leaflet carefully before you start using 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. See section 4.

What is in this leaflet

1. What Olanzapine Apotex is and what it is used for

Olanzapine Apotex contains the active substance olanzapine. Olanzapine Apotex 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 Apotex 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 Apotex

Do not take Olanzapine Apotex
- If 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 taking Olanzapine Apotex.
- The use of Olanzapine Apotex 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 Apotex 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 Apotex. You and your doctor should check your weight regularly. Consider referral to a dietician or help with a diet plan if necessary.
- High blood sugar and high levels of fat (triglycerides and cholesterol) have been seen in patients taking Olanzapine Apotex. Your doctor should do blood tests to check blood sugar and certain fat levels before you start taking Olanzapine Apotex 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 know that you may have salt depletion as a result of prolonged severe diarrhoea and vomiting (being sick) or usage of diuretics (water tablets)

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 Apotex is not for patients who are under 18 years.

Other medicines and Olanzapine Apotex
Only take other medicines while you are on Olanzapine Apotex if your doctor tells you that you can. You might feel drowsy if Olanzapine Apotex 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 Apotex dose.

Olanzapine Apotex with alcohol
Do not drink any alcohol if you have been given Olanzapine Apotex 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 Apotex can pass into breast milk.

The following symptoms may occur in newborn babies, of mothers that have used Olanzapine Apotex 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 Apotex. If this happens do not drive or operate any tools or machines. Tell your doctor.

Olanzapine Apotex 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 Apotex

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

You should take your Olanzapine Apotex 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 Apotex film-coated tablets are for oral use. You should swallow the Olanzapine Apotex tablets whole with water.

If you take more Olanzapine Apotex than you should
Patients who have taken more Olanzapine Apotex 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 confusion, 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 straight away if you experience any of the above symptoms. Show the doctor your pack of tablets.

If you forget to take Olanzapine Apotex
Take your tablets as soon as you remember. Do not take two doses in one day.

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

If you suddenly stop taking Olanzapine Apotex, 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); restless legs syndrome problems with speech; stuttering; slow heart rate; sensitivity to sunlight; bleeding from the nose; abdominal distension; drooling; 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.

Very rare side effects include serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia).

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 Apotex may worsen the symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Olanzapine Apotex

Keep this medicine out of sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

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 protect the environment.

6. Contents of the pack and other information

What Olanzapine Apotex contains
The active substance is olanzapine.
- Each Olanzapine Apotex 2.5 mg film-coated tablet contains 2.5 mg olanzapine.
- Each Olanzapine Apotex 5 mg film-coated tablet contains 5 mg olanzapine.
- Each Olanzapine Apotex 7.5 mg film-coated tablet contains 7.5 mg olanzapine.
- Each Olanzapine Apotex 10 mg film-coated tablet contains 10 mg olanzapine.

The other ingredients are (tablet core) lactose monohydrate, microcrystalline cellulose, maize starch, magnesium stearate, (tablet coat) hypromellose, hydroxypropylcellulose, macrogol 8000, titanium dioxide (E171).

What Olanzapine Apotex looks like and contents of the pack
- Olanzapine Apotex 2.5 mg are white, round, biconvex film-coated tablets engraved 'APO' on one side and 'OLA' over '2.5' on the other side.
- Olanzapine Apotex 5 mg are white, round biconvex film-coated tablets engraved 'APO' on one side and 'OLA' over '5' on the other side.
- Olanzapine Apotex 7.5 mg are white, round biconvex film-coated tablets engraved 'APO' on one side and 'OLA' over '7.5' on the other side.
- Olanzapine Apotex 10 mg are white, round biconvex film-coated tablets engraved 'APO' on one side and 'OLA' over '10' on the other side.

- Olanzapine Apotex 2.5 mg film-coated tablets are available in blisters packs of 28 tablets.
- Olanzapine Apotex 7.5 mg film-coated tablets are available in blisters packs of 28 and 56 tablets.
- Olanzapine Apotex 5 mg and 10 mg film- coated tablets are available in blister packs of 28, 56 and 98 tablets..

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

Manufacturer
Generis Farmacêutica, S.A.
Rua João de Deus, 19
2700-487 Amadora
Portugal

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
NV Apotex SA
Tél/Tel:(32) 475.35.40

България
Apotex Europe B.V.
тел. (31) 35. 542.99. 33

Česká republika
Aurovitas, spol. s r.o.
Tel: (420) 234.705.721

Danmark
Apotex Europe B.V.
Tlf.: (31) 35. 542.99. 33

Deutschland
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Eesti
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Ελλάδα
Apotex Europe B.V.
Τηλ: (31) 35. 542.99. 33

España
Aurovitas Spain, S.A.U.Tel: (34) 91.630.86.45

France
NV Apotex SA
Tél: (32) 475.35.40

Hrvatska
Apotex Europe B.V..
Tel: (31) 35. 542.99. 33

Ireland
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Ísland
Apotex Europe B.V.
Sími: (31) 35. 542.99. 33

Italia
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Κύπρος
Apotex Europe B.V.
Τηλ: (31) 35. 542.99. 33

Latvija
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Lietuva
Apotex Europe B.V.
Tel. (31) 35. 542.99. 33

Luxembourg/Luxemburg
NV Apotex SA
Tél/Tel:(32) 475.35.40

Magyarország
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Malta
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Nederland
Apotex Nederland B.V.
Tel: (31) 71. 52.43.100

Norge
Apotex Europe B.V.
Tlf.: (31) 35. 542.99. 33

Österreich
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Polska
Aurovitas Pharma Polska Sp. z o.o.
Tel: (048) 22.311.20.00

Portugal
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

România
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Slovenija
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Slovenská republika
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Suomi/Finland
Apotex Europe B.V.
Puh/Tel: (31) 35. 542.99. 33

Sverige
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

United Kingdom
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

This leaflet was last revised in {month XXXX}.

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

Package leaflet: Information for the user

Olanzapine Apotex 5 mg orodispersible tablets
Olanzapine Apotex 10 mg orodispersible tablets
Olanzapine Apotex 15 mg orodispersible tablets
Olanzapine Apotex 20 mg orodispersible tablets

Olanzapine

Read all of this leaflet carefully before you start using 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. See section 4.

What is in this leaflet

1. What Olanzapine Apotex is and what it is used for

Olanzapine Apotex contains the active substance olanzapine. Olanzapine Apotex 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 Apotex 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 Apotex

Do not take Olanzapine Apotex
- If 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 taking Olanzapine Apotex.
- The use of Olanzapine Apotex 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 Apotex 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 Apotex. You and your doctor should check your weight regularly. Consider referral to a dietician or help with a diet plan if necessary.
- High blood sugar and high levels of fat (triglycerides and cholesterol) have been seen in patients taking Olanzapine Apotex. Your doctor should do blood tests to check blood sugar and certain fat levels before you start taking Olanzapine Apotex 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 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 know that you may have salt depletion as a result of prolonged severe diarrhoea and vomiting (being sick) or usage of diuretics (water tablets)

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 Apotex is not for patients who are under 18 years.

Other medicines and Olanzapine Apotex
Only take other medicines while you are on Olanzapine Apotex if your doctor tells you that you can. You might feel drowsy if Olanzapine Apotex 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 Apotex dose.

Olanzapine Apotex with alcohol
Do not drink any alcohol if you have been given Olanzapine Apotex 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 OlanzapineApotex can pass into breast milk

The following symptoms may occur in newborn babies, of mothers that have used Olanzapine Apotex 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 Apotex. If this happens do not drive or operate any tools or machines. Tell your doctor.

3. How to take Olanzapine Apotex

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

You should take your Olanzapine Apotex 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 Apotex orodispersible tablets are for oral use.

Olanzapine Apotex tablets break easily, so you should handle the tablets carefully. Do not handle the tablets with wet hands as the tablets may break up.

You can also place the tablet in a full glass or cup of water, orange juice, apple juice, milk or or coffee and stir. With some drinks, the mixture may change colour and possibly become cloudy. Drink it straight away.

If you take more Olanzapine Apotex than you should
Patients who have taken more Olanzapine Apotex 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 confusion, 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 straight away if you experience any of the above symptoms. Show the doctor your pack of tablets.

If you forget to take Olanzapine Apotex
Take your tablets as soon as you remember. Do not take two doses in one day.

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

If you suddenly stop taking Olanzapine Apotex, 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); restless legs syndrome problems with speech; stuttering; slow heart rate; sensitivity to sunlight; bleeding from the nose; abdominal distension; drooling; 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.

Very rare side effects include serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia).

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 Apotex may worsen the symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Olanzapine Apotex

Keep this medicine out of sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

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 protect the environment.

6. Contents of the pack and other information

What Olanzapine Apotex contains
The active substance is olanzapine.
- Each Olanzapine Apotex 5 mg orodispersible tablet contains 5 mg olanzapine.
- Each Olanzapine Apotex 10 mg orodispersible tablet contains 10 mg olanzapine.
- Each Olanzapine Apotex 15 mg orodispersible tablet contains 15 mg olanzapine.
- Each Olanzapine Apotex 20 mg orodispersible tablet contains 20 mg olanzapine.

The other ingredients are mannitol (E421), microcrystalline cellulose, carmellose calcium, sucralose, magnesium stearate and colloidal anhydrous silica.

What Olanzapine Apotex looks like and contents of the pack
Orodispersible tablet is the technical name for a tablet which dissolves directly in your mouth, so that it can be easily swallowed.

- Olanzapine Apotex 5 mg orodispersible tablets are yellow round flat faced radial edge tablets engraved 'APO' on one side and 'OL' over '5' on the other side.
- Olanzapine Apotex 10 mg orodispersible tablets are yellow round flat faced radial edge tablets engraved 'APO' on one side and 'OL' over '10' on the other side.
- Olanzapine Apotex 15 mg orodispersible tablets are yellow round flat faced radial edge tablets engraved 'APO' on one side and 'OL' over '15' on the other side
- Olanzapine Apotex 20 mg orodispersible tablets are yellow round flat faced radial edge tablets engraved 'APO' on one side and 'OL' over '20' on the other side.

- Olanzapine Apotex 5 mg and 10 mg orodispersible tablets are available in blisters packs of 28 , 56 and 98 tablets.
- Olanzapine Apotex 20 mg orodispersible tablets are available in blister packs of 28 and 56 tablets.
- Olanzapine Apotex 15 mg orodispersible tablets are available in blisters packs of 28 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Apotex Europe B.V.
Baarnsche Dijk 1
3741 LN Baarn
The Netherlands

Manufacturer

APL Swift Services (Malta) Ltd.
HF26 Hal Far Industrial Estate,
Hal Far, Birzebbugia,
BBG 3000, Malta.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
NV Apotex SA
Tél/Tel:(32) 475.35.40

България
Apotex Europe B.V.
тел. (31) 35. 542.99. 33

Česká republika
Aurovitas, spol. s r.o.Tel: (420) 234.705.721

Danmark
Apotex Europe B.V.
Tlf.: (31) 35. 542.99. 33

Deutschland
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Eesti
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Ελλάδα
Apotex Europe B.V.
Τηλ: (31) 35. 542.99. 33

España
Aurovitas Spain, S.A.U.Tel: (34) 91.630.86.45

France
NV Apotex SA
Tél: (32) 475.35.40

Hrvatska
Apotex Europe B.V..
Tel: (31) 35. 542.99. 33

Ireland
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Ísland
Apotex Europe B.V.
Sími: (31) 35. 542.99. 33

Italia
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Luxembourg/Luxemburg
NV Apotex SA
Tél/Tel:(32) 475.35.40

Magyarország
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Malta
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Nederland
Apotex Nederland B.V.
Tel: (31) 71. 52.43.100

Norge
Apotex Europe B.V.
Tlf.: (31) 35. 542.99. 33

Österreich
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Polska
Aurovitas Pharma Polska Sp. z o.o.
Tel: (048) 22.311.20.00

Portugal
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

România
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Slovenija
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Slovenská republika
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Suomi/Finland
Apotex Europe B.V.
Puh/Tel: (31) 35. 542.99. 33

Κύπρος
Apotex Europe B.V.
Τηλ: (31) 35. 542.99. 33

Latvija
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

Lietuva
Apotex Europe B.V.
Tel. (31) 35. 542.99. 33

Sverige
Apotex Europe B.V.
Tel: (31) 35. 542.99. 33

United Kingdom
Apotex Europe B.V.
Tel: (31) 35. 542.99. 3335. 542.99. 33

This leaflet was last revised in {month XXXX}.

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