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MHRA

Public Assessment Report

Decentralised Procedure

Olanzapine 2.5mg, 5mg, 7.5mg & 10mg Film Coated Tablets
UK/H/1198/001-004/DC
UK licence no: PL 10622/0324-7

PLIVA Pharma Limited

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted PLIVA Pharma Limited Marketing Authorisations (licences) for the medicinal products Olanzapine 2.5mg, 5mg 7.5mg & 10mg Film Coated Tablets. These medicines are available on prescription only.

Olanzapine 2.5mg, 5mg, 7.5mg & 10mg Film-Coated Tablets contain the active ingredient, olanzapine, which belongs to a group of medicines called antipsychotics and is used to treat the symptoms of schizophrenia. Such symptoms include hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness and becoming withdrawn.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.

The test product was considered to be a generic version of the reference product Zyprexa 10mg Tablets authorised to Lilly Laboratories, based on the bioequivalence study submitted and no new safety issues arose as a result of this study.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Olanzapine 2.5mg, 5mg, 7.5mg & 10mg Film-Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Product Name	Olanzapine 2.5mg, 5mg, 7.5mg & 10mg Film-Coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Olanzapine
Form	Film-Coated Tablet
Strength	2.5mg, 5mg, 7.5mg & 10mg
MA Holder	PLIVA Pharma Limited
RMS	UK
CMS	Czech Republic, Germany, Estonia, Hungary, Ireland, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia
Procedure Number	UK/H/1198/001-004/DC
Timetable	Day 210 - 30/09/2008

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Olanzapine 2.5mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 2.5mg Olanzapine.

Excipient(s): 72mg lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Olanzapine 2.5mg Film-coated tablets are white, round, biconvex, film-coated tablets, embossed with 'OL' on one side and '2.5' on the other.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
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
Schizophrenia: The recommended starting dose for olanzapine is 10mg/day.

Manic episode: The starting dose is 15mg as a single daily dose in monotherapy or 10mg daily in combination therapy (see section 5.1).

Preventing recurrence in bipolar disorder: The recommended starting dose is 10mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

During treatment for schizophrenia, manic episode, and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours. Olanzapine can be given without regard for meals, as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

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

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

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

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

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

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

(See also section 4.5 and section 5.2.)

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Patients with known risk for narrow-angle glaucoma.

4.4 Special warnings and precautions for use

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

Dementia-related psychosis and/or behavioural disturbances

Olanzapine is not approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4mg) 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 2.5mg/day and titrated to a maximum of 15mg/day based on investigator judgement.

Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially life-threatening condition associated with antipsychotic medicinal product. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high

fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including olanzapine must be discontinued.

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (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 particularly in diabetic patients and in patients with risk factors for the development of diabetes mellitus for which regular glucose control is recommended.

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.

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 transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised 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 medicinal products. In the event of elevated ALT and/or AST during treatment, followup should be organised and dose reduction should be considered. 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 medicinal products 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 very rarely (<0.01%) when olanzapine is stopped abruptly.

QT interval
In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥ 500 milliseconds [msec] at any time post baseline in patients with baseline QTcF<500 msec) were uncommon (0.1% to 1%) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. However, as with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicinal products 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 very rarely (< 0.01%) been reported. 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 medicinal products 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 rarely in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

Tardive Dyskinesia
In comparator studies of one year or less duration, olanzapine was associated with a statistically significant lower incidence of treatment emergent dyskinesia. However the risk of tardive dyskinesia increases with long term exposure, and therefore if signs or symptoms of tardive dyskinesia appear in a patient on olanzapine, a dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Postural hypotension
Postural hypotension was infrequently observed in the elderly in olanzapine clinical trials. As with other antipsychotics, it is recommended that blood pressure is measured periodically in patients over 65 years.

Use in children and adolescents under 18 years of age
Olanzapine is not indicated for use in the treatment of children and adolescents. Studies in patients aged 13-17 years showed various adverse reactions, including weight gain, changes in metabolic parameters and increases in prolactin levels. Long-term outcomes associated with these events have not been studied and remain unknown (see sections 4.8 and 5.1).

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

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* (eg, 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.

CNS medicinal products
Caution should be exercised in patients who receive medicinal products that can cause central nervous system depression and alcohol.

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 Pregnancy and lactation

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.

Spontaneous reports have been very rarely received of tremor, hypertonia, lethargy, and sleepiness, in infants born to mothers who had used olanzapine during the 3rd trimester.

In a study in breast-feeding, healthy women, olanzapine was excreted in breast milk. Mean infant exposure (mg/kg) at steady-state was estimated to be 1.8% of the maternal olanzapine dose (mg/kg). Patients should be advised not to breast-feed an infant if they are taking olanzapine.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequencies of the following undesirable effects are:

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)

Adults
The most frequently reported (very common) 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 (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic transaminases (see section 4.4), rash, asthenia, fatigue and oedema.

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.

Very common	Common	Uncommon	Not known
Blood and the lymphatic system disorders			
	Eosinophilia	Leukopenia Neutropenia	Thrombocytopenia
Immune system disorders			
			Allergic reaction
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) Hypothermia
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 Neuroleptic malignant syndrome (see section 4.4) Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms[7]
Cardiac disorders			
		Bradycardia QTc prolongation (see section 4.4)	Ventricular tachycardia/fibrillation, sudden death (see section 4.4)
Vascular disorders			
	Orthostatic hypotension		Thromboembolism (including pulmonary embolism and deep vein thrombosis)
Gastrointestinal disorders			
	Mild, transient anticholinergic effects including constipation and dry mouth		Pancreatitis
Hepato-biliary disorders			
	Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury)
Skin and subcutaneous tissue disorders			
	Rash	Photosensitivity reaction Alopecia	
Musculoskeletal and connective tissue disorders			
			Rhabdomyolysis

Very common	Common	Uncommon	Not known
Renal and urinary disorders			
			Urinary hesitation
Reproductive system and breast disorders			
			Priapism
General disorders and administration site conditions			
	Asthenia Fatigue Oedema		
Investigations			
Elevated plasma prolactin levels[8]			
		High creatine phosphokinase Increased total bilirubin	Increased alkaine phosphatase

[1] Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Weight gain ≥ 7% of baseline body weight was very common and ≥ 15% of baseline body weight was common.

[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) to high (≥ 6.2 mmol) were very common.

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

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

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

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

[8] Associated clinical manifestations (e.g., gynaecomastia, galactorrhoea, and breast enlargement) were rare. In most patients, levels returned to normal ranges without cessation of treatment.

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

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

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

Children and adolescents
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 clinical trials in adolescent patients. Clinically significant weight gain (≥ 7%) appears to occur more frequently in the adolescent population.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders *Very common:* Weight gain[9], elevated triglyceride levels[10], increased appetite. *Common:* Elevated cholesterol levels[11]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth
Hepato-biliary disorders *Very common:* Elevations of hepatic transaminases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[12.]

[9] Weight gain ≥ 7% of baseline body weight (kg) was very common and ≥ 15% of baseline body weight was common.

[10] 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).

[11] 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.

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

4.9 Overdose
Signs and Symptoms

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

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome (NMS), respiratory depression, aspiration, hypertension or

hypotension, cardiac arrhythmias (<2% of overdose cases), and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450mg, but survival has also been reported following acute overdose of 1,500mg.

Management of Overdose

There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (ie, 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: Antipsychotics; diazepines, oxazepines and thiazepines. *ATC code:* N05A H03.

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 (Ki; <100nM) for serotonin $5HT_{2A/2C}$, $5HT_3$, $5HT_6$; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors m_1-m_5; $alpha_1$ adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin $5HT_2$ than dopamine D_2 receptors and greater $5HT_2$ than D_2 activity in *in vivo* models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responses in an 'anxiolytic' test.

In a single oral dose (10mg) Positron Emission Tomography (PET) study in healthy volunteers, olanzapine produced a higher $5HT_{2A}$ than dopamine D_2 receptor occupancy. In addition, a Single Photon Emission Computed Tomography (SPECT) imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D_2 occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

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 10mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

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

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

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

5.2 Pharmacokinetic properties

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.

Olanzapine is metabolised in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites; both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent, olanzapine. 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 hours) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia >65 years of age, dosing from 5 to 20mg/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 hours) and the clearance was reduced (18.9 versus 27.3 l/hr). However, olanzapine (5-20mg) demonstrated a comparable safety profile in female (n = 467) as in male patients (n = 869).

In renally impaired patients (creatinine clearance <10ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hours) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57% of radiolabelled olanzapine appeared in urine, principally as metabolites.

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

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

The plasma protein binding of olanzapine was about 93% over the concentration range of about 7 to about 1,000ng/ml. Olanzapine is bound predominantly to albumin and alpha$_1$-acid-glycoprotein.

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 210mg/kg (mice) and 175mg/kg (rats). Dogs tolerated single oral doses up to 100mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, laboured respiration, miosis, and anorexia. In monkeys, single oral doses up to 100mg/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 leucocytes in mice and non-specific reductions of circulating leucocytes 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 10mg/kg/day (total olanzapine exposure [area under the curve - AUC] is 12- to 15-fold greater than that of a man given a 12mg dose). In cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

Reproductive Toxicity

Olanzapine had no teratogenic effects. Sedation affected mating performance of male rats. Oestrous cycles were affected at doses of 1.1mg/kg (3-times the maximum human dose) and reproduction parameters were influenced in rats given 3mg/kg (9-times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

Mutagenicity

Olanzapine was not mutagenic or clastogenic in a full range of standard tests, which included bacterial mutation tests and *in vitro* and *in vivo* mammalian tests.

Carcinogenicity

Based on the results of studies in mice and rats, it was concluded that olanzapine is not carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Maize starch
Silica, colloidal anhydrous
Magnesium stearate

Sub-coating
Hypromellose

Coating
Hypromellose, lactose monohydrate, titanium dioxide (E171), macrogol 4000 and sodium citrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package to protect from moisture.

6.5 Nature and contents of container

Blisters (OPA/ Al/ PVC// Al foil) within a carton box.
Olanzapine 2.5mg Film-coated tablets: 28, 30, 35, 56, 60 or 70 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

PLIVA Pharma Ltd
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 10622/0324

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/12/2008

10 DATE OF REVISION OF THE TEXT

04/12/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Olanzapine PLIVA 5 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg Olanzapine.

Excipient(s): 144 mg lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Olanzapine 5mg Film-coated tablets are white, round, biconvex, film-coated tablets, embossed with 'OL' on one side and '5' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Schizophrenia: The recommended starting dose for olanzapine is 10mg/day.

Manic episode: The starting dose is 15mg as a single daily dose in monotherapy or 10mg daily in combination therapy (see section 5.1).

Preventing recurrence in bipolar disorder: The recommended starting dose is 10mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

During treatment for schizophrenia, manic episode, and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours. Olanzapine can be given without regard for meals, as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

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

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

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

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

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

When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.
(See also section 4.5 and section 5.2.)

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Dementia-related psychosis and/or behavioural disturbances
Olanzapine is not approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4mg) 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 2.5mg/day and titrated to a maximum of 15mg/day based on investigator judgement.

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal product. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including olanzapine must be discontinued.

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (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 particularly in diabetic patients and in patients with risk factors for the development of diabetes mellitus for which regular glucose control is recommended.

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.

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 transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised 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 medicinal products. In the event of elevated ALT and/or AST during treatment, followup should be organised and dose reduction should be considered. 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 medicinal products 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 very rarely (<0.01%) when olanzapine is stopped abruptly.

QT interval
In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥ 500 milliseconds [msec] at any time post baseline in patients with baseline QTcF<500 msec) were uncommon (0.1% to 1%) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. However, as with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicinal products 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 very rarely (< 0.01%) been reported. 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 medicinal products 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 rarely in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

Tardive Dyskinesia
In comparator studies of one year or less duration, olanzapine was associated with a statistically significant lower incidence of treatment emergent dyskinesia. However the risk of tardive dyskinesia increases with long term exposure, and therefore if signs or symptoms of tardive dyskinesia appear in a patient on olanzapine, a dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Postural hypotension
Postural hypotension was infrequently observed in the elderly in olanzapine clinical trials. As with other antipsychotics, it is recommended that blood pressure is measured periodically in patients over 65 years.

Use in children and adolescents under 18 years of age
Olanzapine is not indicated for use in the treatment of children and adolescents. Studies in patients aged 13-17 years showed various adverse reactions, including weight gain, changes in metabolic parameters and increases in prolactin levels. Long-term outcomes associated with these events have not been studied and remain unknown (see sections 4.8 and 5.1).

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

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* (eg, 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.

CNS medicinal products
Caution should be exercised in patients who receive medicinal products that can cause central nervous system depression and alcohol.

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 Pregnancy and lactation

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.

Spontaneous reports have been very rarely received of tremor, hypertonia, lethargy, and sleepiness, in infants born to mothers who had used olanzapine during the 3rd trimester.

In a study in breast-feeding, healthy women, olanzapine was excreted in breast milk. Mean infant exposure (mg/kg) at steady-state was estimated to be 1.8% of the maternal olanzapine dose (mg/kg). Patients should be advised not to breast-feed an infant if they are taking olanzapine.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequencies of the following undesirable effects are:

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)

Adults
The most frequently reported (very common) 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 (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic transaminases (see section 4.4), rash, asthenia, fatigue and oedema.

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.

Very common	Common	Uncommon	Not known
Blood and the lymphatic system disorders			
	Eosinophilia	Leukopenia Neutropenia	Thrombocytopenia
Immune system disorders			
			Allergic reaction
Metabolism and nutrition disorders			
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5]		Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal

Very common	Common	Uncommon	Not known
	Glucosuria Increased appetite		cases (see section 4.4) Hypothermia
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 Neuroleptic malignant syndrome (see section 4.4) Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms[7]
Cardiac disorders			
		Bradycardia QTc prolongation (see section 4.4)	Ventricular tachycardia/fibrillation, sudden death (see section 4.4)
Vascular disorders			
	Orthostatic hypotension		Thromboembolism (including pulmonary embolism and deep vein thrombosis)
Gastrointestinal disorders			
	Mild, transient anticholinergic effects including constipation and dry mouth		Pancreatitis
Hepato-biliary disorders			
	Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury)
Skin and subcutaneous tissue disorders			
	Rash	Photosensitivity reaction Alopecia	
Musculoskeletal and connective tissue disorders			
			Rhabdomyolysis
Renal and urinary disorders			
			Urinary hesitation
Reproductive system and breast disorders			
			Priapism
General disorders and administration site conditions			
	Asthenia Fatigue Oedema		
Investigations			
Elevated plasma			

Very common	Common	Uncommon	Not known
prolactin levels[8]			
		High creatine phosphokinase Increased total bilirubin	Increased alkaine phosphatase

[1] Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Weight gain ≥ 7% of baseline body weight was very common and ≥ 15% of baseline body weight was common.

[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) to high (≥ 6.2 mmol) were very common.

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

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

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

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

[8] Associated clinical manifestations (e.g., gynaecomastia, galactorrhoea, and breast enlargement) were rare. In most patients, levels returned to normal ranges without cessation of treatment.

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

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

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

Children and adolescents
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 clinical trials in adolescent patients. Clinically significant weight gain (≥ 7%) appears to occur more frequently in the adolescent population.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders *Very common:* Weight gain[9], elevated triglyceride levels[10], increased appetite. *Common:* Elevated cholesterol levels[11]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth
Hepato-biliary disorders *Very common:* Elevations of hepatic transaminases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[12.]

[9] Weight gain ≥ 7% of baseline body weight (kg) was very common and ≥ 15% of baseline body weight was common.

[10] 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).

[11] 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.

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

4.9 Overdose
Signs and Symptoms

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

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome (NMS), respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (<2% of overdose cases), and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450mg, but survival has also been reported following acute overdose of 1,500mg.

Management of Overdose

There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (ie, 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: Antipsychotics; diazepines, oxazepines and thiazepines. *ATC code:* N05A H03.

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 (Ki; <100nM) for serotonin $5HT_{2A/2C}$, $5HT_3$, $5HT_6$; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors m_1-m_5; $alpha_1$ adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin $5HT_2$ than dopamine D_2 receptors and greater $5HT_2$ than D_2 activity in *in vivo* models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responses in an 'anxiolytic' test.

In a single oral dose (10mg) Positron Emission Tomography (PET) study in healthy volunteers, olanzapine produced a higher $5HT_{2A}$ than dopamine D_2 receptor occupancy. In addition, a Single Photon Emission Computed Tomography (SPECT) imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D_2 occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

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 10mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

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

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

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

5.2 Pharmacokinetic properties

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.

Olanzapine is metabolised in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites; both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent, olanzapine. 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 hours) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia >65 years of age, dosing from 5 to 20mg/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 hours) and the clearance was reduced (18.9 versus 27.3 l/hr). However, olanzapine (5-20mg) demonstrated a comparable safety profile in female (n = 467) as in male patients (n = 869).

In renally impaired patients (creatinine clearance <10ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hours) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57% of radiolabelled olanzapine appeared in urine, principally as metabolites.

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

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

The plasma protein binding of olanzapine was about 93% over the concentration range of about 7 to about 1,000ng/ml. Olanzapine is bound predominantly to albumin and $alpha_1$-acid-glycoprotein.

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 210mg/kg (mice) and 175mg/kg (rats). Dogs tolerated single oral doses up to 100mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, laboured respiration, miosis, and anorexia. In monkeys, single oral doses up to 100mg/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 leucocytes in mice and non-specific reductions of circulating leucocytes 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 10mg/kg/day (total olanzapine exposure [area under the curve - AUC] is 12- to 15-fold greater than that of a man given a 12mg dose). In cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

Reproductive Toxicity

Olanzapine had no teratogenic effects. Sedation affected mating performance of male rats. Oestrous cycles were affected at doses of 1.1mg/kg (3-times the maximum human dose) and reproduction parameters were influenced in rats given 3mg/kg (9-times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

Mutagenicity

Olanzapine was not mutagenic or clastogenic in a full range of standard tests, which included bacterial mutation tests and *in vitro* and *in vivo* mammalian tests.

Carcinogenicity

Based on the results of studies in mice and rats, it was concluded that olanzapine is not carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Maize starch
Silica, colloidal anhydrous
Magnesium stearate

Sub-coating
Hypromellose

Coating
Hypromellose, lactose monohydrate, titanium dioxide (E171), macrogol 4000 and sodium citrate.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months

6.4 Special precautions for storage
Do not store above 25°C.

Store in the original package to protect from moisture.

6.5 Nature and contents of container
Blisters (OPA/ Al/ PVC// Al foil) within a carton box.
Olanzapine 5mg Film-coated tablets: 28, 30, 35, 56, 60 or 70 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
PLIVA Pharma Ltd
Vision house
Bedford Road
Hampshire
GU32 3QB
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 10622/0325

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/12/2008

10 DATE OF REVISION OF THE TEXT
04/12/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Olanzapine PLIVA 7.5mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 7.5mg Olanzapine.

Excipient(s): 216mg lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Olanzapine 7.5mg Film-coated tablets are white, round, biconvex, film-coated tablets, embossed with 'OL' on one side and '7.5' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Schizophrenia: The recommended starting dose for olanzapine is 10mg/day.

Manic episode: The starting dose is 15mg as a single daily dose in monotherapy or 10mg daily in combination therapy (see section 5.1).

Preventing recurrence in bipolar disorder: The recommended starting dose is 10mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

During treatment for schizophrenia, manic episode, and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours. Olanzapine can be given without regard for meals, as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

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

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

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

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

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

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

(See also section 4.5 and section 5.2.)

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Patients with known risk for narrow-angle glaucoma

4.4 Special warnings and precautions for use

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

Dementia-related psychosis and/or behavioural disturbances

Olanzapine is not approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4mg) 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 2.5mg/day and titrated to a maximum of 15mg/day based on investigator judgement.

Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially life-threatening condition associated with antipsychotic medicinal product. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including olanzapine must be discontinued.

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (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 particularly in diabetic patients and in patients with risk factors for the development of diabetes mellitus for which regular glucose control is recommended.

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.

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 transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised 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 medicinal products. In the event of elevated ALT and/or AST during treatment, followup should be organised and dose reduction should be considered. 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 medicinal products 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 very rarely (<0.01%) when olanzapine is stopped abruptly.

QT interval
In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥ 500 milliseconds [msec] at any time post baseline in patients with baseline QTcF<500 msec) were uncommon (0.1% to 1%) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. However, as with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicinal products 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 very rarely (< 0.01%) been reported. 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 medicinal products 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 rarely in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

Tardive Dyskinesia
In comparator studies of one year or less duration, olanzapine was associated with a statistically significant lower incidence of treatment emergent dyskinesia. However the risk of tardive dyskinesia increases with long term exposure, and therefore if signs or symptoms of tardive dyskinesia appear in a patient on olanzapine, a dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Postural hypotension
Postural hypotension was infrequently observed in the elderly in olanzapine clinical trials. As with other antipsychotics, it is recommended that blood pressure is measured periodically in patients over 65 years.

Use in children and adolescents under 18 years of age
Olanzapine is not indicated for use in the treatment of children and adolescents. Studies in patients aged 13-17 years showed various adverse reactions, including weight gain, changes in metabolic parameters and increases in prolactin levels. Long-term outcomes associated with these events have not been studied and remain unknown (see sections 4.8 and 5.1).

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

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* (eg, 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.

CNS medicinal products
Caution should be exercised in patients who receive medicinal products that can cause central nervous system depression and alcohol.

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 Pregnancy and lactation

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.

Spontaneous reports have been very rarely received of tremor, hypertonia, lethargy, and sleepiness, in infants born to mothers who had used olanzapine during the 3rd trimester.

In a study in breast-feeding, healthy women, olanzapine was excreted in breast milk. Mean infant exposure (mg/kg) at steady-state was estimated to be 1.8% of the maternal olanzapine dose (mg/kg). Patients should be advised not to breast-feed an infant if they are taking olanzapine.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequencies of the following undesirable effects are:

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)

Adults
The most frequently reported (very common) 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 (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic transaminases (see section 4.4), rash, asthenia, fatigue and oedema.

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.

Very common	Common	Uncommon	Not known
Blood and the lymphatic system disorders			
	Eosinophilia	Leukopenia Neutropenia	Thrombocytopenia
Immune system disorders			
			Allergic reaction
Metabolism and nutrition disorders			
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose		Development or exacerbation of diabetes occasionally

Very common	Common	Uncommon	Not known
	levels[4] Elevated triglyceride levels[2,5] Glucosuria Increased appetite		associated with ketoacidosis or coma, including some fatal cases (see section 4.4) Hypothermia
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 Neuroleptic malignant syndrome (see section 4.4) Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms[7]
Cardiac disorders			
		Bradycardia QTc prolongation (see section 4.4)	Ventricular tachycardia/fibrillation, sudden death (see section 4.4)
Vascular disorders			
	Orthostatic hypotension		Thromboembolism (including pulmonary embolism and deep vein thrombosis)
Gastrointestinal disorders			
	Mild, transient anticholinergic effects including constipation and dry mouth		Pancreatitis
Hepato-biliary disorders			
	Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury)
Skin and subcutaneous tissue disorders			
	Rash	Photosensitivity reaction Alopecia	
Musculoskeletal and connective tissue disorders			
			Rhabdomyolysis
Renal and urinary disorders			
			Urinary hesitation
Reproductive system and breast disorders			
			Priapism
General disorders and administration site conditions			
	Asthenia Fatigue Oedema		

Very common	Common	Uncommon	Not known
Investigations			
Elevated plasma prolactin levels[8]			
		High creatine phosphokinase Increased total bilirubin	Increased alkaine phosphatase

[1] Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Weight gain ≥ 7% of baseline body weight was very common and ≥ 15% of baseline body weight was common.

[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) to high (≥ 6.2 mmol) were very common.

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

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

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

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

[8] Associated clinical manifestations (e.g., gynaecomastia, galactorrhoea, and breast enlargement) were rare. In most patients, levels returned to normal ranges without cessation of treatment.

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

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

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

Children and adolescents
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 clinical trials in adolescent patients. Clinically significant weight gain (≥ 7%) appears to occur more frequently in the adolescent population.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders *Very common:* Weight gain[9], elevated triglyceride levels[10], increased appetite. *Common:* Elevated cholesterol levels[11]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth
Hepato-biliary disorders *Very common:* Elevations of hepatic transaminases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[12.]

[9] Weight gain ≥ 7% of baseline body weight (kg) was very common and ≥ 15% of baseline body weight was common.

[10] 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).

[11] 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.

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

4.9 Overdose
Signs and Symptoms

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

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome (NMS), respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (<2% of overdose cases), and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450mg, but survival has also been reported following acute overdose of 1,500mg.

Management of Overdose

There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (ie, 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: Antipsychotics; diazepines, oxazepines and thiazepines. *ATC code:* N05A H03.

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 (Ki; <100nM) for serotonin $5HT_{2A/2C}$, $5HT_3$, $5HT_6$; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors m_1-m_5; $alpha_1$ adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin $5HT_2$ than dopamine D_2 receptors and greater $5HT_2$ than D_2 activity in *in vivo* models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responses in an 'anxiolytic' test.

In a single oral dose (10mg) Positron Emission Tomography (PET) study in healthy volunteers, olanzapine produced a higher $5HT_{2A}$ than dopamine D_2 receptor occupancy. In addition, a Single Photon Emission Computed Tomography (SPECT) imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D_2 occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

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 10mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

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

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

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

5.2 Pharmacokinetic properties

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.

Olanzapine is metabolised in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites; both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent, olanzapine. 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 hours) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia >65 years of age, dosing from 5 to 20mg/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 hours) and the clearance was reduced (18.9 versus 27.3 l/hr). However, olanzapine (5-20mg) demonstrated a comparable safety profile in female (n = 467) as in male patients (n = 869).

In renally impaired patients (creatinine clearance <10ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hours) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57% of radiolabelled olanzapine appeared in urine, principally as metabolites.

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

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

The plasma protein binding of olanzapine was about 93% over the concentration range of about 7 to about 1,000ng/ml. Olanzapine is bound predominantly to albumin and $alpha_1$-acid-glycoprotein.

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 210mg/kg (mice) and 175mg/kg (rats). Dogs tolerated single oral doses up to 100mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, laboured respiration, miosis, and anorexia. In monkeys, single oral doses up to 100mg/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 leucocytes in mice and non-specific reductions of circulating leucocytes 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 10mg/kg/day (total olanzapine exposure [area under the curve - AUC] is 12- to 15-fold greater than that of a man given a 12mg dose). In cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

Reproductive Toxicity

Olanzapine had no teratogenic effects. Sedation affected mating performance of male rats. Oestrous cycles were affected at doses of 1.1mg/kg (3-times the maximum human dose) and reproduction parameters were influenced in rats given 3mg/kg (9-times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

Mutagenicity

Olanzapine was not mutagenic or clastogenic in a full range of standard tests, which included bacterial mutation tests and *in vitro* and *in vivo* mammalian tests.

Carcinogenicity

Based on the results of studies in mice and rats, it was concluded that olanzapine is not carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Maize starch
Silica, colloidal anhydrous
Magnesium stearate

Sub-coating
Hypromellose

Coating
Hypromellose, lactose monohydrate, titanium dioxide (E171), macrogol 4000 and sodium citrate.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months

6.4 Special precautions for storage
Do not store above 25°C.

Store in the original package to protect from moisture.

6.5 Nature and contents of container
Blisters (OPA/ Al/ PVC// Al foil) within a carton box.

Olanzapine 7.5mg Film-coated tablets: 28, 30, 35, 56, 60 or 70 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
PLIVA Pharma Ltd
Vision house
Bedford Road
Petersfield
Hampshire
GU 32 3QB
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 10622/ 0326

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/12/2008

10 DATE OF REVISION OF THE TEXT
04/12/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Olanzapine PLIVA 10mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg Olanzapine.

Excipient(s): 288mg lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Olanzapine 10mg Film-coated tablets are white, round, biconvex, film-coated tablets, embossed with 'OL' on one side and '10' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Schizophrenia: The recommended starting dose for olanzapine is 10mg/day.

Manic episode: The starting dose is 15mg as a single daily dose in monotherapy or 10mg daily in combination therapy (see section 5.1).

Preventing recurrence in bipolar disorder: The recommended starting dose is 10mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

During treatment for schizophrenia, manic episode, and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours. Olanzapine can be given without regard for meals, as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

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

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

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

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

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

When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.
(See also section 4.5 and section 5.2.)

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Patients with known risk for narrow-angle glaucoma.

4.4 Special warnings and precautions for use

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

Dementia-related psychosis and/or behavioural disturbances
Olanzapine is not approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4mg) 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 2.5mg/day and titrated to a maximum of 15mg/day based on investigator judgement.

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal product. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including olanzapine must be discontinued.

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (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 particularly in diabetic patients and in patients with risk factors for the development of diabetes mellitus for which regular glucose control is recommended.

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.

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 transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised 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 medicinal products. In the event of elevated ALT and/or AST during treatment, followup should be organised and dose reduction should be considered. 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 medicinal products 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 very rarely (<0.01%) when olanzapine is stopped abruptly.

QT interval
In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥ 500 milliseconds [msec] at any time post baseline in patients with baseline QTcF<500 msec) were uncommon (0.1% to 1%) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. However, as with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicinal products 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 very rarely (< 0.01%) been reported. 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 medicinal products 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 rarely in patients

when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

Tardive Dyskinesia
In comparator studies of one year or less duration, olanzapine was associated with a statistically significant lower incidence of treatment emergent dyskinesia. However the risk of tardive dyskinesia increases with long term exposure, and therefore if signs or symptoms of tardive dyskinesia appear in a patient on olanzapine, a dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Postural hypotension
Postural hypotension was infrequently observed in the elderly in olanzapine clinical trials. As with other antipsychotics, it is recommended that blood pressure is measured periodically in patients over 65 years.

Use in children and adolescents under 18 years of age
Olanzapine is not indicated for use in the treatment of children and adolescents. Studies in patients aged 13-17 years showed various adverse reactions, including weight gain, changes in metabolic parameters and increases in prolactin levels. Long-term outcomes associated with these events have not been studied and remain unknown (see sections 4.8 and 5.1).

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

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* (eg, 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.

CNS medicinal products
Caution should be exercised in patients who receive medicinal products that can cause central nervous system depression and alcohol.

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 Pregnancy and lactation

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.

Spontaneous reports have been very rarely received of tremor, hypertonia, lethargy, and sleepiness, in infants born to mothers who had used olanzapine during the 3rd trimester.

In a study in breast-feeding, healthy women, olanzapine was excreted in breast milk. Mean infant exposure (mg/kg) at steady-state was estimated to be 1.8% of the maternal olanzapine dose (mg/kg). Patients should be advised not to breast-feed an infant if they are taking olanzapine.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequencies of the following undesirable effects are:

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)

Adults
The most frequently reported (very common) 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 (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic transaminases (see section 4.4), rash, asthenia, fatigue and oedema.

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.

Very common	Common	Uncommon	Not known
Blood and the lymphatic system disorders			
	Eosinophilia	Leukopenia Neutropenia	Thrombocytopenia
Immune system disorders			
			Allergic reaction
Metabolism and nutrition disorders			
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5]		Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal

Very common	Common	Uncommon	Not known
	Glucosuria Increased appetite		cases (see section 4.4) Hypothermia
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 Neuroleptic malignant syndrome (see section 4.4) Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms[7]
Cardiac disorders			
		Bradycardia QTc prolongation (see section 4.4)	Ventricular tachycardia/fibrillation, sudden death (see section 4.4)
Vascular disorders			
	Orthostatic hypotension		Thromboembolism (including pulmonary embolism and deep vein thrombosis)
Gastrointestinal disorders			
	Mild, transient anticholinergic effects including constipation and dry mouth		Pancreatitis
Hepato-biliary disorders			
	Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury)
Skin and subcutaneous tissue disorders			
	Rash	Photosensitivity reaction Alopecia	
Musculoskeletal and connective tissue disorders			
			Rhabdomyolysis
Renal and urinary disorders			
			Urinary hesitation
Reproductive system and breast disorders			
			Priapism
General disorders and administration site conditions			
	Asthenia Fatigue Oedema		
Investigations			
Elevated plasma prolactin levels[8]			

Very common	Common	Uncommon	Not known
		High creatine phosphokinase Increased total bilirubin	Increased alkaine phosphatase

[1] Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Weight gain ≥ 7% of baseline body weight was very common and ≥ 15% of baseline body weight was common.

[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) to high (≥ 6.2 mmol) were very common.

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

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

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

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

[8] Associated clinical manifestations (e.g., gynaecomastia, galactorrhoea, and breast enlargement) were rare. In most patients, levels returned to normal ranges without cessation of treatment.

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

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

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

Children and adolescents
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 clinical trials in adolescent patients. Clinically significant weight gain (≥ 7%) appears to occur more frequently in the adolescent population.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders *Very common:* Weight gain[9], elevated triglyceride levels[10], increased appetite. *Common:* Elevated cholesterol levels[11]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth
Hepato-biliary disorders *Very common:* Elevations of hepatic transaminases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[12.]

[9] Weight gain ≥ 7% of baseline body weight (kg) was very common and ≥ 15% of baseline body weight was common.

[10] 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).

[11] 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.

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

4.9 Overdose

Signs and Symptoms

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

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome (NMS), respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (<2% of overdose cases), and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450mg, but survival has also been reported following acute overdose of 1,500mg.

Management of Overdose

There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (ie, 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: Antipsychotics; diazepines, oxazepines and thiazepines. *ATC code:* N05A H03.

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 (Ki; <100nM) for serotonin $5HT_{2A/2C}$, $5HT_3$, $5HT_6$; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors m_1-m_5; $alpha_1$ adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin $5HT_2$ than dopamine D_2 receptors and greater $5HT_2$ than D_2 activity in *in vivo* models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responses in an 'anxiolytic' test.

In a single oral dose (10mg) Positron Emission Tomography (PET) study in healthy volunteers, olanzapine produced a higher $5HT_{2A}$ than dopamine D_2 receptor occupancy. In addition, a Single Photon Emission Computed Tomography (SPECT) imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D_2 occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

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 10mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

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

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

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

5.2 Pharmacokinetic properties

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.

Olanzapine is metabolised in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites; both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent, olanzapine. 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 hours) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia >65 years of age, dosing from 5 to 20mg/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 hours) and the clearance was reduced (18.9 versus 27.3 l/hr). However, olanzapine (5-20mg) demonstrated a comparable safety profile in female (n = 467) as in male patients (n = 869).

In renally impaired patients (creatinine clearance <10ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hours) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57% of radiolabelled olanzapine appeared in urine, principally as metabolites.

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

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

The plasma protein binding of olanzapine was about 93% over the concentration range of about 7 to about 1,000ng/ml. Olanzapine is bound predominantly to albumin and $alpha_1$-acid-glycoprotein.

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 210mg/kg (mice) and 175mg/kg (rats). Dogs tolerated single oral doses up to 100mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, laboured respiration, miosis, and anorexia. In monkeys, single oral doses up to 100mg/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 leucocytes in mice and non-specific reductions of circulating leucocytes 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 10mg/kg/day (total olanzapine exposure [area under the curve - AUC] is 12- to 15-fold greater than that of a man given a 12mg dose). In cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

Reproductive Toxicity

Olanzapine had no teratogenic effects. Sedation affected mating performance of male rats. Oestrous cycles were affected at doses of 1.1mg/kg (3-times the maximum human dose) and reproduction parameters were influenced in rats given 3mg/kg (9-times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

Mutagenicity

Olanzapine was not mutagenic or clastogenic in a full range of standard tests, which included bacterial mutation tests and *in vitro* and *in vivo* mammalian tests.

Carcinogenicity

Based on the results of studies in mice and rats, it was concluded that olanzapine is not carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Maize starch
Silica, colloidal anhydrous
Magnesium stearate

Sub-coating

Hypromellose

Coating

Hypromellose, lactose monohydrate, titanium dioxide (E171), macrogol 4000 and sodium citrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
18 months

6.4 Special precautions for storage
Do not store above 25°C.

Store in the original package to protect from moisture.

6.5 Nature and contents of container
Blisters (OPA/ Al/ PVC// Al foil) within a carton box.
Olanzapine 10mg Film-coated tablets: 7, 28, 30, 35, 56, 60 or 70 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
PLIVA Pharma Ltd
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 10622/ 0327

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/12/2008

10 DATE OF REVISION OF THE TEXT
04/12/2008

Module 3
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Olanzapine 2.5mg Film-coated tablets Olanzapine 5mg Film-coated tablets Olanzapine 7.5mg Film-coated tablets Olanzapine 10mg Film-coated tablets

Olanzapine

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

In this leaflet:

❶ What olanzapine is and what it is used for

Olanzapine belongs to a group of medicines called antipsychotics.

Olanzapine is used to treat 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.

Olanzapine is used to treat a condition with symptoms such as feeling 'high' having excessive amounts of energy, needing much less sleep less than usual, talking very quickly with racing ideas and sometimes severe irritability. It is also a mood stabiliser that prevents further occurrences of the disabling high and low (depressed) extremes of mood associated with this condition.

❷ Before you take olanzapine

Do not take olanzapine
- If you are allergic (hypersensitive) to olanzapine or any of the other ingredients of the tablets. 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 certains kinds of glaucoma (increased pressure in the eye)

Take special care with olanzapine
- Medicines of this type may cause unusual movements mainly of the face or tongue. If this happens after you have been given olanzapine 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
- The use of olanzapine in elderly patients is not recommended as it may have serious side effects

If you suffer from any of the following illnesses tell your doctor as soon as possible:
- Diabetes
- Heart disease
- Liver or kidney problems
- Parkinson's disease
- Epilepsy
- Prostate problems
- A blocked intestine (paralytic ileus)
- Blood disorders
- Stroke or 'mini' stroke (temporary symptoms of stroke)

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.

Olanzapine is not for patients who are under 18 years.

Taking other medicines

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

You should tell your doctor if you are taking fluvoxamine (an antidepressant or ciprofloxacin (an antibiotic) as it may be necessary to change your olanzapine dose.

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obained without a prescription. Especially tell your doctor if you are taking medicines for Parkinson's disease.

Taking olanzapine with food and drink

Do not drink any alcohol if you have been given olanzapine as olanzapine and alcohol together may make you feel drowsy.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant or think you may be pregnant or are trying to become pregnant. You should not take this medicine when pregnant unless you have discussed this with your doctor.

You should not be given this medicine when breast-feeding as small amounts of olanzapine can pass into breast milk.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

There is a risk of feeling drowsy when you are given olanzapine. If this happens do not drive or operate any tools or machines. Tell your doctor.

Important information about some of the ingredients of Olanzapine tablets

Olanzapine tablets contain lactose, a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

❸ How to take olanzapine

Always take olanzapine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

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

You should take your Olanzapine 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 if you take them with or without food. Olanzapine coated tablets are for oral use. You should swallow the tablets whole with water.

If you take more olanzapine than you should

Patients who have taken more olanzapine 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 consciousness.

Other symptoms may be: accute 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. Show the doctor your pack of tablets.

If you forget to take olanzapine

Take your tablets as soon as you remember. Do not take two doses in one day.

If you stop taking olanzapine

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

If you suddenly stop taking olanzapine, 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 medicinal product, ask your doctor or pharmacist.

4 Possible side effects

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

Very common side effects:
affect more than 1 user in 10
- Sleepiness or drowsiness
- Weight gain
- Increased prolactin levels in the blood

Common side effects:
affect 1 to 10 users in 100
- Changes in the levels of some blood cells and circulating fats
- Increases in the level of sugars in the blood and urine
- Feeling more hungry
- Dizziness
- Restlessness
- Tremor
- Muscle stiffness or spasm, including eye movements
- Problems with speech
- Unusual movement, especially of the face or tongue
- Constipation
- Dry mouth
- Rash
- Loss of strength
- Extreme tiredness
- Water retention leading to swelling of hands, ankles or feet
- 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

Uncommon side effects:
affect 1 to 10 users in 1,000
- Slow heart rate
- Make you sensitive to light
- Hair loss

Rare side effects:
affect 1 to 10 users in 10,000
- Male or female breast enlargement

Other possible side effects:
frequency cannot be estimated from the available data
- Allergic reaction (e.g. swelling in the mouth and throat, itching, rash)
- Diabetes or worsening of diabetes occasionally associated with ketoacidosis (ketones in the blood or urine), or coma
- Lowering of normal body temperature
- Seizures, usually associated with a history of seizures (epilepsy)
- Combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness
- Spasms of the eye muscle causing rolling movement of the eye
- Abnormal rhythms of the heart
- Sudden unexplained death
- Blood clots such as deep venous thrombosis of the leg or blood clot on the lung
- 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
- Difficulty in passing urine
- Prolonged and/or painful erection

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

In patients with Parkinson's disease, olanzapine may worsen the symptoms.

Rarely, women taking medicines of this type for a long time have started to secrete milk and have missed periods or had irregular periods. If this persists tell your doctor. Very rarely, babies born to mothers who have taken olanzapine in the last stage of pregnancy (3rd trimester) may have tremors, be sleepy or drowsy.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5 How to store olanzapine

Keep out of the reach and sight of children.

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

Do not store above 25°C.

Store in the original package, in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further information

What Olanzapine tablets contain
- The active substance is olanzapine. Each tablet contains either 2.5mg, 5mg, 7.5mg or 10mg of olanzapine
- The other ingredients are:
(tablet core) lactose monohydrate; maize starch; silica, colloidal anhydrous; magnesium stearate
(tablet coating) hypromellose, lactose, titanium dioxide (E171), macrogol 4000 and sodium citrate

What Olanzapine tablets look like and contents of the pack

Olanzapine 2.5mg are white, round, biconvex, film-coated tablets, embossed with 'OL' on one side and '2.5' on the other. They are available in blister packs of 28, 30, 35, 56, 60 or 70 tablets.

Olanzapine 5mg are white, round, biconvex, film-coated tablets, embossed with 'OL' on one side and '5' on the other. They are available in blister packs of 28, 30, 35, 56, 60 or 70 tablets.

Olanzapine 7.5mg are white, round, biconvex, film-coated tablets, embossed with 'OL' on one side and '7.5' on the other. They are available in blister packs of 28, 30, 35, 56, 60 or 70 tablets.

Olanzapine 10mg are white, round, biconvex, film-coated tablets, embossed with 'OL' on one side and '10' on the other. They are available in blister packs of 7, 28, 30, 35, 56, 60 or 70 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

PLIVA Pharma Ltd
Vision House, Bedford Road, Petersfield
Hampshire GU32 3QB
United Kingdom

Manufacturer

PLIVA Kraków S.A.
80 Mogilska str.
31546 Kraków, Poland

This medicinal product is authorised in the Member States of the EEA under the following names:

The Czech Republic:	Olanzapin PLIVA 5mg, 7.5mg, 10mg film coated tablets
Germany:	Olanzapin PLIVA 2.5mg, 5mg, 7.5mg, 10mg filmtabletten
Estonia:	Olanzapine PLIVA 5mg, 10mg film coated tablets
Hungary:	Olanzapine PLIVA 5mg, 7.5mg, 10mg filmtabletta
Ireland:	Olanzapine PLIVA 2.5mg, 5mg, 7.5mg, 10mg Film-coated tablets
Lithuania:	Olanzapin PLIVA 5mg, 10mg plėvele dengtos tabletės
Latvia:	Olanzapin PLIVA 5mg, 10mg apvalkotās tabletes
Poland:	Olanzapin PLIVA 2.5mg, 5mg, 7.5mg, 10mg
Romania:	Olanzapină PLIVA 5mg, 10mg Comprimate filmate
Slovenia:	Olanzapin PLIVA 2.5mg, 5mg, 7.5mg, 10mg filmsko obložene tablete
Slovakia:	Olanzapin PLIVA 5mg, 10mg
United Kingdom:	Olanzapine PLIVA 2.5mg, 5mg, 7.5mg, 10mg Film-coated tablets

This leaflet was last revised in October/2008.

PL 10622/0324
PL 10622/0325
PL 10622/0326
PL 10622/0327

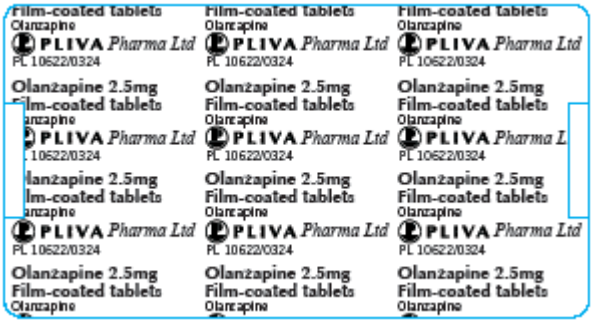
2250904-P1

PLIVA

Module 4
Labelling

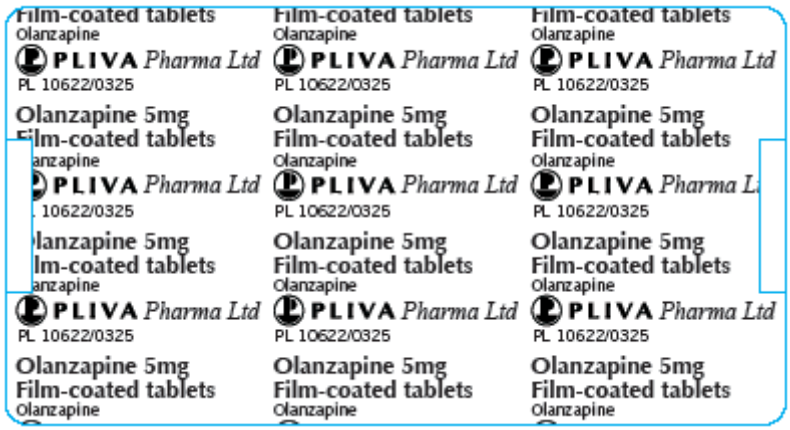
Carton-Olanzapine 2.5mg Film Coated Tablets
Pack size- 28 film coated tablets

Blister foil



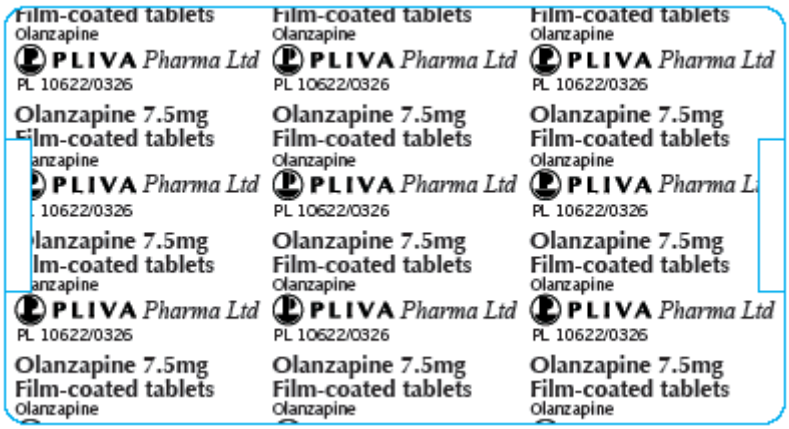
Carton-Olanzapine 5mg Film Coated Tablets
Pack size- 28 film coated tablets

Blister foil



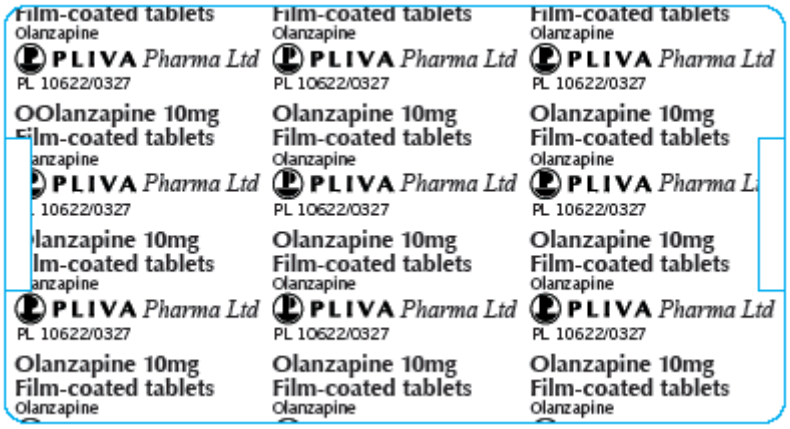
Carton-Olanzapine 7.5mg Film Coated Tablets
Pack size- 56 film coated tablets

Blister foil



Carton-Olanzapine 7.5mg Film Coated Tablets
Pack size- 28 film coated tablets

Blister foil



Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Olanzapine 2.5mg, 5mg, 7.5mg, 10mg film-coated tablets for the treatment of schizophrenia, manic episodes and preventing recurrence in bipolar disorder is approvable.

This report evaluates the chemical-pharmaceutical aspects of a decentralised application for Marketing Authorisation, using the abridged procedure as described in article 10(1) of Directive 2001/83/EC: Generic Application. The reference product in the EEA licensed for not less than 10 years is Zyprexa 10 mg Tablets (Eli Lilly Netherland BV, The Netherlands). The tablets were licensed via the centralised procedure in September 1996. The reference medicinal products in the UK are Zyprexa 2.5/5/7.5.10 mg Tablets authorised to Lilly Laboratories. A bioequivalence study was performed using Zyprexa 10 mg tablets (UK) as the reference. The UK acts as RMS. No paediatric development plan exists for these products.

Olanzapine is a second generation “atypical” antipsychotic indicated for the treatment of schizophrenia, manic episodes and preventing recurrence in bipolar disorder. The starting dose is 10 mg/day for the treatment of schizophrenia and preventing recurrence in bipolar disorder and 15 mg/day (single dose in monotherapy) for treatment of manic episodes.

No new preclinical or clinical studies were conducted and none are required for an application of this type. The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, batch release and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS has been reassured that the submitted studies have been carried out in accordance with GCP, and agreed ethical principles.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Olanzapine 2.5mg, 5mg, 7.5mg and 10mg Film Coated Tablets
Name(s) of the active substance(s) (INN)	Olanzapine
Pharmacotherapeutic classification (ATC code)	N05A H03
Pharmaceutical form and strength(s)	Film-Coated Tablet, 2.5mg, 5mg, 7.5mg & 10mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1198/01-04/DC
Reference Member State	United Kingdom
Member States concerned	Czech Republic, Germany, Estonia, Hungary,

	Ireland, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia
Marketing Authorisation Number(s)	PL 10622/0324-7
Name and address of the authorisation holder	PLIVA Pharma Limited Vision House, Bedford Road, Petersfield, Hampshire, GU32 3QB, United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

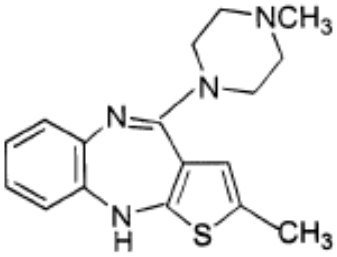
General Information

Nomenclature

INN: Olanzapine

Chemical name(s): 2-Methyl-4-(4-methyl- l -piperzinyl)- l0H thieno-[2,3-b][l,5] benzodiazepine

C.A.S Registration number: 132539-06-1



Molecular formula: $C_{17}H_{20}N_4S$

Solubility: Freely soluble in Chloroform

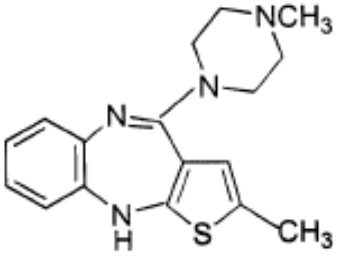
Physical characteristics: Pale yellow to yellow colour crystalline powder

Polymorphism: Olanzapine exhibits polymorphism.

Potential isomerism: None

Melting point: 188 - 194ºC

Structure



Manufacture

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance olanzapine. The active substance specification provided is acceptable.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

The drug substance, olanzapine, is packed in a translucent polyethylene bag, sealed with a plastic strip, inside a triple laminated bag, sealed with a sealer. The bags are placed in high density polyethylene (HDPE) containers.
Satisfactory specifications and certificates of analysis are provided.

Satisfactory batch data for five production scale batches are provided by the active substance manufacturer and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer during validation studies.

Appropriate stability data have been generated supporting a re-test period of 18 months. This is accepted.

P Medicinal Product

Other ingredients consist of pharmaceutical excipients lactose monohydrate, maize starch, colloidal anhydrous silica, magnesium stearate, hypromellose and Opadry II 31F58914 White. All ingredients comply with relevant Ph Eur monographs with the exception of Opadry II 31F58914 White which comply to in-house specifications. Satisfactory certificates of analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

Dissolution and impurity profiles

Dissolution and impurity profiles of drug product were found to be similar to those for the reference product.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Validations of the analytical methods have been presented. Process validation has been carried out on a pilot batch with the applicant committing to validate three consecutive production batches, this is satisfactory. The batch analysis results show that the finished products meet the specifications proposed. Certificates of analysis have been provided for any working standards used.

Container Closure System

The product is packaged in blisters composed of aluminium and polyethylene chloride (PVC). Specifications and a certificate of analysis for the packaging type used have been provided. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 28, 30, 35, 56, 60 and 70 tablets. Not all pack sizes may be marketed.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set, which is satisfactory. Storage conditions are “Do not store above 25oC” and “Store in the original package to protect from moisture”.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

The proposed product has met the requirements of a generic medicinal product with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

III.2 Non clinical aspects

No specific non-clinical studies have been performed, which is acceptable for this application for a generic product. Pharmacodynamic, pharmacokinetic and toxicological properties of olanzapine are well known and further non-clinical studies are not required.

III.3 Clinical aspects

Introduction
The clinical overview refers to a comprehensive bibliography of 59 references up to year 2004 and provides a brief but adequate review of the bioequivalence data. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

Clinical study reports
This application concerns 4 tablet strengths containing 2.5, 5, 7.5, 10 mg of the active substance olanzapine. To support the application, the applicant has submitted the report of one single dose bioequivalence study on the highest strength under fasting conditions.

The bioequivalence study was performed with the 10mg immediate release tablet comparing the bioavailability of the generic olanzapine product of Pliva, Krakow, Pharmaceutical Company, S.A., Poland, with the reference product Zyprexa 10mg (manufacturer Eli Lilly UK).

No other clinical studies were conducted to support this application.

Biowaiver

The applicant provides one bioequivalence study for all 4 strengths of the product. The clinical overview provides a consideration of the multiple strength waiver criteria according to the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence", section 5.4. A full justification is also provided in module 1.5 of the dossier.

Assessor's comment:

It is known that pharmacokinetics are linear over the therapeutic dose range (Kando et al. 1997) and a single bioequivalence study has been accepted for earlier generic olanzapine tablet applications. There is acceptable justification for a single bioequivalence study on the highest tablet strength to support the four applications from the clinical assessor's point of view.

Pharmacokinetic studY CR-BE-082-OLAN-2004

Methods

Study design

This was a single-dose, 2-way cross-over study with 26 healthy, male adult subjects. Each subject received a single dose (1 x 10mg tablet) of both test and reference olanzapine formulation in fasting conditions. The tablets were administered orally after an overnight fast with 240ml of drinking water.

The wash-out period was 17 days, which was sufficient to ensure non-quantifiable drug concentrations at baseline of the second treatment period.

Sampling times were Pre-dose and at 1.00, 2.00, 3.00, 4.00, 5.00 5.50, 5.75, 6.00, 6.33, 6.67, 7.00, 7.50, 8.00, 10.00, 12.00, l6, 24, 48, 72, 96and 144 hours post-dose. The higher sampling frequency around T_{max} was satisfactory for estimating C_{max} and overall the regimen proved to be adequate to define the profile of the concentration-time curve and to estimate the area under the concentration-time curve.

Test and reference products

Test product: Olanzapine 10mg, Manufacturer Pliva Krakow, Pharmaceutical Company, S.A., Poland

Reference product: Zyprexa 10mg Tablet, Manufacturer Eli Lilly and Company, UK

Population(s) studied

26 healthy male and female adult subjects entered the study. 2 subjects failed to complete both the periods of the study. Justification is provided for the exclusion of these subjects. A further subject was excluded from the analysis. A satisfactory explanation has been provided for excluding the data from this subject.

Analytical methods

See pharmaceutical assessment.

Pharmacokinetic Variables

The following pharmacokinetic parameters were calculated for olanzapine for the bioequivalence analyses: AUC_{0-t}, AUC0-inf, C_{max}, T_{max}.

Conclusion of bioequivalence was based on 90 % confidence intervals (80 to 125%) of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max}.

Statistical methods

The calculations were performed using WinNonLin software version 4.1. ANOVA for AUC, C_{max}. Non-parametric for T_{max}. Analysis of sequence/period effects.

Results

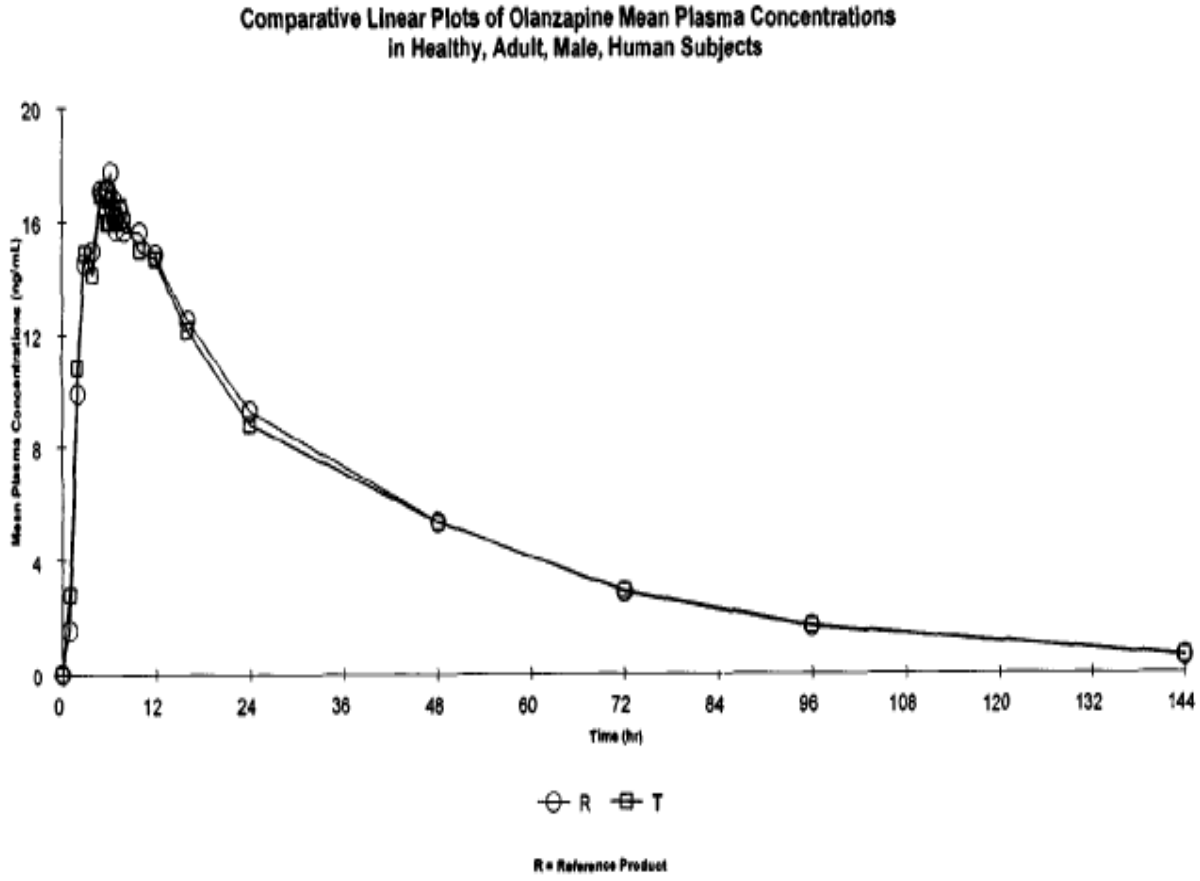
The pharmacokinetic results from the untransformed data of 23 subjects following administration of Treatment T and Treatment R are as follows: (Refer Table 13.1.3, Table 13.1.4 and Table 7.6 of bioanalytical report).

PK Parameters	Olanzapine Mean (S.D. ±)	
	T	R
T_{max} (hrs)	5.294 (1.6281)	5.435 (1.6404)
C_{max} (ng/mL)	19.57786 (5.899681)	20.52717 (5.022676)
AUC_{0-t} (ng*hr/mL)	673.67932 (175.992214)	684.92155 (140.747010)
$AUC_{0-\infty}$ (ng*hr/mL)	707.47106 (186.236653)	716.14218 (153.700335)
$T_{1/2}$ (hr)	31.514 (6.5620)	29.864 (5.3897)
K_{el} (1/hr)	0.023 (0.0045)	0.024 (0.0039)

Pharmacokinetic parameters of olanzapine (log-transformed values; geometric mean for AUC and Cmax):

PK Parameters	90 % CI
C_{max} (ng/mL)	88.80 % - 101.27 %
AUC_{0-t} (ng*hr/mL)	91.72 % - 104.19 %
$AUC_{0-\infty}$ (ng*hr/mL)	92.24 % - 104.63 %

13.2.1 Comparative Linear and Semi-Log Plots of Mean Plasma Olanzapine Concentrations Versus Time (N=23)



Pharmacokinetic conclusion
The 90% Confidence Intervals for the test/reference ratios for $AUC_{0\text{-}t}$, $AUC_{0\text{-}72hours}$ and C_{max} for olanzapine were all within conventional bioequivalence criteria.
The graphical illustrations show similar absorption profiles and the individual subject data do not suggest any difference between formulations.
Although the calculated AUC extrapolated to infinity appeared to differ between the two products this cannot be related to drug absorption as the measured AUCs to 72 hours were virtually identical and this covers the complete absorption period. Calculation of the extrapolated part beyond 72 hours is highly unreliable and is of no relevance to an assessment of bioequivalence.
In conclusion the test and reference formulations can be considered to be bioequivalent in the fasted state.

Pharmacodynamic studies
Not applicable.

Additional data
Not applicable.

Post marketing experience
No post-marketing data are available. The medicinal product has not been marketed in any country.

Olanzapine has a well-recognised efficacy and an acceptable level of safety in the indications approved for Zyprexa 2.5, 5, 7.5, 10, 15, 20 mg strength tablets and corresponding products have been widely used in many countries. The PSUR submission cycle is 5 yearly.

Benefit-Risk assessment
The application contains an adequate review of published clinical data and the bioequivalence has been shown. Approval is recommended from the clinical point of view.

V OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The important quality characteristics of Olanzapine 2.5mg, 5mg, 7.5mg & 10mg Film Coated Tablets well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

No new preclinical data were submitted and none are required for an application of this type.

Bioequivalence data has been demonstrated between the applicant's Olanzapine 10mg Film-Coated Tablets and Zyprexa 10 mg Tablets (Lilly Laboratories).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with olanazapine considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome