COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Olanzapine SmeltTab Mylan 5 mg, 10 mg, 15 mg and 20 mg, orodispersible tablets (olanzapine)

NL/H/4500/001-004/DC

Date: 24 February 2023

This module reflects the scientific discussion for the approval of Olanzapine SmeltTab Mylan 5 mg, 10 mg, 15 mg and 20 mg, orodispersible tablets. The procedure was finalised in the United Kingdom (UK/H/4492/001-004/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

OLANZAPINE JENSON PHARMACEUTICAL SERVICES LIMITED 5 MG ORODISPERSIBLE TABLETS

OLANZAPINE JENSON PHARMACEUTICAL SERVICES LIMITED 10 MG ORODISPERSIBLE TABLETS

OLANZAPINE JENSON PHARMACEUTICAL SERVICES LIMITED 15 MG ORODISPERSIBLE TABLETS

OLANZAPINE JENSON PHARMACEUTICAL SERVICES LIMITED 20 MG ORODISPERSIBLE TABLETS

(Olanzapine)

Procedure No: UK/H/4492/001-4/DC, UK/H/4681/001-4/DC & UK/H/4761/001-3/DC

UK Licence No: PL 17871/0153-63

JENSON PHARMACEUTICAL SERVICES LIMITED

LAY SUMMARY

On 18 January 2012, Austria, Belgium, Cyprus, Czech Republic, Germany, Greece, France, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Slovenia, Spain, Slovakia and the UK agreed to grant Marketing Authorisations to Jenson Pharmaceutical Services Limited for the medicinal products Olanzapine Jenson Pharmaceutical Services Limited 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets (PL 17871/0153-63; UK/H/4492, 4681/001-4 and 4761/001-3/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 17 February 2012. These are Prescription-Only Medicines (POM).

These products will be referred to as Olanzapine Jenson Pharma 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets throughout the remainder of this report.

Olanzapine Jenson Pharma 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets contain the active ingredient olanzapine which 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such as hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness, and becoming withdrawn.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.

This medicine is used to treat a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep 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.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Olanzapine Jenson Pharma 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets outweigh the risks and Marketing Authorisations were granted.

TABLE OF CONTENTS

Module 1

Product Name	Olanzapine Jenson Pharma 5 mg orodispersible tablets Olanzapine Jenson Pharma 10 mg orodispersible tablets Olanzapine Jenson Pharma 15 mg orodispersible tablets Olanzapine Jenson Pharma 20 mg orodispersible tablets
Type of Application	Generic, Article 10(1)
Active Substances	Olanzapine
Form	Orodispersible tablets
Strength	5 mg, 10 mg, 15 mg and 20 mg
MA Holder	Jenson Pharmaceutical Services Limited, Carradine House, 237 Regents Park Road, London N3 3LF, UK.
Reference Member State (RMS)	UK
Concerned Member State (CMS)	UK/H/4492/001-2/DC:Austria, Belgium, Cyprus, Czech Republic, Germany, Greece, France, Hungary, Ireland, Netherlands, Poland, Portugal, Romania, Slovenia and Slovakia. UK/H/4492/003-4/DC: Austria, Belgium, Cyprus, Czech Republic, Germany, Greece, France, Hungary, Ireland, Netherlands, Poland, Portugal, Romania and Slovenia. UK/H/4681/001/DC: France and Italy. UK/H/4681/002-4/DC: Belgium, France and Italy. UK/H/4716/001-3/DC: Spain.
Procedure Number	UK/H/4492/001-4/DC UK/H/4681/001-4/DC UK/H/4761/001-3/DC
Timetable	Day 209– 18 January 2012.

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Olanzapine Jenson Pharmaceutical Services Limited 5 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each orodispersible tablet contains 5 mg olanzapine

Excipient(s) with known effect:

Each 5 mg orodispersible tablet contains 1.975 mg aspartame

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Orodispersible tablet

Light yellow to yellow coloured, plain to mottled, round, flat faced, beveled edged tablets debossed with "M" on one side and "OE1" on other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

Adults
Olanzapine is indicated for the treatment of schizophrenia.

Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Olanzapine is indicated for the treatment of moderate to severe manic episode.

In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder (see section 5.1).

4.2 Posology and method of administration

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

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

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

During treatment for schizophrenia, manic episode and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20 mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours.

Olanzapine can be given without regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

Olanzapine Jenson Pharmaceutical Services Limited tablets break easily, so you should handle the tablets carefully. Do not handle the tablets with wet hands as the tablets may break up. For perforated blisters, hold the blister strip at the edges and separate one blister cell from the rest of the strip by

gently tearing along the perforations around it. Carefully peel off the backing. For non-perforated blisters, take care not to peel off the backing of adjacent tablets. Then, gently push the tablet out.

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

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

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

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

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.

In cases where dose increments of 2.5 mg are considered necessary, Olanzapine coated tablets should be used. (See sections 4.5 and 5.2.)

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

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

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

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient ischemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in patients treated with olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All olanzapine- and placebo-treated patients who experienced a cerebrovascular event had pre-existing risk factors. Age > 75 years and vascular/mixed type dementia were identified as risk factors for CVAE in association with olanzapine treatment. The efficacy of olanzapine was not established in these trials.

Parkinson's disease
The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended. In clinical trials, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo (see section 4.8), and olanzapine was not more effective than placebo in the treatment of psychotic symptoms. In these trials, patients were initially required to be stable on the lowest effective dose of anti-Parkinsonian medicinal products (dopamine agonist) and to remain on the same anti-Parkinsonian medicinal products and dosages throughout the study. Olanzapine was started at 2.5 mg/day and titrated to a maximum of 15 mg/day based on investigator judgement.

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal 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 creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported 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 in accordance with utilised antipsychotic guidelines, e.g., measuring of blood glucose at baseline, 12 weeks after starting olanzapine treatment and annually thereafter.
Patients treated with any antipsychotic agents, including Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablets, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly, e.g., at baseline, 4, 8 and 12 weeks after starting olanzapine treatment and quarterly thereafter.

Lipid alterations
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic agents, including Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablets, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines, e.g., at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter.

Anticholinergic activity
While olanzapine demonstrated anticholinergic activity *in vitro*, experience during the clinical trials revealed a low incidence of related events. However, as clinical experience with olanzapine in patients with concomitant illness is limited, caution is advised when prescribing for patients with prostatic hypertrophy, or paralytic ileus and related conditions.

Hepatic function
Transient, asymptomatic elevations of hepatic transaminases, alanine transferase (ALT), aspartate transferase (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 medicines. In the event of elevated ALT and/or AST during treatment, follow-up 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 medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

Discontinuation of treatment
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported 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 medicines known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Thromboembolism
Temporal association of olanzapine treatment and venous thromboembolism has been reported uncommonly (≥ 0.1% and < 1%). A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

General CNS activity
Given the primary CNS effects of olanzapine, caution should be used when it is taken in combination with other centrally acting medicines and alcohol. As it exhibits *in vitro* dopamine antagonism, olanzapine may antagonize the effects of direct and indirect dopamine agonists.

Seizures
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur 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.

Sudden cardiac death
In postmarketing reports with olanzapine, the event of sudden cardiac death has been reported in patients with olanzapine. In a retrospective observational cohort study, the risk of presumed sudden cardiac death in patients treated with olanzapine was approximately twice the risk in patients not using

antipsychotics. In the study, the risk of olanzapine was comparable to the risk of atypical antipsychotics included in a pooled analysis.

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).

Phenylalanine
Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablet contains aspartame, which is a source of phenylalanine. May be harmful for people with phenylketonuria.

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 Cmax following fluvoxamine was 54 % in female nonsmokers and 77 % in male smokers. The mean increase in olanzapine AUC was 52 % and 108 % respectively. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.

Decreased bioavailability
Activated charcoal reduces the bioavailability of oral olanzapine by 50 to 60% and should be taken at least 2 hours before or after olanzapine.

Fluoxetine (a CYP2D6 inhibitor), single doses of antacid (aluminium, magnesium) or cimetidine have not been found to significantly affect the pharmacokinetics of olanzapine.

Potential for olanzapine to affect other medicinal products
Olanzapine may antagonise the effects of direct and indirect dopamine agonists.

Olanzapine does not inhibit the main CYP450 isoenzymes *in vitro* (e.g. 1A2, 2D6, 2C9, 2C19, 3A4). Thus no particular interaction is expected as verified through *in vivo* studies where no inhibition of metabolism of the following active substances was found: tricyclic antidepressant (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2) or diazepam (CYP3A4 and 2C19).

Olanzapine showed no interaction when co-administered with lithium or biperiden.

Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant olanzapine.

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

The concomitant use of olanzapine with anti-Parkinsonian medicinal products in patients with Parkinson's disease and dementia is not recommended (see section 4.4).

QTc interval

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with olanzapine. Nevertheless, because human experience is limited, olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Neonates exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonis, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast feeding

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adults

The most frequently (seen in 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism (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. The frequency terms listed are defined as follows: Very common (≥10%), common (≥1% and < 10%), uncommon (≥0.1% and < 1%), rare (≥0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the data available).

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			

Very common	Common	Uncommon	Not known
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) (see section 4.4)	
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 incontinence	Urinary hesitation
Pregnancy, puerperium and perinatal conditions			
			Drug withdrawal syndrome neonatal (see section 4.6)
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 alkaline phosphatase

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

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

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

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

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

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

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

[8] In clinical trials of up to 12 weeks, plasma prolactin concentrations exceeded the upper limit of normal range in approximately 30% of olanzapine treated patients with normal baseline prolactin value. In the majority of these patients the elevations were generally mild, and remained below two times the upper limit of normal range. In patients with schizophrenia, mean prolactin level changes decreased with continued treatment, whereas mean increases were seen in patients with other diagnoses. The mean changes were modest. Generally in olanzapine-treated patients potentially associated breast- and menstrual related clinical manifestations (e.g. amenorrhoea, breast enlargement, galactorrhea in females, and gynaecomastia/breast enlargement in males) were uncommon. Potentially associated sexual function-related adverse reactions (e.g. erectile dysfunction in males and decreased libido in both genders) were commonly observed.

Long-term exposure (at least 48 weeks)

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

Additional information on special populations

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

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

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

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 short-term clinical trials in adolescent patients. Clinically significant weight gain (≥7%) appears to occur more frequently in the adolescent population compared to adults with comparable exposures. The magnitude of weight gain and the proportion of adolescent patients who had clinically significant weight gain were greater with long-term exposure (at least 24 weeks) than with short-term exposure.

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

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] Following short term treatment (median duration 22 days), weight gain ≥7% of baseline body weight (kg) was very common (40.6 %), ≥15% of baseline body weight was common (7.1 %) and ≥25 % was common (2.5 %). With long-term exposure (at least 24 weeks), 89.4 % gained ≥7 %, 55.3 % gained ≥15 % and 29.1 % gained ≥25% of their baseline body weight.

[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, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diazepines, oxazepines and thiazepines, ATC code: N05A H03.

Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

In preclinical studies, olanzapine exhibited a range of receptor affinities (K_i < 100 nM) for serotonin 5 $HT_{2A/2C}$, 5 HT_3, 5 HT_6; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors M_1-M_5; adrenergic; and histamine H_1 receptors. Animal behavioral studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin $5HT_2$ than dopamine D_2 receptors and greater 5 HT_2 than D_2 activity *in vivo* models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an "anxiolytic" test.

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

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

In a multinational, double-blind, comparative study of schizophrenia, schizoaffective, and related disorders which included 1,481 patients with varying degrees of associated depressive symptoms (baseline mean of 16.6 on the Montgomery-Asberg Depression Rating Scale), a prospective secondary analysis of baseline to endpoint mood score change demonstrated a statistically significant improvement (p= 0.001) favouring olanzapine (-6.0) versus haloperidol (-3.1).

In patients with a manic or mixed episode of bipolar disorder, olanzapine demonstrated superior efficacy to placebo and valproate semisodium (divalproex) in reduction of manic symptoms over 3 weeks. Olanzapine also demonstrated comparable efficacy results to haloperidol in terms of the proportion of patients in symptomatic remission from mania and depression at 6 and 12 weeks. In a co-

therapy study of patients treated with lithium or valproate for a minimum of 2 weeks, the addition of olanzapine 10 mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

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

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

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

5.2 Pharmacokinetic properties

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

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 metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hr) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia > 65 years of age, dosing from 5 to 20 mg/day was not associated with any distinguishing profile of adverse events.

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

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

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

In non-smoking versus smoking subjects (males and females) the mean elimination half-life was prolonged (38.6 versus 30.4 hr) and the clearance was reduced (18.6 versus 27.7 l/hr).

The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals.

In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations.

The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α1-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 210 mg/kg (mice) and 175 mg/kg (rats). Dogs tolerated single oral doses up to 100 mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, labored respiration, miosis, and anorexia. In monkeys, single oral doses up to 100 mg/kg resulted in prostration and, at higher doses, semi-consciousness.

Repeated-dose toxicity
In studies up to 3 months duration in mice and up to 1 year in rats and dogs, the predominant effects were CNS depression, anticholinergic effects, and peripheral haematological disorders. Tolerance developed to the CNS depression. Growth parameters were decreased at high doses. Reversible effects consistent with elevated prolactin in rats included decreased weights of ovaries and uterus and morphologic changes in vaginal epithelium and in mammary gland.

Haematologic toxicity: Effects on haematology parameters were found in each species, including dose-related reductions in circulating leukocytes in mice and non-specific reductions of circulating leukocytes in rats; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia, or anemia developed in a few dogs treated with 8 or 10 mg/kg/day (total olanzapine exposure [area under the curve] is 12- to 15-fold greater than that of a man given a 12-mg dose). In cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

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

Mutagenicity
Olanzapine was not mutagenic or clastogenic in a full range of standard tests, which included bacterial mutation tests and *in vitro* and *in vivo* mammalian tests.
Carcinogenicity
Based on the results of studies in mice and rats, it was concluded that olanzapine is not carcinogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Microcrystalline cellulose and Guar gum (Avicel CE 15)
Crospovidone (Type A)
Magnesium stearate
Silica, colloidal anhydrous
Aspartame (E951)
Sodium laurilsulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original container to protect from light and moisture.

6.5 Nature and contents of container

For PL 17871/0153 and PL 17871/0161 only:
HDPE bottles with polypropylene screw cap with induction sealing liner and with absorbent cotton and desiccant (silica gel).
7, 10, 14, 28, 30, 56, 98, 100, 250, 500 tablets.

All PL numbers:
OPA/Al/PVC blisters: Cold-formed laminated blister consisting of OPA/AL/PVC laminate on one side and aluminium foil (Paper/polyester/AL/Heat Seal lacquer) laminate on the other.
7, 10, 14, 28, 30, 35, 56, 60, 70, 98, 100 tablets.
(7, 10, 14, 28, 30, 35, 56, 60, 70, 98, 100) x 1 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House
237 Regents Park Road
London N3 3LF

8 MARKETING AUTHORISATION NUMBER(S)

PL 17871/0153
PL 17871/0157
PL 17871/0161

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/02/2012

10 DATE OF REVISION OF THE TEXT

17/02/2012

1 NAME OF THE MEDICINAL PRODUCT

Olanzapine Jenson Pharmaceutical Services Limited 10 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 10 mg olanzapine

Excipient(s) with known effect:

Each 10 mg orodispersible tablet contains 3.950 mg aspartame

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet

Light yellow to yellow coloured, plain to mottled, round, flat faced, beveled edged tablets debossed with "M" on one side and "OE2" on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Olanzapine is indicated for the treatment of schizophrenia.

Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Olanzapine is indicated for the treatment of moderate to severe manic episode.

In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder (see section 5.1).

4.2 Posology and method of administration

Adults

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

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

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

During treatment for schizophrenia, manic episode and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20 mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours.

Olanzapine can be given without regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

Olanzapine Jenson Pharmaceutical Services Limited tablets break easily, so you should handle the tablets carefully. Do not handle the tablets with wet hands as the tablets may break up. For perforated blisters, hold the blister strip at the edges and separate one blister cell from the rest of the strip by gently tearing along the perforations around it. Carefully peel off the backing. For non-perforated blisters, take care not to peel off the backing of adjacent tablets. Then, gently push the tablet out.

Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablet should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact

orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or other suitable beverage (orange juice, apple juice, milk or coffee) immediately before administration.

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

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

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

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.

In cases where dose increments of 2.5 mg are considered necessary, Olanzapine coated tablets should be used. (See sections 4.5 and 5.2.)

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

4.4 Special warnings and precautions for use

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

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

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient ischemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in patients treated with olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All

olanzapine- and placebo-treated patients who experienced a cerebrovascular event had pre-existing risk factors. Age > 75 years and vascular/mixed type dementia were identified as risk factors for CVAE in association with olanzapine treatment. The efficacy of olanzapine was not established in these trials.

Parkinson's disease
The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended. In clinical trials, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo (see section 4.8), and olanzapine was not more effective than placebo in the treatment of psychotic symptoms. In these trials, patients were initially required to be stable on the lowest effective dose of anti-Parkinsonian medicinal products (dopamine agonist) and to remain on the same anti-Parkinsonian medicinal products and dosages throughout the study. Olanzapine was started at 2.5 mg/day and titrated to a maximum of 15 mg/day based on investigator judgement.

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal 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 creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported 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 in accordance with utilised antipsychotic guidelines, e.g., measuring of blood glucose at baseline, 12 weeks after starting olanzapine treatment and annually thereafter.
Patients treated with any antipsychotic agents, including Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablets, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly, e.g., at baseline, 4, 8 and 12 weeks after starting olanzapine treatment and quarterly thereafter.

Lipid alterations
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic agents, including Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablets, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines, e.g., at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter.

Anticholinergic activity
While olanzapine demonstrated anticholinergic activity *in vitro*, experience during the clinical trials revealed a low incidence of related events. However, as clinical experience with olanzapine in patients with concomitant illness is limited, caution is advised when prescribing for patients with prostatic hypertrophy, or paralytic ileus and related conditions.

Hepatic function
Transient, asymptomatic elevations of hepatic transaminases, alanine transferase (ALT), aspartate transferase (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 medicines. In the event of elevated ALT and/or AST during treatment, follow-up 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 medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

Discontinuation of treatment
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported 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 medicines known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Thromboembolism
Temporal association of olanzapine treatment and venous thromboembolism has been reported uncommonly (≥ 0.1% and < 1%). A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

General CNS activity
Given the primary CNS effects of olanzapine, caution should be used when it is taken in combination with other centrally acting medicines and alcohol. As it exhibits *in vitro* dopamine antagonism, olanzapine may antagonize the effects of direct and indirect dopamine agonists.

Seizures
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur 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.

Sudden cardiac death
In postmarketing reports with olanzapine, the event of sudden cardiac death has been reported in patients with olanzapine. In a retrospective observational cohort study, the risk of presumed sudden cardiac death in patients treated with olanzapine was approximately twice the risk in patients not using antipsychotics. In the study, the risk of olanzapine was comparable to the risk of atypical antipsychotics included in a pooled analysis.

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).

Phenylalanine
Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablet contains aspartame, which is a source of phenylalanine. May be harmful for people with phenylketonuria.

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 Cmax following fluvoxamine was 54 % in female nonsmokers and 77 % in male smokers. The mean increase in olanzapine AUC was 52 % and 108 % respectively. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.

Decreased bioavailability
Activated charcoal reduces the bioavailability of oral olanzapine by 50 to 60% and should be taken at least 2 hours before or after olanzapine.

Fluoxetine (a CYP2D6 inhibitor), single doses of antacid (aluminium, magnesium) or cimetidine have not been found to significantly affect the pharmacokinetics of olanzapine.

Potential for olanzapine to affect other medicinal products
Olanzapine may antagonise the effects of direct and indirect dopamine agonists.

Olanzapine does not inhibit the main CYP450 isoenzymes *in vitro* (e.g. 1A2, 2D6, 2C9, 2C19, 3A4). Thus no particular interaction is expected as verified through *in vivo* studies where no inhibition of metabolism of the following active substances was found: tricyclic antidepressant (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2) or diazepam (CYP3A4 and 2C19).

Olanzapine showed no interaction when co-administered with lithium or biperiden.

Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant olanzapine.

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

The concomitant use of olanzapine with anti-Parkinsonian medicinal products in patients with Parkinson's disease and dementia is not recommended (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with olanzapine. Nevertheless, because human experience is limited, olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Neonates exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonis, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast feeding

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adults

The most frequently (seen in 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism (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. The frequency terms listed are defined as follows: Very common (≥10%), common (≥1% and < 10%), uncommon (≥0.1% and < 1%), rare (≥0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the data available).

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			

Very common	Common	Uncommon	Not known
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) (see section 4.4)	
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 incontinence	Urinary hesitation
Pregnancy, puerperium and perinatal conditions			
			Drug withdrawal syndrome neonatal (see section 4.6)
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 alkaline phosphatase

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

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

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

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

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

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

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

[8] In clinical trials of up to 12 weeks, plasma prolactin concentrations exceeded the upper limit of normal range in approximately 30% of olanzapine treated patients with normal baseline prolactin value. In the majority of these patients the elevations were generally mild, and remained below two times the upper limit of normal range. In patients with schizophrenia, mean prolactin level changes decreased with continued treatment, whereas mean increases were seen in patients with other diagnoses. The mean changes were modest. Generally in olanzapine-treated patients potentially associated breast- and menstrual related clinical manifestations (e.g. amenorrhoea, breast enlargement, galactorrhea in females, and gynaecomastia/breast enlargement in males) were uncommon. Potentially associated sexual function-related adverse reactions (e.g. erectile dysfunction in males and decreased libido in both genders) were commonly observed.

Long-term exposure (at least 48 weeks)

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

Additional information on special populations

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

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

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

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 short-term clinical trials in adolescent patients. Clinically significant weight gain (≥7%) appears to occur more frequently in the adolescent population compared to adults with comparable exposures. The magnitude of weight gain and the proportion of adolescent patients who had clinically significant weight gain were greater with long-term exposure (at least 24 weeks) than with short-term exposure.

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

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] Following short term treatment (median duration 22 days), weight gain ≥7% of baseline body weight (kg) was very common (40.6 %), ≥15% of baseline body weight was common (7.1 %) and ≥25 % was common (2.5 %). With long-term exposure (at least 24 weeks), 89.4 % gained ≥7 %, 55.3 % gained ≥15 % and 29.1 % gained ≥25% of their baseline body weight.

[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, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diazepines, oxazepines and thiazepines, ATC code: N05A H03.

Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

In preclinical studies, olanzapine exhibited a range of receptor affinities (K_i < 100 nM) for serotonin 5 $HT_{2A/2C}$, 5 HT_3, 5 HT_6; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors M_1-M_5; adrenergic; and histamine H_1 receptors. Animal behavioral studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin $5HT_2$ than dopamine D_2 receptors and greater 5 HT_2 than D_2 activity *in vivo* models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an "anxiolytic" test.

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

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

In a multinational, double-blind, comparative study of schizophrenia, schizoaffective, and related disorders which included 1,481 patients with varying degrees of associated depressive symptoms (baseline mean of 16.6 on the Montgomery-Asberg Depression Rating Scale), a prospective secondary analysis of baseline to endpoint mood score change demonstrated a statistically significant improvement (p= 0.001) favouring olanzapine (-6.0) versus haloperidol (-3.1).

In patients with a manic or mixed episode of bipolar disorder, olanzapine demonstrated superior efficacy to placebo and valproate semisodium (divalproex) in reduction of manic symptoms over 3 weeks. Olanzapine also demonstrated comparable efficacy results to haloperidol in terms of the proportion of patients in symptomatic remission from mania and depression at 6 and 12 weeks. In a co-

therapy study of patients treated with lithium or valproate for a minimum of 2 weeks, the addition of olanzapine 10 mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

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

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

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

5.2 Pharmacokinetic properties

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

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 metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hr) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia > 65 years of age, dosing from 5 to 20 mg/day was not associated with any distinguishing profile of adverse events.

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

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

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

In non-smoking versus smoking subjects (males and females) the mean elimination half-life was prolonged (38.6 versus 30.4 hr) and the clearance was reduced (18.6 versus 27.7 l/hr).

The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals.

In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations.

The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α1-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 210 mg/kg (mice) and 175 mg/kg (rats). Dogs tolerated single oral doses up to 100 mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, labored respiration, miosis, and anorexia. In monkeys, single oral doses up to 100 mg/kg resulted in prostration and, at higher doses, semi-consciousness.

Repeated-dose toxicity
In studies up to 3 months duration in mice and up to 1 year in rats and dogs, the predominant effects were CNS depression, anticholinergic effects, and peripheral haematological disorders. Tolerance developed to the CNS depression. Growth parameters were decreased at high doses. Reversible effects consistent with elevated prolactin in rats included decreased weights of ovaries and uterus and morphologic changes in vaginal epithelium and in mammary gland.

Haematologic toxicity: Effects on haematology parameters were found in each species, including dose-related reductions in circulating leukocytes in mice and non-specific reductions of circulating leukocytes in rats; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia, or anemia developed in a few dogs treated with 8 or 10 mg/kg/day (total olanzapine exposure [area under the curve] is 12- to 15-fold greater than that of a man given a 12-mg dose). In cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

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

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Microcrystalline cellulose and Guar gum (Avicel CE 15)
Crospovidone (Type A)
Magnesium stearate
Silica, colloidal anhydrous
Aspartame (E951)
Sodium laurilsulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original container to protect from light and moisture.

6.5 Nature and contents of container

For PL 17871/0154 and 0162:
HDPE bottles with polypropylene screw cap with induction sealing liner and with absorbent cotton and desiccant (silica gel).
7, 10, 14, 28, 30, 56, 98, 100, 250, 500 tablets.

For all PL numbers:
OPA/Al/PVC blisters: Cold-formed laminated blister consisting of OPA/AL/PVC laminate on one side and aluminium foil (Paper/polyester/AL/Heat Seal lacquer) laminate on the other.
7, 10, 14, 28, 30, 35, 56, 60, 70, 98, 100 tablets.
(7, 10, 14, 28, 30, 35, 56, 60, 70, 98, 100) x 1 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House
237 Regents Park Road
London N3 3LF

8 MARKETING AUTHORISATION NUMBER(S)

PL 17871/0154
PL 17871/0158
PL 17871/0162

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/02/2012

10 DATE OF REVISION OF THE TEXT

17/02/2012

1 NAME OF THE MEDICINAL PRODUCT

Olanzapine Jenson Pharmaceutical Services Limited 15 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 15 mg olanzapine

Excipient(s) with known effect:

Each 15 mg orodispersible tablet contains 5.925 mg aspartame

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet

Light yellow to yellow coloured, plain to mottled, round, flat faced, beveled edged tablets debossed with "M" on one side and "OE3" on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Olanzapine is indicated for the treatment of schizophrenia.

Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Olanzapine is indicated for the treatment of moderate to severe manic episode.

In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder (see section 5.1).

4.2 Posology and method of administration

Adults

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

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

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

During treatment for schizophrenia, manic episode and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20 mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours.

Olanzapine can be given without regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

Olanzapine Jenson Pharmaceutical Services Limited tablets break easily, so you should handle the tablets carefully. Do not handle the tablets with wet hands as the tablets may break up. For perforated blisters, hold the blister strip at the edges and separate one blister cell from the rest of the strip by gently tearing along the perforations around it. Carefully peel off the backing. For non-perforated blisters, take care not to peel off the backing of adjacent tablets. Then, gently push the tablet out.

Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablet should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact

orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or other suitable beverage (orange juice, apple juice, milk or coffee) immediately before administration.

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

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

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

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.

In cases where dose increments of 2.5 mg are considered necessary, Olanzapine coated tablets should be used. (See sections 4.5 and 5.2.)

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

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

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

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient ischemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in patients treated with olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All olanzapine- and placebo-treated patients who experienced a cerebrovascular event had pre-existing risk

factors. Age > 75 years and vascular/mixed type dementia were identified as risk factors for CVAE in association with olanzapine treatment. The efficacy of olanzapine was not established in these trials.

Parkinson's disease
The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended. In clinical trials, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo (see section 4.8), and olanzapine was not more effective than placebo in the treatment of psychotic symptoms. In these trials, patients were initially required to be stable on the lowest effective dose of anti-Parkinsonian medicinal products (dopamine agonist) and to remain on the same anti-Parkinsonian medicinal products and dosages throughout the study. Olanzapine was started at 2.5 mg/day and titrated to a maximum of 15 mg/day based on investigator judgement.

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal 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 creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported 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 in accordance with utilised antipsychotic guidelines, e.g., measuring of blood glucose at baseline, 12 weeks after starting olanzapine treatment and annually thereafter.
Patients treated with any antipsychotic agents, including Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablets, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly, e.g., at baseline, 4, 8 and 12 weeks after starting olanzapine treatment and quarterly thereafter.

Lipid alterations
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic agents, including Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablets, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines, e.g., at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter.

Anticholinergic activity
While olanzapine demonstrated anticholinergic activity *in vitro*, experience during the clinical trials revealed a low incidence of related events. However, as clinical experience with olanzapine in patients with concomitant illness is limited, caution is advised when prescribing for patients with prostatic hypertrophy, or paralytic ileus and related conditions.

Hepatic function
Transient, asymptomatic elevations of hepatic transaminases, alanine transferase (ALT), aspartate transferase (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 medicines. In the event of elevated ALT and/or AST during treatment, follow-up 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 medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

Discontinuation of treatment
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported 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 medicines known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Thromboembolism
Temporal association of olanzapine treatment and venous thromboembolism has been reported uncommonly (≥ 0.1% and < 1%). A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

General CNS activity
Given the primary CNS effects of olanzapine, caution should be used when it is taken in combination with other centrally acting medicines and alcohol. As it exhibits *in vitro* dopamine antagonism, olanzapine may antagonize the effects of direct and indirect dopamine agonists.

Seizures
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur 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.

Sudden cardiac death
In postmarketing reports with olanzapine, the event of sudden cardiac death has been reported in patients with olanzapine. In a retrospective observational cohort study, the risk of presumed sudden cardiac death in patients treated with olanzapine was approximately twice the risk in patients not using antipsychotics. In the study, the risk of olanzapine was comparable to the risk of atypical antipsychotics included in a pooled analysis.

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).

Phenylalanine
Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablet contains aspartame, which is a source of phenylalanine. May be harmful for people with phenylketonuria.

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 Cmax following fluvoxamine was 54 % in female nonsmokers and 77 % in male smokers. The mean increase in olanzapine AUC was 52 % and 108 % respectively. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.

Decreased bioavailability
Activated charcoal reduces the bioavailability of oral olanzapine by 50 to 60% and should be taken at least 2 hours before or after olanzapine.

Fluoxetine (a CYP2D6 inhibitor), single doses of antacid (aluminium, magnesium) or cimetidine have not been found to significantly affect the pharmacokinetics of olanzapine.

Potential for olanzapine to affect other medicinal products
Olanzapine may antagonise the effects of direct and indirect dopamine agonists.

Olanzapine does not inhibit the main CYP450 isoenzymes *in vitro* (e.g. 1A2, 2D6, 2C9, 2C19, 3A4). Thus no particular interaction is expected as verified through *in vivo* studies where no inhibition of metabolism of the following active substances was found: tricyclic antidepressant (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2) or diazepam (CYP3A4 and 2C19).

Olanzapine showed no interaction when co-administered with lithium or biperiden.

Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant olanzapine.

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

The concomitant use of olanzapine with anti-Parkinsonian medicinal products in patients with Parkinson's disease and dementia is not recommended (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with olanzapine. Nevertheless, because human experience is limited, olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Neonates exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonis, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adults
The most frequently (seen in 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism (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. The frequency terms listed are defined as follows: Very common (≥10%), common (≥1% and < 10%), uncommon (≥0.1% and < 1%), rare (≥0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the data available).

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			

Very common	Common	Uncommon	Not known
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) (see section 4.4)	
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 incontinence	Urinary hesitation
Pregnancy, puerperium and perinatal conditions			
			Drug withdrawal syndrome neonatal (see section 4.6)
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 alkaline phosphatase

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

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

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

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

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

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

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

[8] In clinical trials of up to 12 weeks, plasma prolactin concentrations exceeded the upper limit of normal range in approximately 30% of olanzapine treated patients with normal baseline prolactin value. In the majority of these patients the elevations were generally mild, and remained below two times the upper limit of normal range. In patients with schizophrenia, mean prolactin level changes decreased with continued treatment, whereas mean increases were seen in patients with other diagnoses. The mean changes were modest. Generally in olanzapine-treated patients potentially associated breast- and menstrual related clinical manifestations (e.g. amenorrhoea, breast enlargement, galactorrhea in females, and gynaecomastia/breast enlargement in males) were uncommon. Potentially associated sexual function-related adverse reactions (e.g. erectile dysfunction in males and decreased libido in both genders) were commonly observed.

Long-term exposure (at least 48 weeks)

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

Additional information on special populations

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

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

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

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 short-term clinical trials in adolescent patients. Clinically significant weight gain (≥7%) appears to occur more frequently in the adolescent population compared to adults with comparable exposures. The magnitude of weight gain and the proportion of adolescent patients who had clinically significant weight gain were greater with long-term exposure (at least 24 weeks) than with short-term exposure.

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

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] Following short term treatment (median duration 22 days), weight gain ≥7% of baseline body weight (kg) was very common (40.6 %), ≥15% of baseline body weight was common (7.1 %) and ≥25 % was common (2.5 %). With long-term exposure (at least 24 weeks), 89.4 % gained ≥7 %, 55.3 % gained ≥15 % and 29.1 % gained ≥25% of their baseline body weight.

[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, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diazepines, oxazepines and thiazepines, ATC code: N05A H03.

Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

In preclinical studies, olanzapine exhibited a range of receptor affinities (K_i < 100 nM) for serotonin 5 $HT_{2A/2C}$, 5 HT_3, 5 HT_6; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors M_1-M_5; adrenergic; and histamine H_1 receptors. Animal behavioral studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin $5HT_2$ than dopamine D_2 receptors and greater 5 HT_2 than D_2 activity *in vivo* models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an "anxiolytic" test.

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

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

In a multinational, double-blind, comparative study of schizophrenia, schizoaffective, and related disorders which included 1,481 patients with varying degrees of associated depressive symptoms (baseline mean of 16.6 on the Montgomery-Asberg Depression Rating Scale), a prospective secondary analysis of baseline to endpoint mood score change demonstrated a statistically significant improvement (p= 0.001) favouring olanzapine (-6.0) versus haloperidol (-3.1).

In patients with a manic or mixed episode of bipolar disorder, olanzapine demonstrated superior efficacy to placebo and valproate semisodium (divalproex) in reduction of manic symptoms over 3 weeks. Olanzapine also demonstrated comparable efficacy results to haloperidol in terms of the proportion of patients in symptomatic remission from mania and depression at 6 and 12 weeks. In a co-

therapy study of patients treated with lithium or valproate for a minimum of 2 weeks, the addition of olanzapine 10 mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

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

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

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

5.2 Pharmacokinetic properties

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

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 metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hr) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia > 65 years of age, dosing from 5 to 20 mg/day was not associated with any distinguishing profile of adverse events.

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

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

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

In non-smoking versus smoking subjects (males and females) the mean elimination half-life was prolonged (38.6 versus 30.4 hr) and the clearance was reduced (18.6 versus 27.7 l/hr).

The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals.

In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations.

The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α1-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 210 mg/kg (mice) and 175 mg/kg (rats). Dogs tolerated single oral doses up to 100 mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, labored respiration, miosis, and anorexia. In monkeys, single oral doses up to 100 mg/kg resulted in prostration and, at higher doses, semi-consciousness.

Repeated-dose toxicity
In studies up to 3 months duration in mice and up to 1 year in rats and dogs, the predominant effects were CNS depression, anticholinergic effects, and peripheral haematological disorders. Tolerance developed to the CNS depression. Growth parameters were decreased at high doses. Reversible effects consistent with elevated prolactin in rats included decreased weights of ovaries and uterus and morphologic changes in vaginal epithelium and in mammary gland.

Haematologic toxicity: Effects on haematology parameters were found in each species, including dose-related reductions in circulating leukocytes in mice and non-specific reductions of circulating leukocytes in rats; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia, or anemia developed in a few dogs treated with 8 or 10 mg/kg/day (total olanzapine exposure [area under the curve] is 12- to 15-fold greater than that of a man given a 12-mg dose). In cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

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

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Microcrystalline cellulose and Guar gum (Avicel CE 15)
Crospovidone (Type A)
Magnesium stearate
Silica, colloidal anhydrous
Aspartame (E951)
Sodium laurilsulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original container to protect from light and moisture.

6.5 Nature and contents of container

For PL 17871/0155 and PL 17871/0163:
HDPE bottles with polypropylene screw cap with induction sealing liner and with absorbent cotton and desiccant (silica gel).
7, 10, 14, 28, 30, 56, 98, 100, 250, 500 tablets.

For all PL numbers:
OPA/Al/PVC blisters: Cold-formed laminated blister consisting of OPA/AL/PVC laminate on one side and aluminium foil (Paper/polyester/AL/Heat Seal lacquer) laminate on the other.
7, 10, 14, 28, 30, 35, 56, 60, 70, 98, 100 tablets.
(7, 10, 14, 28, 30, 35, 56, 60, 70, 98, 100) x 1 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House
237 Regents Park Road
London N3 3LF

8 MARKETING AUTHORISATION NUMBER(S)

PL 17871/0155
PL 17871/0159
PL 17871/0163

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/02/2012

10 DATE OF REVISION OF THE TEXT

17/02/2012

1 NAME OF THE MEDICINAL PRODUCT

Olanzapine Jenson Pharmaceutical Services Limited 20 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 20 mg olanzapine

Excipient(s) with known effect:

Each 20 mg orodispersible tablet contains 7.900 mg aspartame

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet

Light yellow to yellow coloured, plain to mottled, round, flat faced, beveled edged tablets debossed with "M" on one side and "OE4" on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Olanzapine is indicated for the treatment of schizophrenia.

Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Olanzapine is indicated for the treatment of moderate to severe manic episode.

In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder (see section 5.1).

4.2 Posology and method of administration

Adults

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

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

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

During treatment for schizophrenia, manic episode and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20 mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours.

Olanzapine can be given without regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

Olanzapine Jenson Pharmaceutical Services Limited tablets break easily, so you should handle the tablets carefully. Do not handle the tablets with wet hands as the tablets may break up. For perforated blisters, hold the blister strip at the edges and separate one blister cell from the rest of the strip by gently tearing along the perforations around it. Carefully peel off the backing. For non-perforated blisters, take care not to peel off the backing of adjacent tablets. Then, gently push the tablet out.

Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablet should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact

orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or other suitable beverage (orange juice, apple juice, milk or coffee) immediately before administration.

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

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

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

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.

In cases where dose increments of 2.5 mg are considered necessary, Olanzapine coated tablets should be used. (See sections 4.5 and 5.2.)

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

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

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

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient ischemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in patients treated with olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All olanzapine- and placebo-treated patients who experienced a cerebrovascular event had pre-existing risk

factors. Age > 75 years and vascular/mixed type dementia were identified as risk factors for CVAE in association with olanzapine treatment. The efficacy of olanzapine was not established in these trials.

Parkinson's disease
The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended. In clinical trials, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo (see section 4.8), and olanzapine was not more effective than placebo in the treatment of psychotic symptoms. In these trials, patients were initially required to be stable on the lowest effective dose of anti-Parkinsonian medicinal products (dopamine agonist) and to remain on the same anti-Parkinsonian medicinal products and dosages throughout the study. Olanzapine was started at 2.5 mg/day and titrated to a maximum of 15 mg/day based on investigator judgement.

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal 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 creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported 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 in accordance with utilised antipsychotic guidelines, e.g., measuring of blood glucose at baseline, 12 weeks after starting olanzapine treatment and annually thereafter.
Patients treated with any antipsychotic agents, including Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablets, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly, e.g., at baseline, 4, 8 and 12 weeks after starting olanzapine treatment and quarterly thereafter.

Lipid alterations
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic agents, including Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablets, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines, e.g., at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter.

Anticholinergic activity
While olanzapine demonstrated anticholinergic activity *in vitro*, experience during the clinical trials revealed a low incidence of related events. However, as clinical experience with olanzapine in patients with concomitant illness is limited, caution is advised when prescribing for patients with prostatic hypertrophy, or paralytic ileus and related conditions.

Hepatic function
Transient, asymptomatic elevations of hepatic transaminases, alanine transferase (ALT), aspartate transferase (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 medicines. In the event of elevated ALT and/or AST during treatment, follow-up 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 medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

Discontinuation of treatment
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported 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 medicines known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Thromboembolism
Temporal association of olanzapine treatment and venous thromboembolism has been reported uncommonly (≥ 0.1% and < 1%). A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

General CNS activity
Given the primary CNS effects of olanzapine, caution should be used when it is taken in combination with other centrally acting medicines and alcohol. As it exhibits *in vitro* dopamine antagonism, olanzapine may antagonize the effects of direct and indirect dopamine agonists.

Seizures
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur 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.

Sudden cardiac death
In postmarketing reports with olanzapine, the event of sudden cardiac death has been reported in patients with olanzapine. In a retrospective observational cohort study, the risk of presumed sudden cardiac death in patients treated with olanzapine was approximately twice the risk in patients not using antipsychotics. In the study, the risk of olanzapine was comparable to the risk of atypical antipsychotics included in a pooled analysis.

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).

Phenylalanine
Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablet contains aspartame, which is a source of phenylalanine. May be harmful for people with phenylketonuria.

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 Cmax following fluvoxamine was 54 % in female nonsmokers and 77 % in male smokers. The mean increase in olanzapine AUC was 52 % and 108 % respectively. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.

Decreased bioavailability
Activated charcoal reduces the bioavailability of oral olanzapine by 50 to 60% and should be taken at least 2 hours before or after olanzapine.

Fluoxetine (a CYP2D6 inhibitor), single doses of antacid (aluminium, magnesium) or cimetidine have not been found to significantly affect the pharmacokinetics of olanzapine.

Potential for olanzapine to affect other medicinal products
Olanzapine may antagonise the effects of direct and indirect dopamine agonists.

Olanzapine does not inhibit the main CYP450 isoenzymes *in vitro* (e.g. 1A2, 2D6, 2C9, 2C19, 3A4). Thus no particular interaction is expected as verified through *in vivo* studies where no inhibition of metabolism of the following active substances was found: tricyclic antidepressant (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2) or diazepam (CYP3A4 and 2C19).

Olanzapine showed no interaction when co-administered with lithium or biperiden.

Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant olanzapine.

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

The concomitant use of olanzapine with anti-Parkinsonian medicinal products in patients with Parkinson's disease and dementia is not recommended (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with olanzapine. Nevertheless, because human experience is limited, olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Neonates exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonis, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast feeding

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adults

The most frequently (seen in 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism (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. The frequency terms listed are defined as follows: Very common (≥10%), common (≥1% and < 10%), uncommon (≥0.1% and < 1%), rare (≥0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the data available).

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			

Very common	Common	Uncommon	Not known
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) (see section 4.4)	
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 incontinence	Urinary hesitation
Pregnancy, puerperium and perinatal conditions			
			Drug withdrawal syndrome neonatal (see section 4.6)
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 alkaline phosphatase

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

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

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

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

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

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

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

[8] In clinical trials of up to 12 weeks, plasma prolactin concentrations exceeded the upper limit of normal range in approximately 30% of olanzapine treated patients with normal baseline prolactin value. In the majority of these patients the elevations were generally mild, and remained below two times the upper limit of normal range. In patients with schizophrenia, mean prolactin level changes decreased with continued treatment, whereas mean increases were seen in patients with other diagnoses. The mean changes were modest. Generally in olanzapine-treated patients potentially associated breast- and menstrual related clinical manifestations (e.g. amenorrhoea, breast enlargement, galactorrhea in females, and gynaecomastia/breast enlargement in males) were uncommon. Potentially associated sexual function-related adverse reactions (e.g. erectile dysfunction in males and decreased libido in both genders) were commonly observed.

Long-term exposure (at least 48 weeks)

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

Additional information on special populations

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

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

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

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 short-term clinical trials in adolescent patients. Clinically significant weight gain (≥7%) appears to occur more frequently in the adolescent population compared to adults with comparable exposures. The magnitude of weight gain and the proportion of adolescent patients who had clinically significant weight gain were greater with long-term exposure (at least 24 weeks) than with short-term exposure.

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

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] Following short term treatment (median duration 22 days), weight gain ≥7% of baseline body weight (kg) was very common (40.6 %), ≥15% of baseline body weight was common (7.1 %) and ≥25 % was common (2.5 %). With long-term exposure (at least 24 weeks), 89.4 % gained ≥7 %, 55.3 % gained ≥15 % and 29.1 % gained ≥25% of their baseline body weight.

[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, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diazepines, oxazepines and thiazepines, ATC code: N05A H03.

Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

In preclinical studies, olanzapine exhibited a range of receptor affinities (K_i < 100 nM) for serotonin 5 $HT_{2A/2C}$, 5 HT_3, 5 HT_6; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors M_1-M_5; adrenergic; and histamine H_1 receptors. Animal behavioral studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin $5HT_2$ than dopamine D_2 receptors and greater 5 HT_2 than D_2 activity *in vivo* models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an "anxiolytic" test.

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

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

In a multinational, double-blind, comparative study of schizophrenia, schizoaffective, and related disorders which included 1,481 patients with varying degrees of associated depressive symptoms (baseline mean of 16.6 on the Montgomery-Asberg Depression Rating Scale), a prospective secondary analysis of baseline to endpoint mood score change demonstrated a statistically significant improvement (p= 0.001) favouring olanzapine (-6.0) versus haloperidol (-3.1).

In patients with a manic or mixed episode of bipolar disorder, olanzapine demonstrated superior efficacy to placebo and valproate semisodium (divalproex) in reduction of manic symptoms over 3 weeks. Olanzapine also demonstrated comparable efficacy results to haloperidol in terms of the proportion of patients in symptomatic remission from mania and depression at 6 and 12 weeks. In a co-

therapy study of patients treated with lithium or valproate for a minimum of 2 weeks, the addition of olanzapine 10 mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

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

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

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

5.2 Pharmacokinetic properties

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

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 metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hr) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia > 65 years of age, dosing from 5 to 20 mg/day was not associated with any distinguishing profile of adverse events.

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

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

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

In non-smoking versus smoking subjects (males and females) the mean elimination half-life was prolonged (38.6 versus 30.4 hr) and the clearance was reduced (18.6 versus 27.7 l/hr).

The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals.

In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations.

The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α1-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 210 mg/kg (mice) and 175 mg/kg (rats). Dogs tolerated single oral doses up to 100 mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, labored respiration, miosis, and anorexia. In monkeys, single oral doses up to 100 mg/kg resulted in prostration and, at higher doses, semi-consciousness.

Repeated-dose toxicity
In studies up to 3 months duration in mice and up to 1 year in rats and dogs, the predominant effects were CNS depression, anticholinergic effects, and peripheral haematological disorders. Tolerance developed to the CNS depression. Growth parameters were decreased at high doses. Reversible effects consistent with elevated prolactin in rats included decreased weights of ovaries and uterus and morphologic changes in vaginal epithelium and in mammary gland.

Haematologic toxicity: Effects on haematology parameters were found in each species, including dose-related reductions in circulating leukocytes in mice and non-specific reductions of circulating leukocytes in rats; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia, or anemia developed in a few dogs treated with 8 or 10 mg/kg/day (total olanzapine exposure [area under the curve] is 12- to 15-fold greater than that of a man given a 12-mg dose). In cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

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

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Microcrystalline cellulose and Guar gum (Avicel CE 15)
Crospovidone (Type A)
Magnesium stearate
Silica, colloidal anhydrous
Aspartame (E951)
Sodium laurilsulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original container to protect from light and moisture.

6.5 Nature and contents of container

For PL 17871/0156 only:
HDPE bottles with polypropylene screw cap with induction sealing liner and with absorbent cotton and desiccant (silica gel).
7, 10, 14, 28, 30, 56, 98, 100, 250, 500 tablets.

For all PL numbers:
OPA/Al/PVC blisters: Cold-formed laminated blister consisting of OPA/AL/PVC laminate on one side and aluminium foil (Paper/polyester/AL/Heat Seal lacquer) laminate on the other.
7, 10, 14, 28, 30, 35, 56, 60, 70, 98, 100 tablets.
(7, 10, 14, 28, 30, 35, 56, 60, 70, 98, 100) x 1 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House
237 Regents Park Road
London N3 3LF

8 MARKETING AUTHORISATION NUMBER(S)

PL 17871/0156
PL 17871/0160

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/02/2012

10 DATE OF REVISION OF THE TEXT

17/02/2012

Module 3

The following text is the approved Patient Information leaflet (PIL) text as agreed during EU procedure number UK/H/4681/001-4/DC (PL 17871/0157-60) and is included as a representative PIL. The text agreed for procedures UK/H/4492/01-4 and 4761/01-3/DC (PL 17871/0153-56 and PL 17871/0161-63 is consistent with this PIL (with the exception of PL number specific pack size and presentation; these procedure numbers are also available in HDPE bottle containers). No PIL mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the PIL mock-up has been obtained.

Package Leaflet: Information For The User

Olanzapine Jenson Pharmaceutical Services Limited 5 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 10 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 15 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 20 mg orodispersible tablets
olanzapine

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

What is in this leaflet:

1. What Olanzapine Jenson Pharmaceutical Services Limited Is And What It Is Used For

Olanzapine Jenson Pharmaceutical Services Limited belongs to a group of medicines called antipsychotics.

Olanzapine Jenson Pharmaceutical Services Limited 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 Jenson Pharmaceutical Services Limited is used to treat a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep 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.

You must talk to a doctor if you do not feel better or if you feel worse.

2. What You Need To Know Before You Take Olanzapine Jenson Pharmaceutical Services Limited

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

Warnings and precautions
Talk to your doctor before taking Olanzapine Jenson Pharmaceutical Services Limited.
• Medicines of this type may cause unusual movements mainly of the face or tongue. If this happens after you have been given Olanzapine Jenson Pharmaceutical Services Limited 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.
- If you or someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots.
- Weight gain has been seen in patients taking Olanzapine Jenson Pharmaceutical Services Limited. You and your doctor should check your weight regularly.
- High blood sugar and high levels of fat (triglycerides and cholesterol) have been seen in patients taking Olanzapine Jenson Pharmaceutical Services Limited. Your doctor should do blood tests to check blood sugar and certain fat levels before you start taking Olanzapine Jenson Pharmaceutical Services Limited and regularly during treatment.

• The use of Olanzapine Jenson Pharmaceutical Services Limited in elderly patients with dementia 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 disease
• 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.

Children and adolescents
Olanzapine Jenson Pharmaceutical Services Limited is not for patients who are under 18 years.

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

Tell your doctor if you are taking, have recently taken or might take any other medicines. Especially tell your doctor if you are taking medicines for Parkinson's disease.

Olanzapine Jenson Pharmaceutical Services Limited with food, drink and alcohol
Do not drink any alcohol if you have been given Olanzapine Jenson Pharmaceutical Services Limited as taking it with alcohol may make you feel drowsy.

Pregnancy and breast-feeding
Tell your doctor as soon as possible if you are pregnant or think you may be 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 Jenson Pharmaceutical Services Limited can pass into breast milk.

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

Driving and using machines
There is a risk of feeling drowsy when you are given Olanzapine Jenson Pharmaceutical Services Limited. If this happens do not drive or operate any tools or machines. Tell your doctor.

Olanzapine Jenson Pharmaceutical Services Limited contains aspartame
Patients who cannot take phenylalanine should note that Olanzapine Jenson Pharmaceutical Services Limited contains aspartame, which is a source of phenylalanine. May be harmful for people with phenylketonuria.

3. How To Take Olanzapine Jenson Pharmaceutical Services Limited

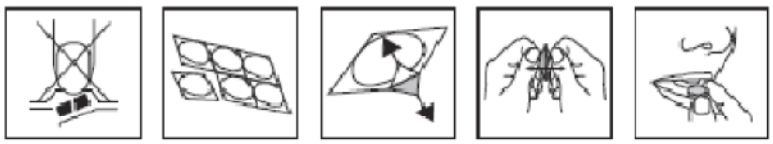
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

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

You should take your Olanzapine Jenson Pharmaceutical Services Limited tablets once a day following the advice of your doctor. Try to take your tablets at the same time each day. It does not matter whether you take them with or without food. Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablets are for oral use.

Olanzapine Jenson Pharmaceutical Services Limited tablets break easily, so you should handle the tablets carefully. Do not handle the tablets with wet hands as the tablets may break up.
1. For perforated blisters, hold the blister strip at the edges and separate one blister cell from the rest of the strip by gently tearing along the perforations around it.
2. Carefully peel off the backing. For non-perforated blisters, take care not to peel off the backing of adjacent tablets.
3. Gently push the tablet out.
4. Put the tablet in your mouth. It will dissolve directly in your mouth, so that it can be easily swallowed.

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



If you take more Olanzapine Jenson Pharmaceutical Services Limited than you should
Patients who have taken more Olanzapine Jenson Pharmaceutical Services Limited than they should have experienced the following symptoms: rapid beating of the heart, agitation/aggressiveness, problems with speech, unusual movements (especially of the face or tongue) and reduced level of consciousness. Other symptoms may be: acute confusion, seizures (epilepsy), coma, a combination of

fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness, slowing of the breathing rate, aspiration, high blood pressure or low blood pressure, abnormal rhythms of the heart. Contact your doctor or hospital straight away. Show the doctor your pack of tablets.

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

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

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

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

4. Possible Side Effects

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

Very common side effects: affect 1 user in 10
- Weight gain.
- Sleepiness.
- Increases in the levels of prolactin 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 the 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.
- Sexual dysfunctions such as decreased libido in males and females or erectile dysfunction in males.

Uncommon side effects: affect 1 to 10 users in 1,000
- Slow heart rate.
- Make you sensitive to sunlight.
- Urinary incontinence.
- Hair loss.
- Absence or decrease in menstrual periods.
- Changes in breasts in males and females such as an abnormal production of breast milk or abnormal growth.
- Blood clots such as deep venous thrombosis of the leg or blood clot on the lung.

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 the worsening of diabetes, occasionally associated with ketoacidosis (ketones in the blood and 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 muscle of the eye causing rolling movement of the eye.
• Abnormal rhythms of the heart.
• Sudden unexplained death.
• Inflammation of the pancreas causing severe stomach pain, fever and sickness.
• Liver disease appearing as yellowing of the skin and white parts of the eyes.
• Muscle disease presenting as unexplained aches and pains.
• 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 Jenson Pharmaceutical Services Limited 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.

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

5. How To Store Olanzapine Jenson Pharmaceutical Services Limited

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

Do not use this medicine after the expiry date, which is stated on the carton and blister/bottle.

Store in the original container to protect from light and moisture.

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

6. Contents of the pack and other information

What Olanzapine Jenson Pharmaceutical Services Limited contains

Olanzapine Jenson Pharmaceutical Services Limited 5 mg contains 5 mg of olanzapine as the active ingredient.
Olanzapine Jenson Pharmaceutical Services Limited 10 mg contains 10 mg of olanzapine as the active ingredient.
Olanzapine Jenson Pharmaceutical Services Limited 15 mg contains 15 mg of olanzapine as the active ingredient.
Olanzapine Jenson Pharmaceutical Services Limited 20 mg contains 20 mg of olanzapine as the active ingredient.
The other ingredients are mannitol, microcrystalline cellulose, guar gum, crospovidone (type A), magnesium stearate, colloidal anhydrous silica, aspartame (E951) and sodium lauril sulfate.

What Olanzapine Jenson Pharmaceutical Services Limited looks like and contents of the pack

Olanzapine Jenson Pharmaceutical Services Limited 5 mg is supplied as light yellow to yellow coloured, plain to mottled, round, flat faced, beveled edged tablets debossed with "M" on one side and "OE1" on other side.

Olanzapine Jenson Pharmaceutical Services Limited 10 mg is supplied as light yellow to yellow coloured, plain to mottled, round, flat faced, beveled edged tablets debossed with "M" on one side and "OE2" on other side.

Olanzapine Jenson Pharmaceutical Services Limited 15 mg is supplied as light yellow to yellow coloured, plain to mottled, round, flat faced, beveled edged tablets debossed with "M" on one side and "OE3" on other side.

Olanzapine Jenson Pharmaceutical Services Limited 20 mg is supplied as light yellow to yellow coloured, plain to mottled, round, flat faced, beveled edged tablets debossed with "M" on one side and "OE4" on other side.

Olanzapine Jenson Pharmaceutical Services Limited orodispersible tablets are supplied in non-perforated blisters containing 28, 35, 56, 70 or 98 tablets and perforated unit-dose blisters containing (28, 35, 56, 70 or 98) x 1 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Jenson Pharmaceutical Services Limited
Carradine House
237 Regents Park Road
London N3 3LF

Manufacturers:

McDermott Laboratories Ltd. T/A Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.

This leaflet was last revised in 02/2012.

Module 4
Labelling

The following text is the approved labelling text as agreed during EU procedure number UK/H/4492/001-4/DC (PL 17871/0153-6) and is included as representative labelling. The text agreed for procedures UK/H/4681/01-4; PL 17871/0157-160 (blister presentation only) and 4761/01-3/DC; PL 17871/0161-63 (blister and HDPE bottle presentations) is consistent with this labelling. No labelling mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the labelling mock-ups has been obtained.

MINIMUM PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Jenson Pharmaceutical Services Limited 5 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 10 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 15 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 20 mg orodispersible tablets

olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains 5 mg olanzapine
Each orodispersible tablet contains 10 mg olanzapine
Each orodispersible tablet contains 15 mg olanzapine
Each orodispersible tablet contains 20 mg olanzapine

3. LIST OF EXCIPIENTS

Contains aspartame (E951). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet
7, 10, 14, 28, 30, 35, 56, 60, 70, 98, 100 tablets
(7, 10, 14, 28, 30, 35, 56, 60, 70, 98, 100) x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original container to protect from light and moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House
237 Regents Park Road
London N3 3LF

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

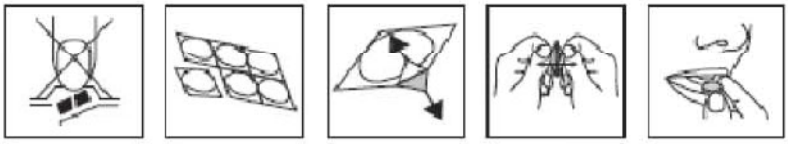
13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE



Instruction for perforated blisters:

1. Separate one blister cell from the strip.
2. Carefully peel off the backing.
3. Gently push the tablet out.
4. Put the tablet in your mouth.

Instruction for non-perforated blisters:

1. Carefully peel off the backing by taking care not to peel off the backing of adjacent tablets.
2. Gently push the tablet out.
3. Put the tablet in your mouth.

16. INFORMATION IN BRAILLE

Olanzapine Jenson Pharmaceutical Services Limited 5 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 10 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 15 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 20 mg orodispersible tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

OPA/AL/PVC BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Jenson Pharmaceutical Services Limited 5 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 10 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 15 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 20 mg orodispersible tablets

olanzapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

OPA/AL/PVC BLISTERS

FOR BELGIUM ONLY (LABELLING DEROGATION)

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Jenson Pharmaceutical Services Limited 5 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 10 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 15 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 20 mg orodispersible tablets

Olanzapine (exception: can be removed if blisters are unit dose)

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

LOT:

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON THE OUTER PACKAGING

HDPE BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Jenson Pharmaceutical Services Limited 5 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 10 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 15 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 20 mg orodispersible tablets

olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains 5 mg olanzapine
Each orodispersible tablet contains 10 mg olanzapine
Each orodispersible tablet contains 15 mg olanzapine
Each orodispersible tablet contains 20 mg olanzapine
(exception for BE for bottle with capacity ≤ 50 ml: statement of active substance will not be mentioned)

3. LIST OF EXCIPIENTS

Contains aspartame (E951). See leaflet for further information.
(exception for BE for bottle with capacity ≤ 50 ml: list of excipients will not be mentioned)

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet
7, 10, 14, 28, 30, 56, 98, 100, 250, 500 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

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

Keep out of the reach and sight of children.

(exception for BE for bottle with capacity ≤ 50 ml: special warning that the medicinal product must be stored out of the reach and sight of the children will not be mentioned)

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original container to protect from light and moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House
237 Regents Park Road
London N3 3LF

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

(exception for BE for bottle with capacity ≤ 50 ml: general classification for supply will not be mentioned)

15. INSTRUCTIONS ON USE

[To be completed nationally]

(exception for BE for bottle with capacity ≤ 50 ml: instructions on use will not be mentioned)

16. INFORMATION IN BRAILLE

Olanzapine Jenson Pharmaceutical Services Limited 5 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 10 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 15 mg orodispersible tablets
Olanzapine Jenson Pharmaceutical Services Limited 20 mg orodispersible tablets

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Olanzapine Jenson Pharma 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets (PL 17871/0153-63; UK/H/4492, 4681/001-4 and 4761/001-3/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Austria, Belgium, Cyprus, Czech Republic, Germany, Greece, France, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Slovenia, Spain and Slovakia as Concerned Member State (CMS). These products are prescription-only medicines (POM).

Olanzapine Jenson Pharma 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets are indicated in adults for:

- the treatment of schizophrenia
- maintaining the clinical improvement during continuation therapy in patients who have shown initial treatment response
- the treatment of moderate to severe manic episode
- the prevention of recurrence of manic episode in patients with bipolar disorder (in patients whose manic episode has responded to olanzapine treatment).

These applications were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Zyprexa Velotab 5mg, 10mg, 15mg and 20mg orodispersible tablets, which were first authorised via the centralised procedure to Eli Lilly Nederland BV, on 03 February 2000.

Olanzapine is an antipsychotic, antimanic, and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

No new non-clinical studies were conducted, which is acceptable given that the products are intended to be generic medicinal products of originator products that have been licensed for over 10 years.

One bioequivalence study (single dose) was submitted to support these applications, comparing the test product Olanzapine Jenson Pharma 5 mg orodispersible tablets (Jenson Pharmaceutical Services Limited) with the reference product Zyprexa Velotab 5mg orodispersible tablets (Eli Lilly Nederland BV).

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were for products that are intended to be generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 209) on 18 January 2012. After a subsequent national phase, the licences were granted in the UK on 17 February 2012.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Olanzapine Jenson Pharma 5 mg orodispersible tablets Olanzapine Jenson Pharma 10 mg orodispersible tablets Olanzapine Jenson Pharma 15 mg orodispersible tablets Olanzapine Jenson Pharma 20 mg orodispersible tablets
Name(s) of the active substance(s) (INN)	Olanzapine
Pharmacotherapeutic classification (ATC code)	Diazepines, oxazepines and thiazepines (N05A H03)
Pharmaceutical form and strength(s)	5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets.
Reference numbers for the Mutual Recognition Procedure	UK/H/4492/001-4/DC UK/H/4681/001-4/DC UK/H/4761/001-3/DC
Reference Member State	United Kingdom
Concerned Member State	UK/H/4492/001-2/DC:Austria, Belgium, Cyprus, Czech Republic, Germany, Greece, France, Hungary, Ireland, Netherlands, Poland, Portugal, Romania, Slovenia and Slovakia. UK/H/4492/003-4/DC: Austria, Belgium, Cyprus, Czech Republic, Germany, Greece, France, Hungary, Ireland, Netherlands, Poland, Portugal, Romania and Slovenia. UK/H/4681/001/DC: France and Italy. UK/H/4681/002-4/DC: Belgium, France and Italy.
Marketing Authorisation Number(s)	PL 17871/0153-63
Name and address of the authorisation holder	Jenson Pharmaceutical Services Limited, Carradine House, 237 Regents Park Road, London N3 3LF, UK.

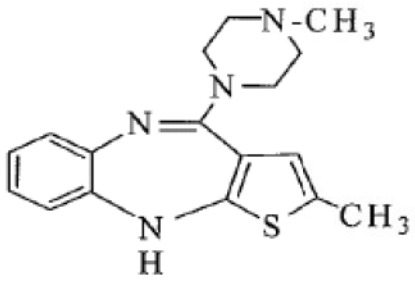
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Olanzapine
Chemical name: 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2 ,3-*b*] [1,5] benzodiazepine.

Structure:



Molecular formula: $C_{17}H_{20}N_4S$
Appearance: Olanzapine is a pale yellow to yellow colour crystalline powder.
Solubility: Olanzapine is freely soluble in chloroform. Olanzapine has no chiral centres and exhibits polymorphism.

Olanzapine is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients mannitol, Avicel CE 15 (comprised of microcrystalline cellulose and Guar gum), crospovidone (Type A), magnesium stearate, silica colloidal anhydrous, aspartame (E951) and sodium laurilsulfate.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Avicel CE 15 which complies with a suitable in-house specification. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to formulate stable, robust, orodispersible tablets containing 5 mg, 10 mg, 15 mg or 20 mg olanzapine, which could be considered generic medicinal products of Zyprexa Velotab 5mg, 10mg, 15mg and 20mg orodispersible tablets (Eli Lilly Nederland BV).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale and has shown satisfactory results. The applicant has committed to perform process validation studies on the first 3 production scale batches of all strengths of product.

Finished Product Specification
The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
For procedure numbers UK/H/4492/001-4 (PL 17871/0153-6) and UK/H/4716/001-3 (PL 17871/0161-3):
All strengths of the finished product are packaged in:

- high density polyethylene (HDPE) bottles with polypropylene screw cap with induction sealing liner and with absorbent cotton and desiccant (silica gel) in pack sizes of 7, 10, 14, 28, 30, 56, 98, 100, 250 and 500 tablets.
- cold formed laminated blisters consisting of oriented polyamide/aluminium/polyvinylchloride (OPA/Al/PVC) laminate on one side and aluminium foil (paper/polyester/aluminium/heat seal lacquer) laminate on the other, in pack sizes of 7, 10, 14, 28, 30, 35, 56, 60, 70, 98 and 100 tablets.

For procedure number UK/H/4681/01-4 (PL 17871/0157-60):
All strengths of the finished product are packaged in cold formed laminated blisters consisting of oriented polyamide/aluminium/polyvinylchloride (OPA/Al/PVC) laminate on one side and aluminium foil (paper/polyester/aluminium/heat seal lacquer) laminate on the other, in pack sizes of 7, 10, 14, 28, 30, 35, 56, 60, 70, 98 and 100 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished products packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions 'Store in the original container to protect from light and moisture.'

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable.

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, as amended. 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.

Marketing Authorisation Application (MAA) form
The MAA forms are satisfactory.

Expert report
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of olanzapine are well-known, no new non-clinical studies are required and none have been provided.

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

Suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with other products already on the market, it is not considered to increase the environmental risk. Thus, the applicant's justification is accepted.

There are no objections to the approval of these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open label, randomised, balanced, single-dose, two-treatment, two-period, two-sequence, crossover, study to compare the pharmacokinetics of the test product Olanzapine Jenson Pharma 5 mg orodispersible tablets (Jenson Pharmaceutical Services Limited) versus the reference product Zyprexa Velotab 5mg orodispersible tablets (Eli Lilly Nederland BV) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 5 mg tablet administered with 20 ml of water after an overnight fast. The subjects were requested to wet their mouth by swallowing 20 ml of water directly before applying the test or reference product on the tongue. The tablet dissolved directly in the mouth and once this was confirmed the subject was requested to swallow. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The washout period between treatment periods was at least 14 days.

The pharmacokinetic results for olanzapine are presented below (log-transformed values; geometric least squares mean, ±Standard deviation (SD), ratios and 90% confidence intervals):

Pharmacokinetics parameters (Test)		C_{max} (ng/ml)	Median t_{max} (hours)	AUC_{0-72} (ng*h/ml)	$t_{1/2}$ (hours)	K_{el} (h^{-1})
	Mean ± SD	8.67 ± 2.42	4.00	222.92 ± 57.26	29.43 ± 9.58	0.03 ± 0.01
Pharmacokinetics parameters (Reference)		C_{max} (ng/ml)	Median t_{max} (hours)	AUC_{0-72} (ng*h/ml)	$t_{1/2}$ (hours)	K_{el} (h^{-1})
	Mean ± SD	8.69 ± 2.43	4.00	232.84 ± 69.36	29.72 ± 8.80	0.03 ± 0.01

Bioequivalence comparison, Primary parameters	Parameter	Ratio % (Test/Reference)	Lower 90% CI	Upper 90% CI
	C_{max}	99.6101	93.7804	105.8023
	AUC_{0-72}	96.4108	91.1386	101.9880

C_{max} : Maximum measured plasma concentration
T_{max} : Time of the maximum measured plasma concentration
AUC_{0-72} : The area under the plasma concentration versus time curve, from time 0 to 72 hours
K_{el} : Elimination rate constant
$t_{1/2}$: Terminal half life

The 90% confidence intervals for AUC and C_{max} for test versus reference product for olanzapine are within predefined acceptance criteria specified in 'Guideline on the Investigation of Bioequivalence' (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Thus, the data support the claim that the 5mg test product is bioequivalent to the 5mg reference product.

As the 5 mg, 10 mg, 15 mg and 20 mg strengths of the product meet the criteria specified in the 'Guideline on the Investigation of Bioequivalence' (CPMP/EWP/QWP/1401/98 Rev 1/, Corr**), the results and conclusions of the bioequivalence study on the 5 mg strength can be extrapolated to the 10 mg, 15 mg and 20 mg strengths.

Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for these applications.

Efficacy
No new efficacy data were submitted and none were required for these applications.

Safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with that for the originator products. The PIL is consistent with the SmPCs and in line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical overview and summary has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of these products from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The quality characteristics of Olanzapine Jenson Pharma 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets are 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.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of olanzapine are well-known.

EFFICACY

With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant's Olanzapine Jenson Pharma 5 mg orodispersible tablets and the respective reference product, Zyprexa Velotab 5mg orodispersible tablets (Eli Lilly Nederland BV). As the 5 mg, 10 mg, 15 mg and 20 mg strengths of the product meet the biowaiver criteria specified in the 'Guideline on the Investigation of Bioequivalence' (CPMP/EWP/QWP/1401/98 Rev 1/, Corr**), the results and conclusions of the bioequivalence study on the 5 mg strength can be extrapolated to the 10 mg, 15 mg and 20 mg strengths.

SAFETY

With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of olanzapine is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products, where appropriate, in line with current guidelines.

BENEFIT-RISK ASSESSMENT

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

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome