National Institute of Pharmacy

Public Assessment Report

Decentralised Procedure

Name of the Product:

Parnassan 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg & 20 mg Film-coated tablets
Zoiros 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg & 20 mg Film-coated tablets

DCP Number: HU/H/0177-0178/001-006/DC

Applicant: Gedeon Richter Plc.

Table of contents

Modul 1
Information about the initial procedure

Product name	Parnassan
Type of application:	Generic, Art 10.1 and 10.2 Dir 2001/ 83
level 1	Abridged
level 2	Initial application
level 3	Generic, Art 10.1 and 10.2 Dir 2001/ 83
level 4	Chemical substance
level 5	Prescription only
Active substance	Olanzapine
Pharmaceutical form	film coated tablet
Strength	2.5 mg, 5 mg, 7.5 mg , 10 mg, 15 mg & 20 mg
MA holder	Gedeon Richter Plc.
RMS	Hungary
CMS	BG, CZ, EE, LT, LV, PL, RO, SK
Procedure number	HU/H/0177/001-006/DC
Timetable	day0 2008.06.03 day70 (PrAR) 2008.08.12 day95 2008.09.06 day100 2008.09.11 day105 2008.09.16 day106 2009.04.22 day120 (DAR) 2009.05.06 day140 2009.05.26 day145 2009.05.31 day150 2009.06.05 day160 2009.06.15 day180 (DAR) 2009.07.05 day195 2009.07.20 day200 2009.07.25 day205 2009.07.30 day210 (FAR) 2009.08.04

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

Product name	Zoiros	
Type of application:	Generic, Art 10.1 and 10.2 Dir 2001/ 83	
level 1	Abridged	
level 2	Initial application	
level 3	Generic, Art 10.1 and 10.2 Dir 2001/ 83	
level 4	Chemical substance	
level 5	Prescription only	
Active substance	Olanzapine	
Pharmaceutical form	film coated tablet	
Strength	2.5 mg, 5 mg, 7.5 mg , 10 mg, 15 mg & 20 mg	
MA holder	Gedeon Richter Plc.	
RMS	Hungary	
CMS	ES	
Procedure number	HU/H/0178/001-006/DC	
Timetable	day0	2008.06.03
	day70 (PrAR)	2008.08.12
	day95	2008.09.06
	day100	2008.09.11
	day105	2008.09.16
	day106	2009.04.22
	day120 (DAR)	2009.05.06
	day140	2009.05.26
	day145	2009.05.31
	day150	2009.06.05
	day160	2009.06.15
	day180 (DAR)	2009.07.05
	day195	2009.07.20
	day200	2009.07.25
	day205	2009.07.30
	day210 (FAR)	2009.08.04

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

Modul 2
Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

{INVENTED NAME} 2.5 mg film-coated tablets
{INVENTED NAME} 5 mg film-coated tablets
{INVENTED NAME} 7. 5 mg film-coated tablets
{INVENTED NAME} 10 mg film-coated tablets
{INVENTED NAME} 15 mg film-coated tablets
{INVENTED NAME} 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5; 5; 7.5; 10; 15; 20 mg olanzapine.
Excipients:
One film-coated tablet contains 54.173; 108.345; 162.518; 216.690; 162.518; 216.690 mg of lactose monohydrate and 0.06; 0.12; 0.18; 0.24; 0.18; 0.24 mg of lecithin soya, respectively.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

{INVENTED NAME} 2.5 mg film-coated tablets – the product is presented as white round, biconvex engraving – on one side N23, diameter 6 mm.
{INVENTED NAME} 5 mg film-coated tablets – the product is presented as white round, biconvex engraving – on one side N24, diameter 8 mm.
{INVENTED NAME} 7.5 mg film-coated tablets – the product is presented as white round, biconvex engraving – on one side N25, diameter 9 mm.
{INVENTED NAME} 10 mg film-coated tablets – the product is presented as white round, biconvex engraving – on one side N26, diameter 10 mm.
{INVENTED NAME} 15 mg film-coated tablets – the product is presented as white oblong, biconvex engraving – on one side N27, diameter 14 x 5.5 mm.
{INVENTED NAME} 20 mg film-coated tablets – the product is presented as white oblong, biconvex engraving – on one side N 28, diameter 15 x 6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:
{INVENTED NAME} is indicated for the treatment of schizophrenia.

{INVENTED NAME} is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

{INVENTED NAME} 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.

Children and adolescents: {INVENTED NAME} is not recommended 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 with adults patients (see 4.4, 4.8, 5.1 and 5.2).

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

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

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

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

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

(See also section 4.5 and section 5.2.)

4.3. Contraindications

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

{INVENTED NAME} tablets contain lecithin soya. Patients that are allergic to soya, should not take this medicine.

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 behavioral disturbances:
{INVENTED NAME} 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 {INVENTED NAME} 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 also 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 medications (dopamine agonist) and to remain on the same anti-Parkinsonian medications 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 medication. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.

Hyperglicaemia and diabetes:
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical

monitoring is advisable particularly in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

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.

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

Hepatic function:
Transient, asymptomatic elevations of hepatic transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic 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 very rarely (<0.01%) been reported. A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

General CNS activity:

Given the primary CNS effects of olanzapine, caution should be used when it is taken in combination with other centrally acting 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.

Use in children and adolescents under 18 years of age:
{INVENTED NAME} 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 4.8 and 5.1).

Lactose:
{INVENTED NAME} tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

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 % 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).

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

4.6 Pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000,), very rare (<1/10,000), not known (cannot be estimated from the data available).

Very common	**Common**	**Uncommon**	**Not known**
Blood and the lymphatic system disorders			
	Eosinophylia	Leucopenia Neutropenia	Thrombocytopenia
Immune system disorders			
			Allergic reaction
Metabolism and nutrition system disorders			
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5] Glucosuria Increased appetite		Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4) Hypothermia
Nervous system disorders			
Somnolence	Dizziness Akatisia[6] Parkinsonism[6] Dyskinezia[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 dyskinezia Discontinuation symptoms[7]
Cardiac disorders			
		Bradycardia QT_c prolongation (see section 4.4)	Ventricular tachycardia/fibrillation, sudden death (see section 4.4)
Vascular disorders			

	Orthostatic hypotension		Thromboembolism (including pulmonary embolism and deep vein thrombosis)
Gastrointestinal disorders			
	Mild transient anticholinergic effects including constipation and dry mouth		Pancreatitis
Hepato-biliary disorders			
	Transient asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury)
Skin and subcutaneous tissue disorders			
	Rash	Photosensitivity reaction Alopecia	
Musculoskeletal and connective tissue disorders			
			Rhabdomyolysis
Renal and urinary disorders			
			Urinary hesitation
Reproductive system and breast disorders			
			Priapism
General disorders and administration site conditions			
	Asthenia Fatigue Oedema		
Investigations			
Elevated plasma prolactin levels[8]		High creatinine phosphokinase Increased total bilirubin	Increased alkaline phosphatase

[1] Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Weight gain ≥7% of baseline body weight was very common and ≥15% of baseline body weight was common. Patients gaining ≥25% of their baseline body weight with long-term exposure were very common.

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

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

[4] Observed for fasting normal levels at baseline (<5.56 mmol/l) which increased to high (≥7 mmol/l).

Changes in fasting glucose from borderline at baseline (≥5.56 - <7 mmol/l) to high (≥7 mmol/l) were very common.

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

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

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

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

Long-term exposure (at least 48 weeks)
The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HCL 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 4-6 months.

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

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

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

Children and adolescents
{INVENTED NAME} 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 summarizes 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] Weight gain ≥7% of baseline body weight (kg) was very common and ≥15% of baseline body weight was common. With long-term exposure (at least 24 weeks), approximately half of adolescent patients gained ≥15% and almost a third gained ≥25% of their baseline body weight. Among adolescent patients, mean weight gain was greatest in patients who were overweight or obese at baseline.

[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 450mg but survival has also been reported following acute overdose of l,500mg.

Management of overdose:

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antipsychotics, ATC code: N05A H03.

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

In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki; < 100 nM) for serotonin 5 HT2A/2C, 5 HT3, 5 HT6; dopamine Dl, D2, D3, D4, D5; cholinergic muscarinic receptors m1-m5; alpha1 adrenergic; and histamine H1 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 5HT2 than dopamine D2 receptors and greater 5 HT2 than D2 activity in vivo, models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A 10) 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 HT2A than dopamine D2 receptor occupancy. In addition, a SPECT imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D2 occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

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 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-hydroxy methyl 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 1/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 1/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 1/hr). A mass balance study showed that approximately 57 % of radiolabeled 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 1/hr) was reduced analogous to non-smoking healthy subjects (48.8 hr and 14.1 1/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 1/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 α_1-acid-glycoprotein.

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

5.3 Preclinical safety data

Acute (single-dose) toxicity
Signs of oral toxicity in rodents were characteristic of potent neuroleptic compounds: hypoactivity, coma, tremors, clonic convulsions, salivation, and depressed weight gain. The median lethal doses were approximately 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 [AUC] is 12- to 15-fold greater than that of a man given a 12-mg dose). In

cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

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

Tablet core:
Crospovidone (type A)
Cellulose, microcrystalline
Ludipress: (Lactose monohydrate; Povidone K30; Crospovidone (type A))
Magnesium stearate
Tablet coat:
OPADRY AMB OY-B-28920 White:
- Polyvinyl alcohol – part. hydrolysed
- Titanium dioxide (E171)
- Talc (E 553b)
- Lecithin (soya) (E 322)
- Xanthan gum (E 415)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

{INVENTED NAME} 2.5; 5; 7.5 and 10 mg film-coated tablets:
18 months.

{INVENTED NAME} 15 and 20 mg film-coated tablets:
2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The film-coated tablets are packed in oPA-Al-PVC/Al blister packs containing 10 tablets. 3 blisters are in one carton box.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

Modul 3
Package leaflets

PACKAGE LEAFLET: INFORMATION FOR THE USER

{INVENTED NAME} 2.5 mg film-coated tablets
{INVENTED NAME} 5 mg film-coated tablets
{INVENTED NAME} 7.5 mg film-coated tablets
{INVENTED NAME} 10 mg film-coated tablets
{INVENTED NAME} 15 mg film-coated tablets
{INVENTED NAME} 20 mg film-coated tablets

olanzapine

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT {INVENTED NAME} IS AND WHAT IT IS USED FOR

{INVENTED NAME} belongs to a group of medicines called antipsychotics.

{INVENTED NAME} 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.

{INVENTED NAME} 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.

2. BEFORE YOU TAKE {INVENTED NAME}

Do not take {INVENTED NAME}

• if you are allergic (hypersensitive) to olanzapine or any of the other ingredients of {INVENTED NAME}. 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).

Take special care with {INVENTED NAME}
• Medicines of this type may cause unusual movements mainly of the face or tongue. If this happens after you have been given {INVENTED NAME} tell your doctor.
• Very rarely, medicines of this type cause a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness. If this happens, contact your doctor at once.
• The use of {INVENTED NAME} 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.
{INVENTED NAME} is not for patients who are under 18 years.

Taking other medicines
Only take other medicines while you are on {INVENTED NAME} if your doctor tells you that you can.

You might feel drowsy if {INVENTED NAME} 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 {INVENTED NAME} dose.

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

Taking {INVENTED NAME} with food and drink
Do not drink any alcohol if you have been given {INVENTED NAME} as {INVENTED NAME} and alcohol together 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 {INVENTED NAME} can pass into breast milk.

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

Important information about some of the ingredients of {INVENTED NAME}
{INVENTED NAME} contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
{INVENTED NAME} contains lecithin soya. If you are allergic to soya, you should not take this medicinal product.

3. HOW TO TAKE {INVENTED NAME}

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

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

You should take your {INVENTED NAME} 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. {INVENTED NAME} film-coated tablets are for oral use. You should swallow the {INVENTED NAME} tablets whole with water.

If you take more {INVENTED NAME} than you should
Patients who have taken more {INVENTED NAME} 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 {INVENTED NAME}
Take your tablets as soon as you remember. Do not take two doses in one day.

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

If you suddenly stop taking {INVENTED NAME}, 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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, {INVENTED NAME} 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.

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

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

Other possible side effects: frequency cannot be estimated from the available data.
- Allergic reaction (e.g. swelling in the mouth and throat, itching, rash).
- Diabetes or 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.
- Blood clots such as deep venous thrombosis of the leg or blood clot on the lung.
- Inflammation of the pancreas causing severe stomach pain, fever and sickness.
- Liver disease appearing as yellowing of the skin and white parts of the eyes.
- Muscle disease presenting as unexplained aches and pains.
- Difficulty in passing urine.
- Prolonged and/or painful erection.

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

In patients with Parkinson's disease {INVENTED NAME} may worsen the symptoms.

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

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

5. HOW TO STORE {INVENTED NAME}

Do not store above 25°C.
Keep out of the reach and sight of children.

Do not use {INVENTED NAME} after the expiry date, which is stated on the carton.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What {INVENTED NAME} contains
The active substance is olanzapine. One film-coated tablet contains 2.5; 5; 7.5; 10; 15; 20 mg of olanzapine.

The other ingredients are:
Tablet core:
Crospovidone (type A)
Cellulose, microcrystalline
Ludipress: (lactose monohydrate; povidone K30; crospovidone (type A))
Magnesium stearate

Tablet coat:
OPADRY AMB OY-B-28920 White:
- Polyvinyl alcohol – part. hydrolysed
- Titanium dioxide (E171)
- Talc (E 553b)
- Lecithin (soya) (E 322)
- Xanthan gum (E 415)

What {INVENTED NAME} looks like and contents of the pack
{INVENTED NAME} 2.5 mg film-coated tablets – the product is presented as white round, biconvex engraving – on one side N23, diameter 6 mm.
{INVENTED NAME} 5 mg film-coated tablets – the product is presented as white round, biconvex engraving – on one side N24, diameter 8 mm.
{INVENTED NAME} 7.5 mg film-coated tablets – the product is presented as white round, biconvex engraving – on one side N25, diameter 9 mm.

{INVENTED NAME} 10 mg film-coated tablets – the product is presented as white round, biconvex engraving – on one side N26, diameter 10 mm.
{INVENTED NAME} 15 mg film-coated tablets – the product is presented as white oblong, biconvex engraving – on one side N27. Length 14 mm and width 5.5 mm.
{INVENTED NAME} 20 mg film-coated tablets – the product is presented as white oblong, biconvex engraving – on one side N 28. Length 15 mm and width 6 mm.

The film-coated tablets are packed in oPA/Al-PVC/Al blister packs containing 10 tablets. 3 blisters are in one carton box.

Marketing Authorisation Holder and Manufacturer
Marketing authorisation holder:
<[To be completed nationally]>

Manufacturer:
Grodziskie Zakłady Farmaceutyczne "Polfa" Sp. Z o.o.
ul. ks. J. Poniatowskiego 5
05-825 Grodzisk Mazowiecki
POLAND

This medicinal product is authorised in the member states of the eea under the following names:

This leaflet was last approved in MM/YYYY.

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

Modul 4
Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX

1. NAME OF THE MEDICINAL PRODUCT

{Invented name} 2.5 mg film-coated tablets
{Invented name} 5 mg film-coated tablets
{Invented name} 7.5 mg film-coated tablets
{Invented name} 10 mg film-coated tablets
{Invented name} 15 mg film-coated tablets
{Invented name} 20 mg film-coated tablets
Olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 2.5 mg olanzapine.
Each film-coated tablet contains 5 mg olanzapine.
Each film-coated tablet contains 7.5 mg olanzapine.
Each film-coated tablet contains 10 mg olanzapine.
Each film-coated tablet contains 15 mg olanzapine.
Each film-coated tablet contains 20 mg olanzapine.

3. LIST OF EXCIPIENTS

Also includes lactose monohydrate and lecithin soya. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

For 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.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

Marketing Authorization Holder:
<[To be completed nationally]>

12. MARKETING AUTHORIZATION NUMBER

Reg. No.:

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{Invented name} 2.5 mg
{Invented name} 5 mg
{Invented name} 7.5 mg
{Invented name} 10 mg
{Invented name} 15 mg
{Invented name} 20 mg

PARTICULARS TO APPEAR ON BLISTERS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

{Invented name} 2.5 mg film-coated tablets
{Invented name} 5 mg film-coated tablets
{Invented name} 7.5 mg film-coated tablets
{Invented name} 10 mg film-coated tablets
{Invented name} 15 mg film-coated tablets
{Invented name} 20 mg film-coated tablets
Olanzapine

2. NAME OF THE MARKETING AUTHORIZATION HOLDER

<[To be completed nationally]>

3. EXPIRY DATE

((Expiry date pressed in the foil))

4. BATCH NUMBER

((Batch number pressed in the foil))

5. OTHER

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

Modul 5
Scientific discussion during the initial procedure

I. INTRODUCTION

This report evaluates the chemical-pharmaceutical aspects of a decentralised application for Marketing Authorisation, using the abridged procedure as described in article 10(1) of Directive 2001/83/EC: Generic Application. The reference product was licensed in the Community for Eli Lilly (Netherland BV, The Netherlands) on 27th September 1996, therefore the legal basis is acceptable. A bioequivalence study was performed using Zyprexa 10 mg tablets (NL) as the reference. HU acted as RMS. No paediatric development plan exists for these products.

Olanzapine, a thienobenzodiazepine derivative, belongs to the relatively new class of the second generation antipsychotic agents, called atypical antipsychotics. Although there is no universal definition of an atypical antipsychotic, these drugs, in contrast to classical antipsychotics (e.g. haloperidol), have greater affinity to serotonin 5-HT2A than to dopamine D2 receptors, cause fewer extrapyramidal symptoms and improve negative symptoms, are generally classified as atypical. Olanzapine has been shown to improve both positive and negative symptoms of schizophrenia with a lower incidence of extrapyramidal symptoms.

The product containing olanzapine (2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets) is indicated for the treatment of schizophrenia and moderate to severe manic episode. Olanzapine is indicated for the prevention of recurrence of manic episode in patients with bipolar disorder.

During development of the products the following guidance documents were followed by the applicant:
CPMP/EWP/QWP/1401/98 and EMEA/CHMP/167068/2004-ICH,
CPMP/QWP/486/95 and CPMP/QWP/848/96,
ICH Q2A and Q2B, Q3A, Q3B, Q3C, ICH Q6A,
CPMP/QWP/4359/03.

The dossier is of good overall quality; however some points for clarification have been highlighted during assessment. No new preclinical or clinical studies were submitted with this application.

The products and the active pharmaceutical ingredient are manufactured and the bioequivalence study has been conducted in compliance with GMP, GLP, GCP rules, respectively, and agreed ethical principles.
The GLP status of literature data cannot be verified. The bioequivalence study is stated to be GCP compliant.

II. QUALITY ASPECTS

II.1 Introduction

The active substance is Olanzapine which is an antipsychotic drug. It is a serotonin and dopamine receptor antagonist with an anticholinergic activity. Olanzapine is used in the treatment of schizophrenia and in the treatment of moderate to severe manic episode.
Olanzapine belongs to the pharmacotherapeutic group of N05A H03 (antipsychotics).
The maximum daily dose is 20 mg according to the SPC.
The original product Zyprexa 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg coated tablets are marketed in Sweden by Eli Lilly Netherland BV since 1996. Zyprexa was approved in EU through the centralised procedure. This was the reference product.
Bioequivalence studies were performed comparing the pharmacokinetics of Olanzapine 10 mg film-coated tablet with Zyprexa® 10 mg coated tablets (manufactured by Eli Lilly Netherland BVS.A.). Olanzapine 10 mg film-coated tablets were found to be essentially similar to the already marketed Zyprexa ® 10 mg coated tablets.
The products are formulated as film-coated tablets. 2.5 mg, 5 mg, 7.5 mg and 10 mg tablets are dose proportional; 15 mg and 20 mg dose tablets are proportional to each other and quasi-proportional to the other doses. The film-coated tablets will be packaged in OPA/Al/PVC//Al blisters and box.

II.2 Drug Substance

Data on the quality and manufacture of the active substance was provided via European DMF procedure. A letter of access to the DMF was submitted.

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

The active substance is a pale yellow to yellow coloured crystalline powder and freely soluble in chloroform, sparingly soluble in acetic acid. It shows polymorphism.
Olanzapine does not contain any chiral center and therefore it does not exhibit stereoisomerism.

The proposed manufacturing process has been adequately described, critical steps and accompanying in-process controls have been defined to ensure the quality of the final compound. In-process controls performed during the synthesis are suitable to control the reaction progress. Appropriate specifications for starting materials, solvents and reagents have been established.
Evidence of the structure has been confirmed by UV, IR, proton/carbon NMR spectroscopy, MS, X-ray crystallography and by elemental analysis.
Potential impurities originating from starting materials, intermediates, by-products, and degradation products have been discussed in according to their origin and potential carry-over into the final drug substance. Residual solvents and heavy metals are routinely controlled.
The substance complies with the requirements of the EMEA guideline on genotoxic impurities.
Olanzapine is not official in the Ph.Eur. Therefore, an in-house specification has been set for the active substance which includes tests for appearance, solubility, identification (IR, XRD), assay and purity (HPLC), residual solvents (GC), loss on drying, heavy metals and sulphated ash.
The specification is in accordance with the Ph.Eur. general monograph on Substances for pharmaceutical use and the ICH Q6A guideline.
The specifications reflect all relevant quality attributes of the active substance and were found to be suitable for the control of the quality of the drug substance. The limits set are properly justified.
Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are well characterised.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.
During the stability studies no significant changes in any parameters were observed. The retest period is 18 months at storage conditions of 25°C ±2°, stored in tight containers protected from light.
GMP compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The aim of the pharmaceutical development was to manufacture film-coated tablets containing 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg or 20 mg Olanzapine as active substance which are bioequivalent and pharmaceutically equivalent to the reference product of Eli Lilly Zyprexa 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg coated tablets.
A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation.
The used excipients are: crospovidone, microcrystalline cellulose, Ludipress and magnesium stearate. Ludipress is a granulate prepared especially for direct compression technology consisting of lactose monohydrate, povidone and crospovidone. The white film-coating contains partially hydrolized poly(vinyl-alcohol), titanium dioxide, talc, soyalecithin and xanthan gum. All excipients used comply with their respective European Pharmacopoeia monograph, (with exception of Ludipress and the white film-coating, which comply with a satisfactory in-house monograph and the components of them also comply with pharmacopoeias). Compliance of the products with the general monograph of the European Pharmacopoeia on the Products with the risk of TSE has been demonstrated by the applicant.
2.5 mg tablets are white, round, biconvex film-coated tablets engraved with “N” 23” on one side, with diameter of 6 mm.
5 mg tablets are white, round, biconvex film-coated tablets engraved with “N” 24” on one side, with diameter of 8 mm.
7.5 mg tablets are white, round, biconvex film-coated tablets engraved with “N” 25” on one side, with diameter of 9 mm.
10 mg tablets are white, round, biconvex film-coated tablets engraved with “N” 26” on one side, with diameter of 10 mm.
15 mg tablets are white, oblong, biconvex film-coated tablets engraved with “N” 27” on one side, tablet size is 14 x 5.5 mm.
20 mg tablets are white, oblong, biconvex film-coated tablets engraved with “N” 28” on one side, tablet size is 15 x 6 mm.
The film-coated tablets are packaged in OPA/Al/PVC foil fastened with Aluminium foil and box.
As regards dissolution and impurity profile the product is shown to be similar to the reference product. Similar dissolution profiles of the different strengths throughout the physiological PH range support bioequivalence of the strengths not involved in bioequivalence study.
A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.
The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the European pharmacopoeia and the ICH Q6A guideline. Appropriate control strategy was selected.
The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented. Certificates of analysis were also provided for the working standard used.
The container closure system of the product is as follows: in OPA/Al/PVC// Al blisters. The same blisters as those proposed for routine storage were used for the stability studies. The selected primary

packaging material complies with the relevant Ph. Eur. Monograph, directive 2002/72/EC and foodstuff legislation.
Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results a shelf-life of 18 months for Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg film-coated tablets and 24 months for the 15 mg, 20 mg film-coated tablets with the storage conditions of "Do not store above 25 °C" is approved.
The SPC, PIL and label are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: The product has been shown to consistently meet the current regulatory requirements with respect to qualitative and quantitative content of the active substance and pharmaceutical form until the end of the approved shelf-life. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of olanzapine are well known. As olanzapine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature search is, thus, appropriate.

The non-clinical overview has been written by Zdenka Dominikova from Czech Republic MSc. The report refers to 77 publications up to year 2006.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

N/A

III.6 Discussion on the non-clinical aspects

No objections to the approval of olanzapine film-coated tablets were raised by the RMS or CMSs from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. The clinical overview refers to a comprehensive bibliography of 173 references up to year 2007 and the clinical summary (Module 2.7) provides a brief review about the bioequivalence study. The clinical overview has been written by Jaroslav Boucek MD, professor of psychiatry at University of Olomouc (Czech Republic).

IV.2 Pharmacokinetics

This application concerns 6 tablet strengths containing 2.5, 5, 7.5, 10, 15 and 20 mg of the active substance olanzapine.

To support the application, the applicant has submitted the report of one single dose bioequivalence study under fasting conditions.

The bioequivalence study was performed with the 10mg immediate release tablet comparing the bioavailability of the generic olanzapine product of GZF Polfa (PL) Poland, with the reference product Zyprexa 10mg (manufacturer Eli Lilly, NL). It is known that pharmacokinetics of olanzapine are linear over the therapeutic dose range and a single bioequivalence study with arbitrary strength is considered acceptable as all other conditions stipulated in "Note for Guidance on the Investigation of Bioavailability and Bioequivalence", section 5.4. are fulfilled.

The bioequivalence study was a single-dose, 2-way cross-over study with 18 healthy adult subjects. Each subject received a single dose (1 x 10mg tablet) of both test and reference olanzapine formulation in fasting conditions. The study was carried out in Poland (clinical part) and Germany (analytical part) and there is no concern regarding to the validity of the data.

The 90% Confidence Intervals for the test/reference ratios for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for olanzapine were all within conventional bioequivalence criteria and subject to these reassurances bioequivalence was concluded.

The results of study with 10 mg formulation can be extrapolated to the other strengths according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4, since the Applicant provided comparative dissolution data at pH 1.5, 4.5 and 6.8 for all strengths

IV.3 Pharmacodynamics

N/A

IV.4 Discussion on the clinical aspects

No other clinical studies were conducted to support this application.

IV.5 Clinical efficacy

N/A

IV.6 Clinical safety

Pharmacovigilance system

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 (QPPV) and has the necessary means for the notification of any adverse reaction suspected to occure either in the Community or in a third country.

Risk Management Plan

Since the reference product (Zyprexa) has been on the market since 27 September 1996, and its safety profile is well established, the applicant proposes to use the routine pharmacovigilance activities as described in Volume 9A. There is no information on any safety concern requiring additional risk minimisation activities with the reference medicinal product.

Periodic Safety Update Report (PSUR)

As the originator products (Zyprexa and Zyprexa Velotab) are subject to 1 yearly reporting interval according to CHMP decision, the same (or immediately upon request) is required for the generic olanzapine products.
Gedeon Richter Plc. would like to harmonise the PSUR cycle of their product according to the first licence approval date of the innovator product Zyprexa in the EU on 27 September 1996. The intended first DLP is 30 September 2009, and thereafter a yearly scheme is intended to follow.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application contains an adequate review of published clinical data and the bioequivalence with reference product has been shown. Safety profile of olanzapine tablets is well known and an appropriate system is available at the MAH to monitor and report clinical safety of the product. Quality of the products is adequately drawn up to support the consistent safety and efficacy of the tablets. Approval was recommended by the RMS and agreed by the CMSs.

This module reflects the scientific discussion for the approval of <name of the product>. The procedure was finalised at <date of day 90/210>. For information on changes after this date please refer to the module 'Update'.

Modul 6
Steps taken after the initial procedure with an influence on the Public Assessment Report

Module 6: Steps taken after the initial procedure with an influence on the Public Assessment Repor (Type II variations, PSURs, commitments) Scope	Procedure number	Type of modification [1]	Date of start of the procedure	Date of end of procedure	Approval/non approval	Assessment report attached
Y/N (version)						