

Produktinformationen för Zapilux 2,5 mg, 5 mg, 7,5 mg, 10 mg, 15 mg, 20 mg, MTnr 24665, 24666, 24667, 24668, 24669, 24670, gäller vid det tillfälle då läkemedlet godkändes. Informationen kommer inte att uppdateras eftersom läkemedlet inte marknadsförs i Sverige. Av samma anledning finns inte någon svensk produktinformation.

Om läkemedelsnamnet i följande produktinformation inte stämmer med namnet på dokumentet, beror det på att läkemedlet i Sverige är godkänt under ett annat namn.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zapilux 2.5 mg film-coated tablets
Zapilux 5 mg film-coated tablets
Zapilux 7.5 mg film-coated tablets
Zapilux 10 mg film-coated tablets
Zapilux 15 mg film-coated tablets
Zapilux 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.5 mg:

Each film-coated tablet contains 2.5 mg olanzapine.
Excipient: 74.11 mg lactose/film-coated tablet

5 mg:

Each film-coated tablet contains 5 mg olanzapine.
Excipient: 148.22 mg lactose/film-coated tablet

7.5 mg:

Each film-coated tablet contains 7.5 mg olanzapine.
Excipient: 222.33 mg lactose/film-coated tablet

10 mg:

Each film-coated tablet contains 10mg olanzapine.
Excipient: 296.44 mg lactose/film-coated tablet

15 mg:

Each film-coated tablet contains 15 mg olanzapine.
Excipient: 169.31 mg lactose/film-coated tablet

20 mg:

Each film-coated tablet contains 20 mg olanzapine.
Excipient: 225.75 mg lactose/film-coated tablet

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

2.5 mg:

white, round (6.5 mm diameter).

5 mg:

white, round (8 mm diameter), with a breaking notch on one side.
The tablet can be divided into equal halves.

7.5 mg:

white, round (9 mm diameter).

10 mg:

white, round (10 mm diameter), with a breaking notch on one side.

The tablet can be divided into equal halves.

15 mg:

light blue, oval (12 mm length), with a breaking notch on both sides.

The tablet can be divided into equal halves.

20 mg:

pink, oval (13 mm length), with a breaking notch on both sides.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Olanzapine is indicated for the treatment of schizophrenia.

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

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

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

4.2 Posology and method of administration

Schizophrenia: The recommended starting dose for olanzapine is 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 regard for meals, as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

There is no experience in children.

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. Patients with known risk for narrow-angle glaucoma.

4.4 Special warnings and precautions for use

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.

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.

Acute symptoms, such as sweating, insomnia, tremor, anxiety, nausea, or vomiting, have been reported very rarely (<0.01%) when olanzapine is stopped abruptly. Gradual dose reduction should be considered when discontinuing olanzapine.

Concomitant illnesses: 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.

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 also 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.

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% versus 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 ischaemic 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% versus 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.

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.

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 medicinal products. 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.

As with other neuroleptic medicinal products, caution should be exercised in patients with low leucocyte and/or neutrophil counts for any reason, in patients receiving medicinal products known to cause neutropenia, in patients with a history of drug-

induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy, and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

There are limited data on co-medication with lithium and valproate (see section 5.1). There are no clinical data available on olanzapine and carbamazepine co-therapy; however, a pharmacokinetic study has been conducted (see section 4.5).

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

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.

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

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.

In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥ 500 milliseconds [msec] at any time post-baseline in patients with baseline QTcF < 500 msec) were uncommon (0.1% to 1%) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. However, as with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicinal products known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia, or hypomagnesaemia.

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

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

4.6 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.

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.

Lactation

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

Assessment of frequencies:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$), not known (cannot be estimated from the available data)

Very common undesirable effects associated with the use of olanzapine in clinical trials were somnolence and weight gain.

In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse events compared to placebo (see also section 4.4). Very common undesirable effects 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 $\geq 7\%$ 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 $\geq 7\%$ from baseline body weight in 39.9% of patients.

The following table of undesirable effects is based on adverse event reporting and laboratory investigations from clinical trials.

<p>Blood and lymphatic system disorders <i>Common:</i> Eosinophilia.</p>
<p>Metabolism and nutrition disorders <i>Very common:</i> Weight gain. <i>Common:</i> Increased appetite. Elevated glucose levels (see note 1 below). Elevated triglyceride levels. Elevated cholesterol levels.</p>
<p>Nervous system disorders <i>Very common:</i> Somnolence. <i>Common:</i> Dizziness, akathisia, parkinsonism, dyskinesia (see also note 2 below).</p>
<p>Cardiac disorders <i>Uncommon:</i> Bradycardia, with or without hypotension or syncope, QT prolongation (see also section 4.4).</p>
<p>Vascular disorders <i>Common:</i> Orthostatic hypotension.</p>
<p>Gastro-intestinal disorders <i>Common:</i> Mild, transient anticholinergic effects including constipation and dry mouth.</p>
<p>Hepato-biliary disorders <i>Common:</i> Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see also section 4.4).</p>
<p>Skin and subcutaneous tissue disorders <i>Uncommon:</i> Photosensitivity reaction.</p>
<p>General disorders and administration site conditions <i>Common:</i> Asthenia, oedema.</p>
<p>Investigations <i>Very common:</i> Elevated plasma prolactin levels, but associated clinical manifestations (e.g. gynaecomastia, galactorrhoea, and breast enlargement) were rare. In most patients, levels returned to normal ranges without cessation of treatment. <i>Uncommon:</i> High creatine phosphokinase</p>

¹In clinical trials with olanzapine in over 5,000 patients with baseline non-fasting glucose levels ≤ 7.8 mmol/l, the incidence of non-fasting plasma glucose levels ≥ 11 mmol/l (suggestive of diabetes) was 1.0% compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels ≥ 8.9 mmol/l but < 11 mmol/l (suggestive of hyperglycaemia) was 2.0% compared to 1.6% with placebo. Hyperglycaemia is also reported as a very rare spontaneous event.

²In 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.

The following table of undesirable effects is based on post-marketing spontaneous reports.

<p>Blood and lymphatic system disorders <i>Rare:</i> Leucopenia. <i>Very rare:</i> Thrombocytopenia. Neutropenia.</p>
<p>Immune system disorders <i>Very rare:</i> Allergic reaction (e.g. anaphylactoid reaction, angioedema, pruritus, or urticaria).</p>
<p>Metabolism and nutrition disorders <i>Very rare:</i> Hyperglycaemia and/or development or exacerbation of diabetes, occasionally associated with ketoacidosis or coma, has been spontaneously reported very rarely, including some fatal cases (see also note 1 above and section 4.4). Hypertriglyceridaemia, hypercholesterolaemia, and hypothermia.</p>
<p>Nervous system disorders <i>Rare:</i> Seizures have been reported to occur rarely in patients treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported. <i>Very rare:</i> Cases reported as Neuroleptic Malignant Syndrome (NMS) have been received in association with olanzapine (see also section 4.4). Parkinsonism, dystonia (including oculogyration), and tardive dyskinesia have been reported very rarely with olanzapine. Acute symptoms, such as sweating, insomnia, tremor, anxiety, nausea, or vomiting, have been reported very rarely when olanzapine is stopped abruptly.</p>
<p>Cardiac disorders <i>Very rare:</i> QTc prolongation, ventricular tachycardia/fibrillation, and sudden death (see also section 4.4).</p>
<p>Vascular disorders <i>Very rare:</i> Thromboembolism (including pulmonary embolism and deep vein thrombosis).</p>
<p>Gastro-intestinal disorders</p>

<i>Very rare:</i> Pancreatitis.
Hepato-biliary disorders <i>Rare:</i> Hepatitis (including hepatocellular, cholestatic, or mixed liver injury).
Musculoskeletal and connective tissue and bone disorders <i>Very rare:</i> Rhabdomyolysis.
Skin and subcutaneous tissue disorders <i>Rare:</i> Rash. <i>Very rare:</i> Alopecia
Renal and urinary disorders <i>Very rare:</i> Urinary hesitation.
Reproductive system and breast disorders <i>Very rare:</i> Priapism.
Investigations Increased transaminases. <i>Very rare:</i> Increased alkaline phosphatase. Increased total bilirubin.

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 1,500 mg.

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: 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 5HT_{2A/2C}, 5HT₃, 5HT₆; dopamine D₁, D₂, D₃, D₄, D₅; cholinergic muscarinic receptors m₁-m₅; alpha₁ adrenergic; and histamine H₁ receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin 5HT₂ than dopamine D₂ receptors and greater 5HT₂ than D₂ activity in *in vivo* models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an 'anxiolytic' test.

In a single oral dose (10 mg) Positron Emission Tomography (PET) study in healthy volunteers, olanzapine produced a higher 5HT_{2A} than dopamine D₂ receptor occupancy. In addition, a Single Photon Emission Computed Tomography (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.

5.2 Pharmacokinetic properties

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

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

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

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

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 1,000 ng/ml. Olanzapine is bound predominantly to albumin and alpha₁-acid-glycoprotein.

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, laboured 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 leucocytes in mice and non-specific reductions of circulating leucocytes in rats; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia, or anaemia developed in a few dogs treated with 8 or 10 mg/kg/day (total olanzapine exposure [area under the curve - 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. Oestrous cycles were affected at doses of 1.1 mg/kg (3-times the maximum human dose) and reproduction parameters were influenced in rats given 3

mg/kg (9-times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

Mutagenicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Hydroxypropylcellulose
Crospovidone
Microcrystalline cellulose
Magnesium stearate

Tablet coat

Polyvinyl alcohol
Macrogol 3350
Titanium dioxide (E 171)
Talc

In addition for Zapilux 15 mg film-coated tablets: indigo carmine (E 132)

In addition for Zapilux 20 mg film-coated tablets: iron oxide red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6 months after first opening of the HDPE-bottle

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium blister containing 7, 10, 14, 20, 28, 30, 35, 50, 56, 60, 70, 98, 100 or 500 film-coated tablets

HDPE-bottles containing 50, 100 or 500 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Lek Pharmaceuticals d.d.

Verovskova 57

SI-1526 Ljubljana

Slovenia

8. MARKETING AUTHORISATION NUMBERS

2.5 mg: 24665

5 mg: 24666

7.5 mg: 24667

10 mg: 24668

15 mg: 24669

20 mg: 24670

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

16 January 2008

10. DATE OF REVISION OF THE TEXT

16 January 2008