Public Assessment Report

Decentralised Procedure

OLANZAPINE APOTEX 2.5MG, 5MG, 7.5MG, 10MG, 15MG AND 20MG TABLETS

UK/H/1297/001-6/DC
UK Licence No: PL 27583/0048-53

APOTEX EUROPE BV
LAY SUMMARY

On 23rd September 2009, the UK granted Apotex Europe BV Marketing Authorisations (licences) for the prescription only medicinal products Olanzapine Apotex 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg Tablets (PL 27583/0048-53; UK/H/1297/001-6/DC).

Olanzapine belongs to a group of medicines called antipsychotics.

Olanzapine is used to treat a disease with symptoms such as hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness, and becoming withdrawn. People with this disease may also feel depressed, anxious or tense.

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

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Olanzapine Apotex 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg Tablets outweigh the risks; hence these Marketing Authorisations have been granted.
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## Module 1

<table>
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<tr>
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<tr>
<td><strong>Type of Application</strong></td>
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<td><strong>Active Substance</strong></td>
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<td><strong>Strength</strong></td>
<td>2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg</td>
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</table>
| **MA Holder**          | Apotex Europe BV  
Darwinweg 20, 2333 CR Leiden, The Netherlands                               |
| **Reference Member State (RMS)** | UK                                                                           |
| **CMS**                | The Czech Republic, Germany, the Netherlands, Poland                          |
| **Procedure Number**   | UK/H/1297/001-6/DC                                                           |
| **End of Procedure**   | Day 210 – 24/08/2009                                                          |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Olanzapine Apotex 2.5 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 2.5 mg olanzapine.
Excipient: 16.34 mg anhydrous lactose per tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
Olanzapine 2.5 mg tablets are yellow, cylindrical, biconvex tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults
Olanzapine is indicated for the treatment of schizophrenia.
Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.
Olanzapine is indicated for the treatment of moderate to severe manic episode.
In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder (see section 5.1).

4.2 Posology and method of administration
Adults
Schizophrenia: The recommended starting dose for olanzapine is 10 mg/day.
Manic episode: The starting dose is 15 mg as a single daily dose in monotherapy or 10 mg daily in combination therapy (See section 5.1).
Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, Olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.
During treatment for schizophrenia, manic episode and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20 mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours.
Olanzapine can be given without regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

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

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

Renal and/or hepatic impairment
A lower starting dose (5 mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5 mg and only increased with caution.
Gender
The starting dose and dose range need not be routinely altered for female patients relative to male patients.

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.
(See sections 4.5 and 5.2.)

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

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

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

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

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

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

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some
cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agents, including olanzapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

**Lipid alterations**
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic agents, including olanzapine, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines.

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

**Hepatic function**
Transient, asymptomatic elevations of hepatic transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicinal products. In the event of elevated ALT and/or AST during treatment, 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 medicinal products known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

**Discontinuation of treatment**
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely (<0.01%) when olanzapine is stopped abruptly.

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

**Thromboembolism**
Temporal association of olanzapine treatment and venous thromboembolism has very rarely (<0.01%) been reported. A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.
General CNS activity
Given the primary CNS effects of olanzapine, caution should be used when it is taken in combination with other centrally acting medicinal products and alcohol. As it exhibits in vitro dopamine antagonism, olanzapine may antagonize the effects of direct and indirect dopamine agonists.

Seizures
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur rarely in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

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

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

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

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

Interaction with other medicinal products and other forms of interaction
Interaction studies have only been performed in adults.

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

Induction of CYP1A2
The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (See section 4.2).

Inhibition of CYP1A2
Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine Cmax following fluvoxamine was 54 % in female non-smokers 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).

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

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

<table>
<thead>
<tr>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000), not known (cannot be estimated from the available data)</th>
</tr>
</thead>
</table>

### Blood and the lymphatic system disorders
- Eosinophilia
- Leukopenia
- Neutropenia
- Thrombocytopenia

### Immune system disorders
- Allergic reaction

### Metabolism and nutrition disorders
- Weight gain
- Elevated cholesterol levels
- Development or
<table>
<thead>
<tr>
<th><strong>Nervous system disorders</strong></th>
<th>Elevated glucose levels&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Elevated triglyceride levels&lt;sup&gt;2,5&lt;/sup&gt;</th>
<th>Glucosuria</th>
<th>Increased appetite</th>
<th>exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4)</th>
<th>Hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>Dizziness</td>
<td>Akathisia&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Parkinsonism&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Dyskinesia&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Seizures where in most cases a history of seizures or risk factors for seizures were reported Neuroleptic malignant syndrome (see section 4.4)</td>
<td>Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>Bradycardia</td>
<td>QTc prolongation (see section 4.4)</td>
<td>Ventricular tachycardia/fibrillation, sudden death (see section 4.4)</td>
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<tr>
<td><strong>Vascular disorders</strong></td>
<td>Orthostatic hypotension</td>
<td>Thromboembolism (including pulmonary embolism and deep vein thrombosis)</td>
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<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Mild, transient anticholinergic effects including constipation and dry mouth</td>
<td>Pancreatitis</td>
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<tr>
<td><strong>Hepato-biliary disorders</strong></td>
<td>Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)</td>
<td>Hepatitis (including hepatocellular, cholestatic or mixed liver injury)</td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Rash</td>
<td>Photosensitivity reaction Alopecia</td>
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<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td>Rhabdomyolysis</td>
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<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td>Urinary hesitation</td>
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<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
<td>Priapism</td>
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<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Asthenia Fatigue Oedema</td>
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<tr>
<td><strong>Investigations</strong></td>
<td>Elevated plasma prolactin levels&lt;sup&gt;8&lt;/sup&gt;</td>
<td>High creatine phosphokinase Increased total bilirubin</td>
<td>Increased alkaline phosphatase</td>
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</tbody>
</table>
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/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 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

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

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

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows:

Very common (≥1/10)
Common (≥1/100 to <1/10)

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: 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.</td>
</tr>
<tr>
<td>Common: Elevated cholesterol levels</td>
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<tr>
<td>Nervous system disorders</td>
</tr>
<tr>
<td>Very common: Sedation (including: hypsomnia, lethargy, somnolence).</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Common: Dry mouth</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
</tr>
<tr>
<td>Very common: Elevations of hepatic transaminases (ALT/AST; see section 4.4).</td>
</tr>
<tr>
<td>Investigations</td>
</tr>
<tr>
<td>Very common: Decreased total bilirubin, increased GGT, elevated plasma prolactin levels.</td>
</tr>
</tbody>
</table>

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 450 mg but survival has also been reported following acute overdose of approximate 2 g of oral olanzapine.

**Management of overdose**

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

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

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

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

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

In preclinical studies, olanzapine exhibited a range of receptor affinities ($Ki; < 100 \text{nM}$) for serotonin 5HT2A/2C, 5HT3, 5HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors m1-m5; α1 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 5HT2 than D2 activity in vivo, models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an “anxiolytic” test.

In a single oral dose (10 mg) Positron Emission tomography (PET) study in healthy volunteers, olanzapine produced a higher 5 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-hydroxymethyl metabolites, both exhibited significantly less in vivo pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

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

In female versus male subjects the mean elimination half-life was somewhat prolonged (36.7 versus 32.3 hrs) and the clearance was reduced (18.9 versus 27.3 l/hr). However, olanzapine (5-20 mg) demonstrated a comparable safety profile in female (n=467) as in male patients (n=869). In renally impaired patients (creatinine clearance < 10 ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hr) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57 % of radiolabelled olanzapine appeared in urine, principally as metabolites.

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

In non-smoking versus smoking subjects (males and females) the mean elimination half-life was prolonged (38.6 versus 30.4 hr) and the clearance was reduced (18.6 versus 27.7 l/hr). The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals.

In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations.
The plasma protein binding of olanzapine was about 93% over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α1-acid-glycoprotein.

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

5.3 Preclinical safety data

**Acute (single-dose) toxicity**
Signs of oral toxicity in rodents were characteristic of potent neuroleptic compounds: hypoactivity, coma, tremors, clonic convulsions, salivation, and depressed weight gain. The median lethal doses were approximately 210 mg/kg (mice) and 175 mg/kg (rats). Dogs tolerated single oral doses up to 100 mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, labored respiration, miosis, and anorexia. In monkeys, single oral doses up to 100 mg/kg resulted in prostration and, at higher doses, semi-consciousness.

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

**Haematologic toxicity**
Effects on haematology parameters were found in each species, including dose-related reductions in circulating leukocytes in mice and non-specific reductions of circulating leukocytes in rats; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia, or anemia developed in a few dogs treated with 8 or 10 mg/kg/day (total olanzapine exposure [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
Lactose monohydrate
Crospovidone
Microcrystalline cellulose
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.
6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Blister packs of 28, 30, 56 or 100 tablets in Aluminium/ aluminium blister.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Apotex Europe BV
Darwinweg 20,
2333 CR Leiden
The Nederlands

8 MARKETING AUTHORISATION NUMBER(S)
PL 27583/0048

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

11 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/09/2009

12 DATE OF REVISION OF THE TEXT
23/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Olanzapine Apotex 5 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg olanzapine.
Excipient: 32.58 mg anhydrous lactose per tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
Olanzapine 5 mg tablets are yellow, cylindrical, biconvex tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults
Olanzapine is indicated for the treatment of schizophrenia.
Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.
Olanzapine is indicated for the treatment of moderate to severe manic episode.
In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder (see section 5.1).

4.2 Posology and method of administration
Adults
Schizophrenia: The recommended starting dose for olanzapine is 10 mg/day.
Manic episode: The starting dose is 15 mg as a single daily dose in monotherapy or 10 mg daily in combination therapy (See section 5.1).
Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, Olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

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

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

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

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

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

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

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers.
When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.
(See sections 4.5 and 5.2.)

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

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

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

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

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

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoadicosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agents, including olanzapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients
with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

**Lipid alterations**
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipid disorders. Patients treated with any antipsychotic agents, including olanzapine, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines.

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

**Hepatic function**
Transient, asymptomatic elevations of hepatic transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicinal products. In the event of elevated ALT and/or AST during treatment, 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 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 myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

**Discontinuation of treatment**
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely (<0.01%) when olanzapine is stopped abruptly.

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

**Thromboembolism**
Temporal association of olanzapine treatment and venous thromboembolism has very rarely (<0.01%) been reported. A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

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

**Seizures**
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur rarely in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

**Tardive Dyskinesia**

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

**Postural hypotension**

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

*Use in children and adolescents under 18 years of age*

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

**Lactose**

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

### 4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

**Potential interactions affecting olanzapine**

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

**Induction of CYP1A2**

The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (See section 4.2).

**Inhibition of CYP1A2**

Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine Cmax following fluvoxamine was 54 % in female non-smokers 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 isozymes in vitro (e.g. 1A2, 2D6, 2C9, 2C19, 3A4). Thus no particular interaction is expected as verified through in vivo studies where no inhibition of metabolism of the following active substances was found: tricyclic antidepressant (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2) or diazepam (CYP3A4 and 2C19). Olanzapine showed no interaction when co-administered with lithium or biperiden. Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant olanzapine.
**General CNS activity**
Caution should be exercised in patients who consume alcohol or receive medicinal products that can cause central nervous system depression.
The concomitant use of olanzapine with anti-Parkinsonian medicinal products in patients with Parkinson's disease and dementia is not recommended (see section 4.4).

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

### 4.7 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:

<table>
<thead>
<tr>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000), not known (cannot be estimated from the available data)</th>
</tr>
</thead>
</table>

**Blood and the lymphatic system disorders**

<table>
<thead>
<tr>
<th>Eosinophilia</th>
<th>Leukopenia</th>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
</tr>
</thead>
</table>

**Immune system disorders**

<table>
<thead>
<tr>
<th>Allergic reaction</th>
</tr>
</thead>
</table>

**Metabolism and nutrition disorders**

| Weight gain¹ | Elevated cholesterol levels²³ | Elevated glucose levels⁴ | Elevated triglyceride levels²⁵ | Glucosuria | Increased appetite | Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4) | Hypothermia |

¹ Weight gain refers to the increase in body weight during treatment with olanzapine.
² Elevated cholesterol levels indicate a rise in serum cholesterol levels.
³ Elevated glucose levels refer to an increase in blood glucose levels.
⁴ Elevated triglyceride levels signify an increase in serum triglyceride levels.
⁵ Glucosuria indicates the presence of glucose in the urine.
⁶ Increased appetite refers to an increase in the desire to eat.
⁷ Development or exacerbation of diabetes is associated with ketoacidosis or coma, including some fatal cases.
<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
<th>Seizures where in most cases a history of seizures or risk factors for seizures were reported Neuroleptic malignant syndrome (see section 4.4) Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td></td>
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</tr>
<tr>
<td>Dizziness Akathisia&lt;br&gt;Parkinsonism&lt;br&gt;Dyskinesia&lt;br&gt;Seizures where in most cases a history of seizures or risk factors for seizures were reported Neuroleptic malignant syndrome (see section 4.4) Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms</td>
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<td></td>
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<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Ventricular tachycardia/fibrillation, sudden death (see section 4.4)</td>
</tr>
<tr>
<td></td>
<td>Bradycardia QTc prolongation (see section 4.4)</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>Thromboembolism (including pulmonary embolism and deep vein thrombosis)</td>
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<tr>
<td></td>
<td>Orthostatic hypotension</td>
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<tr>
<td>Gastrointestinal disorders</td>
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<td>Pancreatitis</td>
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<td></td>
<td>Mild, transient anticholinergic effects including constipation and dry mouth</td>
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<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td>Hepatitis (including hepatocellular, cholestatic or mixed liver injury)</td>
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<tr>
<td></td>
<td>Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)</td>
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<td>Skin and subcutaneous tissue disorders</td>
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<td>Rash</td>
<td>Photosensitivity reaction Alopecia</td>
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<td>Musculoskeletal and connective tissue disorders</td>
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<td>Rhabdomyolysis</td>
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<td>Renal and urinary disorders</td>
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<td>Urinary hesitation</td>
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<td>Reproductive system and breast disorders</td>
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<td>Priapism</td>
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<tr>
<td>General disorders and administration site conditions</td>
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<td>Asthenia Fatigue Oedema</td>
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<tr>
<td>Investigations</td>
<td></td>
<td>Increased alkaline phosphatase</td>
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<tr>
<td>Elevated plasma prolactin levels</td>
<td></td>
<td>High creatine phosphokinase Increased total bilirubin</td>
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</tbody>
</table>

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

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

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.

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.

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.

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

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/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 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 Parkisonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

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

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

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

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows:

Very common (≥1/10)
Common (≥1/100 to <1/10)

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
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<tbody>
<tr>
<td>Very common: Weight gain&lt;sup&gt;9&lt;/sup&gt; ≥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.</td>
</tr>
<tr>
<td>Very common: Elevated triglyceride levels&lt;sup&gt;10&lt;/sup&gt;, increased appetite.</td>
</tr>
<tr>
<td>Common: Elevated cholesterol levels&lt;sup&gt;11&lt;/sup&gt;</td>
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<table>
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<tr>
<th>Nervous system disorders</th>
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<tr>
<td>Very common: Sedation (including: hypersomnia, lethargy, somnolence).</td>
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<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
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<tr>
<td>Common: Dry mouth</td>
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<table>
<thead>
<tr>
<th>Hepato-biliary disorders</th>
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</thead>
<tbody>
<tr>
<td>Very common: Elevations of hepatic transaminases (ALT/AST; see section 4.4).</td>
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<table>
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<tr>
<th>Investigations</th>
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<tbody>
<tr>
<td>Very common: Decreased total bilirubin, increased GGT, elevated plasma prolactin levels&lt;sup&gt;12&lt;/sup&gt;.</td>
</tr>
</tbody>
</table>

<sup>9</sup> 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.

<sup>10</sup> 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).

<sup>11</sup> 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.

<sup>12</sup> Elevated plasma prolactin levels were reported in 47.4% of adolescent patients.

4.9 Overdose

Signs and symptoms

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

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

Management of overdose

There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.
Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Epinephrine, dopamine, or other sympathomimetic agents with betaagonist activity should not be used 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
5.2 Pharmacodynamic properties
Pharmacotherapeutic group: diazepines, oxazepines and thiazepines, ATC code N05A H03.
Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki; < 100 nM) for serotonin 5 HT2A/2C, 5 HT3, 5 HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors m1-m5; α1 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 (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an “anxiolytic” test.

In a single oral dose (10 mg) Positron Emission tomography (PET) study in healthy volunteers, olanzapine produced a higher 5 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-hydroxymethyl metabolites, both exhibited significantly less in vivo pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

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

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

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

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

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

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

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

The plasma protein binding of olanzapine was about 93% over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α1-acid-glycoprotein.

Paediatric population
Adolescents (ages 13 to 17 years): The pharmacokinetics of olanzapine are similar between adolescents and adults. In clinical studies, the average olanzapine exposure was approximately 27% higher in adolescents. Demographic differences between the adolescents and adults include a lower average body weight and fewer adolescents were smokers. Such factors possibly contribute to the higher average exposure observed in adolescents.
5.4 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
Lactose monohydrate
Crospovidone
Microcrystalline cellulose
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Blister packs of 28, 30, 56 or 100 tablets in Aluminium/ aluminium blister.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
PAR Olanzapine Apotex 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg Tablets

7 MARKETING AUTHORISATION HOLDER
Apotex Europe BV
Darwinweg 20,
2333 CR Leiden
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)
PL 27583/0049

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

11 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/09/2009

12 DATE OF REVISION OF THE TEXT
23/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Olanzapine Apotex 7.5 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 7.5 mg olanzapine.
Excipient: 49.02 mg anhydrous lactose per tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
Olanzapine 7.5 mg tablets are yellow, cylindrical, biconvex tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults
Olanzapine is indicated for the treatment of schizophrenia.
Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients
who have shown an initial treatment response.
Olanzapine is indicated for the treatment of moderate to severe manic episode.
In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the
prevention of recurrence in patients with bipolar disorder (see section 5.1).

4.2 Posology and method of administration
Adults
Schizophrenia: The recommended starting dose for olanzapine is 10 mg/day.
Manic episode: The starting dose is 15 mg as a single daily dose in monotherapy or 10 mg daily in
combination therapy (See section 5.1).
Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg/day. For patients
who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing
recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, Olanzapine treatment
should be continued (with dose optimisation as needed), with supplementary therapy to treat mood
symptoms, as clinically indicated.

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

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

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

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

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

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

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients. (See sections 4.5 and 5.2.)

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

**Dementia-related psychosis and/or behavioural disturbances**

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

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

**Parkinson's disease**

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

**Neuroleptic Malignant Syndrome (NMS)**

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

**Hyperglycaemia and diabetes**

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoadioidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agents, including olanzapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients...
with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

**Lipid alterations**
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipid disorders. Patients treated with any antipsychotic agents, including olanzapine, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines.

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

**Hepatic function**
Transient, asymptomatic elevations of hepatic transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicinal products. In the event of elevated ALT and/or AST during treatment, 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 medicinal products known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

**Discontinuation of treatment**
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely (<0.01%) when olanzapine is stopped abruptly.

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

**Thromboembolism**
Temporal association of olanzapine treatment and venous thromboembolism has very rarely (<0.01%) been reported. A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

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

Seizures
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur rarely in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

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

**Postural hypotension**
Postural hypotension was infrequently observed in the elderly in olanzapine clinical trials. As with other antipsychotics, it is recommended that blood pressure is measured periodically in patients over 65 years. Use in children and adolescents under 18 years of age
Olanzapine is not indicated for use in the treatment of children and adolescents. Studies in patients aged 13-17 years showed various adverse reactions, including weight gain, changes in metabolic parameters and increases in prolactin levels. Long-term outcomes associated with these events have not been studied and remain unknown (see sections 4.8 and 5.1).

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

### 4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

**Induction of CYP1A2**
The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (See section 4.2).

**Inhibition of CYP1A2**
Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine Cmax following fluvoxamine was 54% in female non-smokers 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).

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

**4.8 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 available data)

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Leukopenia</td>
<td>Neutropenia</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Allergic reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain¹</td>
<td>Elevated cholesterol levels²³</td>
<td>Elevated glucose levels⁴</td>
<td>Elevated triglyceride levels²⁵</td>
</tr>
<tr>
<td>Glucosuria</td>
<td>Increased appetite</td>
<td>Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4)</td>
<td></td>
</tr>
<tr>
<td>Hypothermia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Nervous system disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Somnolence</th>
<th>Dizziness Akathisia</th>
<th>Parkinsonism</th>
<th>Dyskinesia</th>
<th>Seizures where in most cases a history of seizures or risk factors for seizures were reported Neuroleptic malignant syndrome (see section 4.4) Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms</th>
</tr>
</thead>
</table>

### Cardiac disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Bradycardia</th>
<th>QTc prolongation (see section 4.4)</th>
<th>Ventricular tachycardia/fibrillation, sudden death (see section 4.4)</th>
</tr>
</thead>
</table>

### Vascular disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Orthostatic hypotension</th>
<th>Thromboembolism (including pulmonary embolism and deep vein thrombosis)</th>
</tr>
</thead>
</table>

### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mild, transient anticholinergic effects including constipation and dry mouth</th>
<th>Pancreatitis</th>
</tr>
</thead>
</table>

### Hepato-biliary disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)</th>
<th>Hepatitis (including hepatocellular, cholestatic or mixed liver injury)</th>
</tr>
</thead>
</table>

### Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Rash</th>
<th>Photosensitivity reaction Alopecia</th>
</tr>
</thead>
</table>

### Musculoskeletal and connective tissue disorders

| Symptom                  | | Rhabdomyolysis |
|--------------------------|--------------------------|

### Renal and urinary disorders

| Symptom                  | | Urinary hesitation |
|--------------------------|--------------------------|

### Reproductive system and breast disorders

| Symptom                  | | Priapism |
|--------------------------|--------------------------|

### General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Asthenia Fatigue Oedema</th>
</tr>
</thead>
</table>

### Investigations

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Elevated plasma prolactin levels</th>
<th>High creatine phosphokinase Increased total bilirubin</th>
<th>Increased alkaline phosphatase</th>
</tr>
</thead>
</table>

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/l) to high (≥ 6.2 mmol/l) were very common.

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

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

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

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

8 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/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 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 divalprox, an increase of ≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥ 7% from baseline body weight in 39.9% of patients.

**Children and adolescents**

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

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

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows:

Very common (≥1/10)  
Common (≥1/100 to <1/10)

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Weight gain ≥ 7% of baseline body weight 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.</td>
</tr>
<tr>
<td>Common: Elevated cholesterol levels</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Sedation (including: hypersomnia, lethargy, somnolence).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Dry mouth</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepato-biliary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Elevations of hepatic transaminases (ALT/AST; see section 4.4).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Decreased total bilirubin, increased GGT, elevated plasma prolactin levels</td>
</tr>
</tbody>
</table>

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 450 mg but survival has also been reported following acute overdose of approximate 2 g of oral olanzapine.

Management of overdose

There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.
Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Epinephrine, dopamine, or other sympathomimetic agents with betaagonist activity should not be used 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

5.3 Pharmacodynamic properties
Pharmacotherapeutic group: diazepines, oxazepines and thiazepines, ATC code N05A H03.
Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki; < 100 nM) for serotonin 5 HT2A/2C, 5 HT3, 5 HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors m1-m5; α1 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 (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an “anxiolytic” test.

In a single oral dose (10 mg) Positron Emission tomography (PET) study in healthy volunteers, olanzapine produced a higher 5 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-hydroxymethyl metabolites, both exhibited significantly less in vivo pharmacological activity than olanzapine in animal studies. The predominant pharmacological activity is from the parent olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

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

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

In 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).

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

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

The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α1-acid-glycoprotein.

Paediatric population

Adolescents (ages 13 to 17 years): The pharmacokinetics of olanzapine are similar between adolescents and adults. In clinical studies, the average olanzapine exposure was approximately 27% higher in adolescents. Demographic differences between the adolescents and adults include a lower average body weight and fewer adolescents were smokers. Such factors possibly contribute to the higher average exposure observed in adolescents.
5.5 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
Lactose monohydrate
Crospovidone
Microcrystalline cellulose
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Blister packs of 28, 30, 56 or 100 tablets in Aluminium/ aluminium blister. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
MARKETING AUTHORISATION HOLDER
Apotex Europe BV
Darwinweg 20,
2333 CR Leiden
The Nederlands

MARKETING AUTHORISATION NUMBER(S)
PL 27583/0050

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/09/2009

DATE OF REVISION OF THE TEXT
23/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Olanzapine Apotex 10 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg olanzapine.
Excipient: 65.36 mg anhydrous lactose per tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
Olanzapine 10 mg tablets are yellow, cylindrical, biconvex tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults
Olanzapine is indicated for the treatment of schizophrenia.
Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients
who have shown an initial treatment response.
Olanzapine is indicated for the treatment of moderate to severe manic episode.
In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the
prevention of recurrence in patients with bipolar disorder (see section 5.1).

4.2 Posology and method of administration
Adults
Schizophrenia: The recommended starting dose for olanzapine is 10 mg/day.
Manic episode: The starting dose is 15 mg as a single daily dose in monotherapy or 10 mg daily in
combination therapy (see section 5.1).
Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg/day. For patients
who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing
recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, Olanzapine treatment
should be continued (with dose optimisation as needed), with supplementary therapy to treat mood
symptoms, as clinically indicated.

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

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

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

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

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

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

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers.
When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients. (See sections 4.5 and 5.2.)

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

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

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

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

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

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

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoadiotosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agents, including olanzapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients...
with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

**Lipid alterations**
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic agents, including olanzapine, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines.

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

**Hepatic function**
Transient, asymptomatic elevations of hepatic transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicinal products. In the event of elevated ALT and/or AST during treatment, 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 medicinal products known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

**Discontinuation of treatment**
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely (<0.01%) when olanzapine is stopped abruptly.

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

**Thromboembolism**
Temporal association of olanzapine treatment and venous thromboembolism has very rarely (<0.01%) been reported. A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

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

**Seizures**
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur rarely in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

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

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

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

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

### 4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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

**Induction of CYP1A2**
The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (See section 4.2).

**Inhibition of CYP1A2**
Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine Cmax following fluvoxamine was 54 % in female non-smokers 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).

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

4.9 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 available data)

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Eosinophilia</td>
<td>Leukopenia</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Neutropenia</td>
<td>Allergic reaction</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight gain</td>
<td>Elevated cholesterol levels</td>
<td>Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4)</td>
</tr>
<tr>
<td></td>
<td>Elevated glucose levels</td>
<td>Elevated triglyceride levels</td>
<td>Hypothermia</td>
</tr>
<tr>
<td></td>
<td>Glucosuria</td>
<td>Increased appetite</td>
<td></td>
</tr>
</tbody>
</table>

GL 45
### Nervous system disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>Dizziness Akathisia&lt;sup&gt;6&lt;/sup&gt; Parkinsonism&lt;sup&gt;6&lt;/sup&gt; Dyskinesia&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Seizures where in most cases a history of seizures or risk factors for seizures were reported Neuroleptic malignant syndrome (see section 4.4) Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Cardiac disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bradycardia QTc prolongation (see section 4.4)</td>
</tr>
<tr>
<td></td>
<td>Ventricular tachycardia/fibrillation, sudden death (see section 4.4)</td>
</tr>
</tbody>
</table>

### Vascular disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td>Thromboembolism (including pulmonary embolism and deep vein thrombosis)</td>
</tr>
</tbody>
</table>

### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild, transient anticholinergic effects including constipation and dry mouth</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
</tr>
</tbody>
</table>

### Hepato-biliary disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)</td>
</tr>
<tr>
<td></td>
<td>Hepatitis (including hepatocellular, cholestatic or mixed liver injury)</td>
</tr>
</tbody>
</table>

### Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rash Photosensitivity reaction Alopecia</td>
</tr>
</tbody>
</table>

### Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rhabdomyolysis</td>
</tr>
</tbody>
</table>

### Renal and urinary disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urinary hesitation</td>
</tr>
</tbody>
</table>

### Reproductive system and breast disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Priapism</td>
</tr>
</tbody>
</table>

### General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asthenia Fatigue Oedema</td>
</tr>
</tbody>
</table>

### Investigations

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated plasma prolactin levels&lt;sup&gt;8&lt;/sup&gt;</td>
<td>High creatine phosphokinase Increased total bilirubin</td>
</tr>
<tr>
<td></td>
<td>Increased alkaline phosphatase</td>
</tr>
</tbody>
</table>

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/l) to high (≥ 6.2 mmol/l) were very common.

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

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

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

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

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

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**Long-term exposure (at least 48 weeks)**

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

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

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

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows:

Very common (≥1/10)
Common (≥1/100 to <1/10)

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Weight gain9 ≥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.</td>
</tr>
<tr>
<td>Common: Elevated triglyceride levels10, increased appetite.</td>
</tr>
<tr>
<td>Elevated cholesterol levels11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Sedation (including: hypersomnia, lethargy, somnolence).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Dry mouth</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepato-biliary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Elevations of hepatic transaminases (ALT/AST; see section 4.4).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Decreased total bilirubin, increased GGT, elevated plasma prolactin levels12.</td>
</tr>
</tbody>
</table>

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 450 mg but survival has also been reported following acute overdose of approximate 2 g of oral olanzapine.

Management of overdose

There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.
Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Epinephrine, dopamine, or other sympathomimetic agents with beta agonist activity should not be used 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

5.4 Pharmacodynamic properties

Pharmacotherapeutic group: diazepines, oxazepines and thiazepines, ATC code N05A H03. Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki; < 100 nM) for serotonin 5HT2A/2C, 5 HT3, 5 HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors m1-m5; α1 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 (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an “anxiolytic” test.

In a single oral dose (10 mg) Positron Emission tomography (PET) study in healthy volunteers, olanzapine produced a higher 5 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 semismodium (divalproex) in reduction of manic symptoms over 3 weeks. Olanzapine also demonstrated comparable efficacies 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-hydroxymethyl metabolites, both exhibited significantly less in vivo pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

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

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

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

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

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

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

In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations. The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α1-acid-glycoprotein.

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

50
5.6 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
Lactose monohydrate
Crospovidone
Microcrystalline cellulose
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Blister packs of 28, 30, 56 or 100 tablets in Aluminium/ aluminium blister.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
MARKETING AUTHORISATION HOLDER
Apotex Europe BV
Darwinweg 20,
2333 CR Leiden
The Nederlands

MARKETING AUTHORISATION NUMBER(S)
PL 27583/0051

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DATE OF REVISION OF THE TEXT

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/09/2009

DATE OF REVISION OF THE TEXT
23/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Olanzapine Apotex 15 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 15 mg olanzapine
Excipient: 98.04 mg anhydrous lactose per tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
Olanzapine 15 mg tablets are yellow, cylindrical, biconvex tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults
Olanzapine is indicated for the treatment of schizophrenia.
Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.
Olanzapine is indicated for the treatment of moderate to severe manic episode.
In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder (see section 5.1).

4.2 Posology and method of administration
Adults
Schizophrenia: The recommended starting dose for olanzapine is 10 mg/day.
Manic episode: The starting dose is 15 mg as a single daily dose in monotherapy or 10 mg daily in combination therapy (See section 5.1).
Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, Olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

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

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

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

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

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

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

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers.
When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients. (See sections 4.5 and 5.2.)

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

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

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

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

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

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

_Hyperglycaemia and diabetes_
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoadicosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agents, including olanzapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients
with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

**Lipid alterations**
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic agents, including olanzapine, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines.

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

**Hepatic function**
Transient, asymptomatic elevations of hepatic transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicinal products. In the event of elevated ALT and/or AST during treatment, 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 medicinal products known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

**Discontinuation of treatment**
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely (<0.01%) when olanzapine is stopped abruptly.

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

**Thromboembolism**
Temporal association of olanzapine treatment and venous thromboembolism has very rarely (<0.01%) been reported. A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

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

**Seizures**
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur rarely in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction
Interaction studies have only been performed in adults.

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

Induction of CYP1A2
The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (See section 4.2).

Inhibition of CYP1A2
Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine Cmax following fluvoxamine was 54 % in female non-smokers 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).

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

4.10 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 available data)

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
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<tr>
<td>Eosinophilia</td>
<td>Leukopenia</td>
<td>Thrombocytopenia</td>
<td></td>
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<tr>
<td>Neutropenia</td>
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<td>Immune system disorders</td>
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<tr>
<td>Allergic reaction</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
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<tr>
<td>Weight gain¹</td>
<td>Elevated cholesterol levels²–³</td>
<td>Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4)</td>
<td>Hypothermia</td>
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<tr>
<td>Elevated glucose levels⁴</td>
<td>Elevated triglyceride levels⁵</td>
<td>Glucosuria</td>
<td></td>
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<tr>
<td>Increased appetite</td>
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<tr>
<td>Nervous system disorders</td>
<td>Dizziness Akathisia(^6)</td>
<td>Parkinsonism(^6) Dyskinesia(^6)</td>
<td>Seizures where in most cases a history of seizures or risk factors for seizures were reported Neuroleptic malignant syndrome (see section 4.4) Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms(^7)</td>
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<tr>
<td>Cardiac disorders</td>
<td>Bradycardia QTc prolongation (see section 4.4)</td>
<td>Ventricular tachycardia/fibrillation, sudden death (see section 4.4)</td>
<td></td>
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<tr>
<td>Vascular disorders</td>
<td>Orthostatic hypotension</td>
<td>Thromboembolism (including pulmonary embolism and deep vein thrombosis)</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Mild, transient anticholinergic effects including constipation and dry mouth</td>
<td>Pancreatitis</td>
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<tr>
<td>Hepato-biliary disorders</td>
<td>Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)</td>
<td>Hepatitis (including hepatocellular, cholestatic or mixed liver injury)</td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Photosensitivity reaction Alopecia</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Rhabdomyolysis</td>
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<tr>
<td>Renal and urinary disorders</td>
<td>Urinary hesitation</td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td>Priapism</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia Fatigue Oedema</td>
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<tr>
<td>Investigations</td>
<td>Elevated plasma prolactin levels(^8)</td>
<td>High creatine phosphokinase Increased total bilirubin</td>
<td>Increased alkaline phosphatase</td>
</tr>
</tbody>
</table>

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/l) to high (≥ 6.2 mmol/l) were very common.

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

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

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

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

8 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/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 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
Olanzapine is not indicated for the treatment of children and adolescent patients below 18 years. Although no clinical studies designed to compare adolescents to adults have been conducted, data from the adolescent trials were compared to those of the adult trials.

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

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows:

Very common (≥1/10)
Common (≥1/100 to <1/10)

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Weight gain(^9) elevated triglyceride levels(^{10}), increased appetite.</td>
</tr>
<tr>
<td>Common: Elevated cholesterol levels(^{11})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Sedation (including: hypersomnia, lethargy, somnolence).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Dry mouth</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepato-biliary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Elevations of hepatic transaminases (ALT/AST; see section 4.4).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Decreased total bilirubin, increased GGT, elevated plasma prolactin levels(^{12}).</td>
</tr>
</tbody>
</table>

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, hypertensive or hypotensive, 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 approximate 2 g of oral olanzapine.

Management of overdose
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.
Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Epinephrine, dopamine, or other sympathomimetic agents with betaagonist activity should not be used 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

5.5 Pharmacodynamic properties

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

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

In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki; < 100 nM) for serotonin 5 HT2A/2C, 5 HT3, 5 HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors m1-m5; α1 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 (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an “anxiolytic” test.

In a single oral dose (10 mg) Positron Emission tomography (PET) study in healthy volunteers, olanzapine produced a higher 5 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-hydroxymethyl metabolites, both exhibited significantly less in vivo pharmacological activity than olanzapine in animal studies. The predominant pharmacological activity is from the parent olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

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

In female versus male subjects the mean elimination half-life was somewhat prolonged (36.7 versus 32.3 hrs) and the clearance was reduced (18.9 versus 27.3 l/hr). However, olanzapine (5-20 mg) demonstrated a comparable safety profile in female (n=467) as in male patients (n=869). In renally impaired patients (creatinine clearance < 10 ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hr) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57 % of radiolabelled olanzapine appeared in urine, principally as metabolites.

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

In non-smoking versus smoking subjects (males and females) the mean elimination half-life was prolonged (38.6 versus 30.4 hr) and the clearance was reduced (18.6 versus 27.7 l/hr). The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals.

In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations. The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α1-acid-glycoprotein.

Paediatric population
Adolescents (ages 13 to 17 years): The pharmacokinetics of olanzapine are similar between adolescents and adults. In clinical studies, the average olanzapine exposure was approximately 27% higher in adolescents. Demographic differences between the adolescents and adults include a lower average body weight and fewer adolescents were smokers. Such factors possibly contribute to the higher average exposure observed in adolescents.
5.7 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
Lactose monohydrate
Crospovidone
Microcrystalline cellulose
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
30 months.

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Blister packs of 28, 30, 56 or 100 tablets in Aluminium/ aluminium blister. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
MARKETING AUTHORISATION HOLDER
Apotex Europe BV
Darwinweg 20,
2333 CR Leiden
The Nederlands

MARKETING AUTHORISATION NUMBER(S)
PL 27583/0052

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/09/2009

DATE OF REVISION OF THE TEXT
23/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Olanzapine Apotex 20 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 20 mg olanzapine.
Excipient: 130.72 mg anhydrous lactose per tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
Olanzapine 20 mg tablets are yellow, oblongs, biconvex tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults
Olanzapine is indicated for the treatment of schizophrenia.
Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients
who have shown an initial treatment response.
Olanzapine is indicated for the treatment of moderate to severe manic episode.
In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the
prevention of recurrence in patients with bipolar disorder (see section 5.1).

4.2 Posology and method of administration
Adults
Schizophrenia: The recommended starting dose for olanzapine is 10 mg/day.
Manic episode: The starting dose is 15 mg as a single daily dose in monotherapy or 10 mg daily in
combination therapy (See section 5.1).
Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg/day. For patients
who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing
recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, Olanzapine treatment
should be continued (with dose optimisation as needed), with supplementary therapy to treat mood
symptoms, as clinically indicated.

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

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

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

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

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

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

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers.
When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients. (See sections 4.5 and 5.2.)

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

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

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

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

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

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

*Hyperglycaemia and diabetes*
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoadisis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agents, including olanzapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients
with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

**Lipid alterations**
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic agents, including olanzapine, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines.

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

**Hepatic function**
Transient, asymptomatic elevations of hepatic transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicinal products. In the event of elevated ALT and/or AST during treatment, 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 medicinal products known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

**Discontinuation of treatment**
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely (<0.01%) when olanzapine is stopped abruptly.

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

**Thromboembolism**
Temporal association of olanzapine treatment and venous thromboembolism has very rarely (<0.01%) been reported. A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

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

**Seizures**
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur rarely in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

**Tardive Dyskinesia**

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

**Postural hypotension**

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

**Use in children and adolescents under 18 years of age**

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

**Lactose**

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

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4.5 **Interaction with other medicinal products and other forms of interaction**

Interaction studies have only been performed in adults.

**Potential interactions affecting olanzapine**

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

**Induction of CYP1A2**

The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (See section 4.2).

**Inhibition of CYP1A2**

Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine Cmax following fluvoxamine was 54 % in female non-smokers 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).

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

### 4.11 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 available data)

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Leukopenia</td>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain¹</td>
<td>Elevated cholesterol levels²³</td>
<td>Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4)</td>
<td></td>
</tr>
<tr>
<td>Elevated glucose levels⁴</td>
<td>Elevated triglyceride levels²⁵</td>
<td>Hypothermia</td>
<td></td>
</tr>
<tr>
<td>Glucosuria</td>
<td>Increased appetite</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Nervous system disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Symptoms</th>
<th>Seizures where in most cases a history of seizures or risk factors for seizures were reported Neuroleptic malignant syndrome (see section 4.4) Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>Dizziness Akathisia6 Parkinsonism6 Dyskinesia6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Cardiac disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>BradycardiaQTc prolongation</th>
<th>Ventricular tachycardia/fibrillation, sudden death (see section 4.4)</th>
</tr>
</thead>
</table>

### Vascular disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Orthostatic hypotension</th>
<th>Thromboembolism(including pulmonary embolism and deep vein thrombosis)</th>
</tr>
</thead>
</table>

### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mild, transient anticholinergic effects including constipation and dry mouth</th>
<th>Pancreatitis</th>
</tr>
</thead>
</table>

### Hepato-biliary disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)</th>
<th>Hepatitis (including hepatocellular, cholestatic or mixed liver injury)</th>
</tr>
</thead>
</table>

### Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Rash</th>
<th>Photosensitivity reaction Alopecia</th>
</tr>
</thead>
</table>

### Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Rhabdomyolysis</th>
</tr>
</thead>
</table>

### Renal and urinary disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Urinary hesitation</th>
</tr>
</thead>
</table>

### Reproductive system and breast disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Priapism</th>
</tr>
</thead>
</table>

### General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Asthenia Fatigue Oedema</th>
</tr>
</thead>
</table>

### Investigations

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Elevated plasma prolactin levels8</th>
<th>High creatine phosphokinase Increased total bilirubin</th>
<th>Increased alkaline phosphatase</th>
</tr>
</thead>
</table>

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/l) to high (≥ 6.2 mmol/l) were very common.

4 Observed for fasting normal levels at baseline (< 5.56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 7 mmol/l) to high (≥ 5.56 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**

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

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

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows:

Very common (≥1/10)
Common (≥1/100 to <1/10)

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: 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.</td>
</tr>
<tr>
<td>Common: Elevated cholesterol levels</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Sedation (including: hypersomnia, lethargy, somnolence).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Dry mouth</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepato-biliary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Elevations of hepatic transaminases (ALT/AST; see section 4.4).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Decreased total bilirubin, increased GGT, elevated plasma prolactin levels.</td>
</tr>
</tbody>
</table>

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 450 mg but survival has also been reported following acute overdose of approximate 2 g of oral olanzapine.

Management of overdose

There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.
Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Epinephrine, dopamine, or other sympathomimetic agents with betaagonist activity should not be used 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**

**5.6 Pharmacodynamic properties**

Pharmacotherapeutic group: diazepines, oxazepines and thiazepines, ATC code N05A H03. Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki; < 100 nM) for serotonin 5 HT2A/2C, 5 HT3, 5 HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors m1-m5; α1 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 (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an “anxiolytic” test.

In a single oral dose (10 mg) Positron Emission tomography (PET) study in healthy volunteers, olanzapine produced a higher 5 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-hydroxymethyl metabolites, both exhibited significantly less in vivo pharmacological activity than olanzapine in animal studies. The predominant pharmacological activity is from the parent olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

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

In female versus male subjects the mean elimination half-life was somewhat prolonged (36.7 versus 32.3 hrs) and the clearance was reduced (18.9 versus 27.3 l/hr). In renally impaired patients (creatinine clearance < 10 ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hr) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57 % of radiolabelled olanzapine appeared in urine, principally as metabolites.

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

In non-smoking versus smoking subjects (males and females) the mean elimination half-life was prolonged (38.6 versus 30.4 hr) and the clearance was reduced (18.6 versus 27.7 l/hr). The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals.

In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations. The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α1-acid-glycoprotein.

Paediatric population
Adolescents (ages 13 to 17 years): The pharmacokinetics of olanzapine are similar between adolescents and adults. In clinical studies, the average olanzapine exposure was approximately 27% higher in adolescents. Demographic differences between the adolescents and adults include a lower average body weight and fewer adolescents were smokers. Such factors possibly contribute to the higher average exposure observed in adolescents.
5.8 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
Lactose monohydrate
Crospovidone
Microcrystalline cellulose
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
30 months.

6.4 Special precautions for storage
Store in the original package.

6.5 Nature and contents of container
Blister packs of 28, 30, 56 or 100 tablets in Aluminium/ aluminium blister. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
MARKETING AUTHORISATION HOLDER
Apotex Europe BV
Darwinweg 20,
2333 CR Leiden
The Nederlands

MARKETING AUTHORISATION NUMBER(S)
PL 27583/0053

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DATE OF REVISION OF THE TEXT
23/09/2009

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/09/2009
Module 3
Product Information Leaflet

The Patient Information Leaflet (PIL) below is the leaflet agreed at the end of the decentralised procedure. The marketing authorisation holder has stated that it is not intending to market either product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling for review to the regulatory authority before marketing either product.

PACKAGE LEAFLET: INFORMATION FOR THE USER
olanzapine Apotex 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg 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 olanzapine is and what it is used for.
2. Before you take olanzapine.
3. How to take olanzapine.
4. Possible side effects.
5. How to store olanzapine.
6. Further information

1. WHAT OLANZAPINE IS AND WHAT IT IS USED FOR

Olanzapine belongs to a group of medicines called antipsychotics.

Olanzapine is used to treat a disease with symptoms such as hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness, and becoming withdrawn. People with this disease may also feel depressed, anxious or tense.

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

Do not take olanzapine:

- If you are allergic (hypersensitive) to olanzapine or to any of the other ingredients of olanzapine tablets. An allergic reaction can be recognised as rash, itching, a swollen o face, swollen lips, or shortness of breath. If this 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 olanzapine:

- Medicines of this type may cause unusual movements mainly of the face or tongue. If this happens after you have been given olanzapine tell your doctor.
- Very rarely, medicines of this type cause a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness. If this happens, contact your doctor at once.
- The use of olanzapine in elderly patients 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.

Olanzapine is not for patients who are under 18 years.

Taking other medicines:
- Only take other medicines while you are on olanzapine if your doctor tells you that your can. You may feel drowsy if olanzapine is taken in combination with antidepressants or medicines taken for anxiety or to help you sleep (tranquillisers).
- You should tell your doctor if you are taking fluvoxamine (an antidepressant) or ciprofloxacin (an antibiotic), as it may be necessary to change your olanzapine dose.
- Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Especially tell your doctor if you are taking medicines for Parkinson’s disease.

Taking olanzapine with food and drink:
Do not drink any alcohol while you have been given olanzapine as olanzapine 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 olanzapine can pass into breast milk.

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

Important information about some of the ingredients of olanzapine:
This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
3. HOW TO TAKE olanzapine

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

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

- You should take your olanzapine 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. Olanzapinetabets are for oral use. You should swallow the olanzapine tablets whole with water.

If you take more olanzapine than you should:

Patients who have taken more olanzapine than they should, have experienced the following symptoms: rapid beating of the heart, agitation/aggressiveness, problems with speech, unusual movements (especially of the face or tongue) and reduced level of consciousness. Other symptoms may be: acute confusion, seizures (epilepsy), coma, a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness, slowing of the breathing rate, aspiration, high blood pressure or low blood pressure, abnormal rhythms of the heart. Contact your doctor or hospital straight away. Show the doctor your pack of tablets.

If you forget to take olanzapine:

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

If you stop taking olanzapine:

Do not stop taking your tablets just because you feel better. It is important that you carry on taking olanzapine for as long as your doctor tells you. If you suddenly stop taking olanzapine, symptoms such as sweating, unable to sleep, tremor, anxiety or nausea and vomiting might occur. Your doctor may suggest you to reduce the dose gradually before stopping treatment.

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

4. POSSIBLE SIDE EFFECTS

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

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

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

5. HOW TO STORE OLANZAPINE

Keep out of the reach and sight of children.

Do not use olanzapine after the expiry date which is stated on the carton.

Store in the original package.

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

6. FURTHER INFORMATION

What olanzapine contains

The active substance is olanzapine. Each olanzapine tablet contains either 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg or 20 mg of the active substance.

The other ingredients are: Microcrystalline cellulose, anhydrous lactose, crospovidone, magnesium stearate.

What olanzapine looks like and contents of the pack

Olanzapine is supplied in the form of tablets.

Description: Olanzapine 2,5 mg., 5 mg, 7,5 mg, 10 mg, 15 mg tablets are yellow, cylindrical and biconvex tablets.

Olanzapine 20 mg tablets are yellow, oblong and biconvex.

Olanzapine tablets are available in 28, 30, 56 and 100 tablets packs.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Apotex Europe BV
Darwinweg 20, 2333 CR Leiden, The Netherlands

Manufacturer:
Laboratorios Cínta, S.A.
C/ Olaz-Chipi, 10 – Poligono Industrial Areta 31620 Huarte-Pamplona (Navarra) – Spain

This leaflet was last approved in month/year
Module 4
Labelling

The labelling below is the label agreed at the end of the decentralised procedure. The marketing authorisation holder has stated that it is not intending to market either product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling for review to the regulatory authority before marketing either product.

### PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON OF 28/30/56/100 TABLETS IN BLISTERS

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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</thead>
<tbody>
<tr>
<td>Olanzapine Apotex 2.5/5/7.5/10/15/20 mg tablets</td>
</tr>
<tr>
<td>Olanzapine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
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<tbody>
<tr>
<td>Each tablet contains 2.5/5/7.5/10/15/20 mg of olanzapine.</td>
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</table>

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<tr>
<th>3. LIST OF EXCIPIENTS</th>
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<tr>
<td>This product also contains lactose.</td>
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<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
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<tr>
<td>28/30/56/100 tablets</td>
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</table>

<table>
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<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>For oral use.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
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</tbody>
</table>

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<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
</tbody>
</table>

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<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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<tr>
<th>8. EXPIRY DATE</th>
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<tbody>
<tr>
<td>EXP</td>
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</table>

<table>
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<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
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</thead>
<tbody>
<tr>
<td>Store in the original package.</td>
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</table>

<table>
<thead>
<tr>
<th>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
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</table>
Apotex Europe BV
Darwinweg 20,
2333 CR Leiden
The Nederlands

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

13. BATCH NUMBER
BN

14. GENERAL CLASSIFICATION FOR SUPPLY
Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
olanzapine 2.5/5/7.5/10/15/20 mg tablets
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Olanzapine Apotex 2.5/5/7.5/10/15/20 mg tablets.
Olanzapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Apotex Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Czech Republic, Germany, the Netherlands, Poland and the UK considered that the applications for Olanzapine Apotex 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg Tablets could be approved. These products are prescription only medicines (POM) and are indicated in adults for:

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

These applications for Olanzapine Apotex 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg Tablets are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Zyprexa 10mg Tablets, first authorised in the EU to Eli Lilly Netherland B.V. in September 1996.

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

No new preclinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies with the exception of the bioequivalence study have been performed and none are required for these applications as the pharmacology of olanzapine is well-established.

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

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Olanzapine Apotex 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg Tablets |
| Name(s) of the active substance(s) (INN) | Olanzapine |
| Pharmacotherapeutic classification (ATC code) | Diazepines, oxazepines and thiazepines (N05A H03) |
| Pharmaceutical form and strength(s) | 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg Tablets |
| Reference numbers for the Decentralised Procedure | UK/H/1297/001-6/DC |
| Reference Member State | United Kingdom |
| Member States concerned | The Czech Republic, Germany, the Netherlands, Poland |
| Marketing Authorisation Number(s) | PL 27583/0048-53 |
| Name and address of the authorisation holder | Apotex Europe BV Darwinweg 20, 2333 CR Leiden, The Netherlands |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Active substance

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

Structural formula:

![Structural formula of Olanzapine]

Molecular formula:  C_{17}H_{20}N_{4}S

Appearance:  Pale yellow to yellow crystalline powder
Solubility:  Freely soluble in chloroform, sparingly soluble in acetic acid

Molecular weight:  312.44

Olanzapine complies with in-house specifications.

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

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance olanzapine, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.
Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

**P. Medicinal Product**

**Other Ingredients**
Other ingredients consist of pharmaceutical excipients lactose monohydrate, crospovidone, microcrystalline cellulose, magnesium stearate.

All excipients comply with their relevant European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin. The magnesium stearate contained in this product is sourced from vegetable origin and therefore no European Pharmacopoeia Certificates of suitability for TSE is required.

The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**
The objective of the development programme was to produce products that could be considered generic medicinal products of Zyprexa 10mg Tablets (Eli Lilly Netherland B.V.).

The reference product used in the bioequivalence study is qualitatively and quantitatively identical to the UK reference product.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished products versus the reference products of Zyprexa 10mg Tablets (Eli Lilly Netherland B.V.).

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

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on three pilot scale batches per strength have been provided. The applicant has committed to perform process validation on the first three production-scale batches of each strength.

**Finished Product Specification**
The finished product specification proposed for the products is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.
Container-Closure System
These products are packaged in blisters composed of aluminium and come in pack sizes of 28, 30, 56 and 100 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 3 years for the 2.5mg, 5mg, 7.5mg and 10mg strength tablets. A shelf-life of 30 months for the 15mg and 20mg tablets has been supported by stability data. All strengths have the storage instructions, ‘Store in the original package’.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPCs, PILs and labelling are pharmaceutically acceptable.

User testing results have been submitted for typical PILs for these products. The results indicate that the PILs are well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

MAA forms
The MAA forms are pharmaceutically satisfactory.

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

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
III.2 PRE-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of olanzapine are well-known. As olanzapine is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.
III.3 CLINICAL ASPECTS
1. Introduction
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company's clinical overview and summary and to the clinical file.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports
To support these applications, the marketing authorisation holder has submitted one single dose bioequivalence study.

A two-way crossover, single dose, fasting, bioequivalence study of Olanzapine 10mg Tablets versus Zyprexa (olanzapine) 10mg Tablets in normal, healthy, male and female subjects.

All subjects were in a fasted state before dosing. Blood sampling was performed at baseline and up to 144 hours post dose in each treatment period. The washout period between phases was 14 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$ (ng/ml/h)</th>
<th>$\text{AUC}_{0-72}$ (ng/ml/h)</th>
<th>$\text{C}_{\text{max}}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>669.47±386.85</td>
<td>506.12±238.74</td>
<td>17.845±6.144</td>
</tr>
<tr>
<td>Reference</td>
<td>668.54±339.01</td>
<td>503.88±212.39</td>
<td>17.401±5.650</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>86.7510-103.8245</td>
<td>89.9636-105.7379</td>
<td>96.9155-106.7354</td>
</tr>
</tbody>
</table>

Due to the long elimination life of olanzapine, $\text{AUC}_{0-\infty}$ is not a useful measure of drug absorption. $\text{AUC}_{0-72}$ was used as a pharmacokinetic parameter rather than $\text{AUC}_{0-\infty}$ as 72 hours covers the complete absorption period and is therefore adequate. Calculations beyond 72 hours are highly unreliable and are of no relevance to an assessment of bioequivalence. This is in accordance with page 6 of CPMP/EWP/QWP/1401/98 guideline, for drugs with long elimination half-life.

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for $\text{AUC}_{0-t}$ and $\text{C}_{\text{max}}$ for olanzapine lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

As the 10mg strength product meets all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength can be extrapolated to 2.5mg, 5mg, 7.5mg strengths and also the higher strengths of 15mg and 20mg.

3. Post marketing experience
Olanzapine has a well-recognised efficacy and an acceptable level of safety in the indications approved for Zyprexa Tablets and corresponding products have been widely used in many
countries. Therefore, the submission of PSUR at the renewal of the marketing authorisations is supported.

4. **Benefit-Risk assessment**
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with olanzapine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

5. **Conclusions**
The grant of marketing authorisations for Olanzapine Apotex 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg Tablets is recommended from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Olanzapine Apotex 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Olanzapine Apotex 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg Tablets and the originator products Zyprexa Tablets (Eli Lilly Netherland B.V.).

No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory and consistent with that for the innovator products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with olanzapine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<tbody>
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