OLANZAPINE 2.5MG, 5MG, 7.5MG, 10MG, 15MG AND 20MG FILM-COATED TABLETS
PL 30464/0097-0102

UKPAR

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PL 30464/0097-0102

LAY SUMMARY

On 11th October 2011, the MHRA granted Athlone Pharmaceuticals Limited Marketing Authorisations (licences) for Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg film-coated tablets (PL 30464/0097-0102).

The active ingredient, olanzapine, belongs to a group of medicines called antipsychotics.

Olanzapine film-coated tablets are 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such as hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness, and becoming withdrawn.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 film-coated tablets are also 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.

Olanzapine film-coated tablets are not recommended for use in children and adolescents below 18 years of age.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg film-coated tablets outweigh the risks; hence these Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Marketing Authorisations for the medicinal products Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg film-coated tablets (PL 30464/0097-0102) to Athlone Pharmaceuticals Limited on 11th October 2011. These products are prescription-only medicines (POM) and are 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.

- 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.

Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg film-coated tablets are not recommended for use in children and adolescents below 18 years of age.

These applications for Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg film-coated tablets were submitted according to Article 10c of Directive 2001/83/EC as amended, cross-referring to Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg film-coated tablets (PL 19156/0070-5), which were approved to Jubilant Pharmaceuticals NV on 23rd February 2010.

It is considered that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring.

A Risk Management Plan (RMP) was not submitted and one is not required for an application of this type.

No new data were submitted nor were they necessary for these “simple” applications, as the data are identical to that of the previously granted cross-reference products.
1. INTRODUCTION
These are “simple” applications for Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg film-coated tablets (PL 30464/0097-0102) submitted under Article 10c of Directive 2001/83/EC, as amended. The proposed MA holder is Athlone Pharmaceuticals Limited, Ballymurray, County Roscommon, Ireland.

These applications cross-refer to Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg film-coated tablets (PL 19156/0070-5), which were approved to Jubilant Pharmaceuticals NV on 23rd February 2010.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 NAME(S)
The proposed names of the products are Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg film-coated tablets. The product has been named in-line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The products contain olanzapine in 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg strengths. These are film-coated tablets which are to be taken orally. The finished products are packaged in cold-formed aluminium blisters and then further packaged into cartons.

Pack sizes are:
2.5mg, 5mg, 7.5mg, 10mg and 15mg: 28, 50, 56, 60 or 70 tablets
20mg: 28 tablets

The proposed shelf-life is 2 years with no special storage instructions. This is consistent with the details registered for the cross-reference products.

2.3 Legal status
Prescription-only medicine (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
Athlone Pharmaceuticals Limited, Ballymurray, County Roscommon, Ireland.

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers
The manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.
2.6 Qualitative and quantitative composition
The composition is consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size for each product is stated.

2.8 Finished product/shelf-life specification
The finished product specifications are in-line with the details registered for the cross-reference products.

2.9 Drug substance specification
The drug substance specification is consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
With the exception of lactose, none of the excipients used contain material of animal or human origin. The supplier of magnesium stearate has confirmed that it is of vegetable origin.

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

This information is consistent with the cross-reference products.

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the applications. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearance of the products is identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs)
At the time of assessment, the SmPCs were consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET (PIL)/LABELLING
PIL
The PIL has been prepared in-line with the details registered for the cross-reference product. This PIL is similar to the PIL for Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg film-coated tablets (PL 19156/0070-5); therefore a bridging statement has been provided. This is satisfactory.

The results of consultations with target patient groups ("user testing") are in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.
Labelling
At the time of assessment, the artwork was comparable to the artwork registered for the cross-reference products and complies with statutory requirements. In-line with current legislation, the applicant has included the name of the product in Braille on the packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with the applications are acceptable. The grant of these Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with these applications and none are required for applications of this type.

A satisfactory non-clinical overview has been provided and is accepted in-line with the reference product.

A satisfactory justification for the absence of an Environmental Risk Assessment has been provided.
CLINICAL ASSESSMENT

No new clinical data have been supplied with these applications and none are required for applications of this type.

A satisfactory clinical overview has been provided and is accepted in-line with the reference product.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with that previously approved for the cross-reference products and, as such, has been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are identical to the previously granted applications Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg film-coated tablets (PL 19156/0070-5), which were approved to Jubilant Pharmaceuticals NV on 23rd February 2010.

No new or unexpected safety concerns arise from these applications.

At the time of assessment, the SmPCs, PIL and labelling were satisfactory and consistent with that for the cross-reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. 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.
OLANZAPINE 2.5MG, 5MG, 7.5MG, 10MG, 15MG AND 20MG
FILM-COATED TABLETS
PL 30464/0097-102

STEPS TAKEN FOR ASSESSMENT

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<table>
<thead>
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<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation Applications on 14\textsuperscript{th} December 2010.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 13\textsuperscript{th} January 2011.</td>
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<tr>
<td>3</td>
<td>Following assessment of the application further information was requested regarding the quality section of the dossiers on 14\textsuperscript{th} March 2011, 11\textsuperscript{th} May 2011 and 9\textsuperscript{th} June 2011.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 12\textsuperscript{th} April 2011, 9\textsuperscript{th} June 2011 and 27\textsuperscript{th} July 2011 for the quality section of the dossiers.</td>
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<td>5</td>
<td>The applications were determined on 11\textsuperscript{th} October 2011.</td>
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OLANZAPINE 2.5MG, 5MG, 7.5MG, 10MG, 15MG AND 20MG
FILM-COATED TABLETS
PL 30464/0097-102

STEPS TAKEN AFTER ASSESSMENT

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SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 2.5mg olanzapine.

Excipient: Each film-coated tablet contains 86mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Off-white to pale yellow film-coated tablets debossed with “J” on one side and “2.5” on the other.

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 10mg/day.

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

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

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

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

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

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

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

(See 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 4.4mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

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

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

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal product. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.
HYPERGLYCAEMIA AND DIABETES
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. 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 medicines. In the event of elevated ALT and/or AST during treatment, followup should be organised and dose reduction should be considered. In cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

NEUTROPENIA
Caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hyperesinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

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

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

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

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

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

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

USE IN CHILDREN AND ADOLESCENTS UNDER 18 YEARS OF AGE
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 medicine.

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).

**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.

**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.

**UNDESIRABLE EFFECTS**

**ADULTS**

The most frequently (seen in ≥ 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic transaminases (see section 4.4), rash, asthenia, fatigue and oedema.

The following table lists the adverse reactions and laboratory investigations observed from spontaneous reporting and in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the data available).

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<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
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<td><strong>Blood and the lymphatic system disorders</strong></td>
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<td>Eosinophilia</td>
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<td>Neutropenia</td>
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<td>Allergic reaction</td>
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<td>Metabolism and nutrition disorders</td>
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<td>Elevated cholesterol levels&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>Elevated glucose levels&lt;sup&gt;4&lt;/sup&gt;</td>
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<tr>
<td>Nervous system disorders</td>
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<td>Dizziness</td>
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<td>Gastrointestinal disorders</td>
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<td>Mild, transient anticholinergic effects including constipation and dry mouth</td>
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<td>Hepato-biliary disorders</td>
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<td>Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)</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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<td>Musculoskeletal and connective tissue disorders</td>
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<tr>
<td>Renal and urinary disorders</td>
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<td>Reproductive system and breast disorders</td>
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<tr>
<td>General disorders and administration site conditions</td>
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<tr>
<td>Investigations</td>
<td>Fatigue</td>
<td>Oedema</td>
<td>High creatine phosphokinase</td>
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<tr>
<td>Elevated plasma prolactin levels(^8)</td>
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</table>

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

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

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

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

5 Observed for fasting normal levels at baseline (< 1.69 mmol/l) which increased to high (\(\geq 2.26\) mmol/l). Changes in fasting triglycerides from borderline at baseline (\(\geq 1.69\) mmol/l - < 2.26 mmol/l) to high (\(\geq 2.26\) 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 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, erythaema, 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 (\(\geq10\%\)) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of...
≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥ 7% from baseline body weight in 39.9% of patients.

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

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

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

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
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<tbody>
<tr>
<td>Very common: Weight gain9, elevated triglyceride levels10, increased appetite.</td>
</tr>
<tr>
<td>Common: Elevated cholesterol levels11</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>
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<tr>
<th>Gastrointestinal disorders</th>
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<tr>
<td>Common: Dry mouth</td>
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<tr>
<th>Hepato-biliary disorders</th>
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<tbody>
<tr>
<td>Very common: Elevations of hepatic transaminases (ALT/AST; see section 4.4).</td>
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</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 Following short-term treatment (median duration 22 days), weight gain ≥ 7% of baseline body weight (kg) was very common (40.6 %), ≥ 15% of baseline body weight was common (7.1 %) and ≥ 25 % was common (2.5 %). With long-term exposure (at least 24 weeks), 89.4 % gained ≥ 7 %, 55.3 % gained ≥ 15 % and 29.1 % gained ≥ 25 % of their baseline body weight.

10 Observed for fasting normal levels at baseline (< 1.016 mmol/l) which increased to high (≥ 1.467 mmol/l) and changes in fasting triglycerides from borderline at baseline (≥ 1.016 mmol/l - < 1.467 mmol/l) to high (≥ 1.467 mmol/l).

11 Changes in total fasting cholesterol levels from normal at baseline (< 4.39 mmol/l) to high (≥ 5.17 mmol/l) were observed commonly. Changes in total fasting cholesterol levels from borderline at baseline (≥ 4.39 - < 5.17 mmol/l) to high (≥ 5.17 mmol/l) were very common.

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

4.9 OVERDOSE

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

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

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

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

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: 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; \( \alpha \)1 adrenergic; and histamine H1 receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater \textit{in vitro} affinity for serotonin 5HT2 than dopamine D2 receptors and greater 5 HT2 than D2 activity \textit{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 (10mg) 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 com-theraphy study of patients treated with lithium or valproate for a minimum of 2 weeks, the addition of olanzapine 10mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

In a second 12-month recurrence prevention study in manic episode patients who achieved remission with a combination of olanzapine and lithium and were then randomised to olanzapine or lithium alone, olanzapine was statistically non-inferior to lithium on the primary endpoint of bipolar recurrence (olanzapine 30.0%, lithium 38.3%; p = 0.055).
In an 18-month co-therapy study in manic or mixed episode patients stabilised with olanzapine plus a mood stabiliser (lithium or valproate), long-term olanzapine co-therapy with lithium or valproate was not statistically significantly superior to lithium or valproate alone in delaying bipolar recurrence, defined according to syndromic (diagnostic) criteria.

**PAEDIATRIC POPULATION**

The experience in adolescents (ages 13 to 17 years) is limited to short-term efficacy data in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20mg/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 20mg/day was not associated with any distinguishing profile of adverse events.

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

In renally impaired patients (creatinine clearance < 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.
5.3 PRECLINICAL SAFETY DATA

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

5.3.2 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.

5.3.3 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 anaemia developed in a few dogs treated with 8 or 10mg/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.

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

5.3.5 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.

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Tablet core
Lactose monohydrate
Hydroxypropylcellulose (E463)
Crospovidone (E1202)
Microcrystalline cellulose (E460)
Magnesium stearate (E572)

Tablet coat
Polyvinyl alcohol
Titanium dioxide (E171)
Talc (E553b)
Lactose monohydrate
Triacetin

6.2 INCOMPATIBILITIES
Not applicable.
6.3 **SHELF LIFE**

2 years.

6.4 **SPECIAL PRECAUTIONS FOR STORAGE**

This medicinal product does not require any special storage conditions.

6.5 **NATURE AND CONTENTS OF CONTAINER**

Cold-formed aluminium blisters in cartons of 28, 50, 56, 60 or 70 tablets per carton.

Not all pack sizes may be marketed.

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**

No special requirements.

7 **MARKETING AUTHORITY AND STATEMENT**

Athlone Pharmaceuticals Limited

Ballymurray

Co. Roscommon

Ireland

8 **MARKETING AUTHORISATION NUMBER(S)**

PL 30464/0097

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

11/10/2011

10 **DATE OF REVISION OF THE TEXT**

11/10/2011
1 NAME OF THE MEDICINAL PRODUCT
Olanzapine 5mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 5mg olanzapine.

Excipient: Each film coated tablet contains 172mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Off-white to pale yellow film-coated tablets debossed with “J” on one side and “5” on the other.

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 10mg/day.

Manic episode: The starting dose is 15mg 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 10mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

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

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

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

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

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

(See 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 4.4mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

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

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

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal product. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.
**HYPERGLYCAEMIA AND DIABETES**
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. 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 medicines. In the event of elevated ALT and/or AST during treatment, followup should be organised and dose reduction should be considered. In cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

**NEUTROPENIA**
Caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

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

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

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

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

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

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

USE IN CHILDREN AND ADOLESCENTS UNDER 18 YEARS OF AGE
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 medicine.

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).

### 4.6 PREGNANCY AND LACTATION

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

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

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

### 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

### 4.8 UNDESIRABLE EFFECTS

**ADULTS**

The most frequently (seen in ≥ 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic transaminases (see section 4.4), rash, asthenia, fatigue and oedema.

The following table lists the adverse reactions and laboratory investigations observed from spontaneous reporting and in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the data available).

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and the lymphatic system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Leukopenia</td>
<td>Neutropenia</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></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>Weight gain</td>
<td>Elevated cholesterol levels&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>Elevated glucose levels&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Somnolence</td>
<td>Dizziness</td>
<td>Akathisia&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>Orthostatic hypotension</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Mild, transient anticholinergic effects including constipation and dry mouth</td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td>Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Rash</td>
<td>Photosensitivity reaction</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1 Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Following short-term treatment (median duration 47 days), weight gain ≥ 7% of baseline body weight was very common (22.2 %), ≥ 15% was common (4.2 %) and 25% was uncommon (0.8 %). Patients gaining ≥ 7 %, ≥ 15 % and ≥ 25% of their baseline body weight with long-term exposure (at least 48 weeks) were very common (64.4 %, 31.7 % and 12.3 % respectively).

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

3 Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol) 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 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, erythaema, 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 **Fatigue**  
**Oedema**  
**Elevated prolactin levels**  
**High creatine phosphokinase**  
**Increased total bilirubin**  
**Increased alkaline phosphatase**
≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥ 7% from baseline body weight in 39.9% of patients.

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

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

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

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th>Very common: Weight gain9, elevated triglyceride levels10, increased appetite.</th>
<th>Common: Elevated cholesterol levels11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Very common: Sedation (including: hypersomnia, lethargy, somnolence).</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common: Dry mouth</td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Very common: Elevations of hepatic transaminases (ALT/AST; see section 4.4).</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Very common: Decreased total bilirubin, increased GGT, elevated plasma prolactin levels12.</td>
<td></td>
</tr>
</tbody>
</table>

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

10 Observed for fasting normal levels at baseline (< 1.016 mmol/l) which increased to high (≥ 1.467 mmol/l) and changes in fasting triglycerides from borderline at baseline (≥ 1.016 mmol/l - < 1.467 mmol/l) to high (≥ 1.467 mmol/l).

11 Changes in total fasting cholesterol levels from normal at baseline (< 4.39 mmol/l) to high (≥ 5.17 mmol/l) were observed commonly. Changes in total fasting cholesterol levels from borderline at baseline (≥ 4.39 - < 5.17 mmol/l) to high (≥ 5.17 mmol/l) were very common.

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

4.9 OVERDOSE

SIGNs AND SYMPTOMs

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

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

MANAGEMENT OF OVERDOSE

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

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

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: 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 behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater in vitro affinity for serotonin 5HT2 than dopamine D2 receptors and greater 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 (10mg) 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 10mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

In a second 12-month recurrence prevention study in manic episode patients who achieved remission with a combination of olanzapine and lithium and were then randomised to olanzapine or lithium alone, olanzapine was statistically non-inferior to lithium on the primary endpoint of bipolar recurrence (olanzapine 30.0%, lithium 38.3%; p = 0.055).
In an 18-month co-therapy study in manic or mixed episode patients stabilised with olanzapine plus a mood stabiliser (lithium or valproate), long-term olanzapine co-therapy with lithium or valproate was not statistically significantly superior to lithium or valproate alone in delaying bipolar recurrence, defined according to syndromic (diagnostic) criteria.

**PAEDIATRIC POPULATION**
The experience in adolescents (ages 13 to 17 years) is limited to short-term efficacy data in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20mg/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 20mg/day was not associated with any distinguishing profile of adverse events.

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

In renally impaired patients (creatinine clearance < 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 (36.8 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 210mg/kg (mice) and 175mg/kg (rats). Dogs tolerated single oral doses up to 100mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, laboured respiration, miosis, and anorexia. In monkeys, single oral doses up to 100mg/kg resulted in prostration and, at higher doses, semi-consciousness.

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

HAEMATOLOGIC TOXICITY
Effects on haematology parameters were found in each species, including dose-related reductions in circulating 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 anaemia developed in a few dogs treated with 8 or 10mg/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 1.1mg/kg (3 times the maximum human dose) and reproduction parameters were influenced in rats given 3mg/kg (9 times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

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

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

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Tablet core
Lactose monohydrate
Hydroxypropylcellulose (E463)
Crospovidone (E1202)
Microcrystalline cellulose (E460)
Magnesium stearate (E572)

Tablet coat
Polyvinyl alcohol
Titanium dioxide (E171)
Talc (E553b)
Lactose monohydrate
Triacetin

6.2 INCOMPATIBILITIES
Not applicable.
6.3 **SHELF LIFE**
2 years.

6.4 **SPECIAL PRECAUTIONS FOR STORAGE**
This medicinal product does not require any special storage conditions.

6.5 **NATURE AND CONTENTS OF CONTAINER**
Cold-formed aluminium blisters in cartons of 28, 50, 56, 60 or 70 tablets per carton. Not all pack sizes may be marketed.

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Athlone Pharmaceuticals Limited
Ballymurray
Co. Roscommon
Ireland

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 30464/0098

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
11/10/2011

10 **DATE OF REVISION OF THE TEXT**
11/10/2011
1 **NAME OF THE MEDICINAL PRODUCT**
   Olanzapine 7.5mg film-coated tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
   Each film-coated tablet contains 7.5mg olanzapine.
   Excipient: Each film-coated tablet contains 258mg lactose monohydrate.
   For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
   Film-coated tablet
   Off-white to pale yellow film-coated tablets debossed with “J” on one side and “7.5” on the other.

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 10mg/day.

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

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

   During treatment for schizophrenia, manic episode and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours. Olanzapine can be given without 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 (5mg/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 (5mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5mg and only increased with caution.
**GENDER**
The starting dose and dose range need not be routinely altered for female patients relative to male patients.

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

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

(See 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 4.4mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

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

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

**Neuroleptic Malignant Syndrome (NMS)**
NMS is a potentially life-threatening condition associated with antipsychotic medicinal product. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.
HYPERGLYCAEMIA AND DIABETES
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. 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 \textit{in vitro}, experience during the clinical trials revealed a low incidence of related events. However, as clinical experience with olanzapine in patients with concomitant illness is limited, caution is advised when prescribing for patients with prostatic hypertrophy, or paralytic ileus and related conditions.

HEPATIC FUNCTION
Transient, asymptomatic elevations of hepatic transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicines. In the event of elevated ALT and/or AST during treatment, followup should be organised and dose reduction should be considered. In cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

NEUTROPENIA
Caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

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

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

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

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

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

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

USE IN CHILDREN AND ADOLESCENTS UNDER 18 YEARS OF AGE
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 medicine.

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).

4.6 PREGNANCY AND LACTATION

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

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

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

**ADULTS**

The most frequently (seen in ≥ 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic transaminases (see section 4.4), rash, asthenia, fatigue and oedema.

The following table lists the adverse reactions and laboratory investigations observed from spontaneous reporting and in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the data available).

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
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<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Eosinophilia</td>
<td>Leukopenia</td>
<td>Thrombocytopenia</td>
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<td>Immune system disorders</td>
<td>Neutropenia</td>
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<td>Allergic reaction</td>
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<td>Metabolism and nutrition disorders</td>
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<tr>
<td><strong>Weight gain</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Elevated cholesterol levels&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4)</td>
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<td>Elevated glucose levels&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Hypothermia</td>
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<td>Elevated triglyceride levels&lt;sup&gt;2,5&lt;/sup&gt;</td>
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<td></td>
<td>Glucosuria</td>
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<th>Nervous system disorders</th>
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<td><strong>Somnolence</strong></td>
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<th>Cardiac disorders</th>
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<th>Vascular disorders</th>
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<th>Gastrointestinal disorders</th>
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<th>Hepato-biliary disorders</th>
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<th>Skin and subcutaneous tissue disorders</th>
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<th>Musculoskeletal and connective tissue disorders</th>
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<th>Renal and urinary disorders</th>
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<th>Reproductive system and breast disorders</th>
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<th>General disorders and administration site conditions</th>
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Investigations

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<tr>
<th>Fatigue</th>
<th>Oedema</th>
<th>Elevated plasma prolactin levels(^8)</th>
<th>High creatine phosphokinase</th>
<th>Increased total bilirubin</th>
<th>Increased alkaline phosphatase</th>
</tr>
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</table>

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

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

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

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

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

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

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

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

Long-term exposure (at least 48 weeks)

The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HCL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 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, erythaema, visual hallucinations and urinary incontinence were observed commonly.

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

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

**CHILDREN AND ADOLESCENTS**

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

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

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

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

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

10 Observed for fasting normal levels at baseline (< 1.016 mmol/l) which increased to high (≥ 1.467 mmol/l) and changes in fasting triglycerides from borderline at baseline (≥ 1.016 mmol/l - < 1.467 mmol/l) to high (≥ 1.467 mmol/l).

11 Changes in total fasting cholesterol levels from normal at baseline (< 4.39 mmol/l) to high (≥ 5.17 mmol/l) were observed commonly. Changes in total fasting cholesterol levels from borderline at baseline (≥ 4.39 - < 5.17 mmol/l) to high (≥ 5.17 mmol/l) were very common.

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

**OVERDOSE**

**SIGNS AND SYMPTOMS**

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

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

**MANAGEMENT OF OVERDOSE**

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

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

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: 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 behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater in vitro affinity for serotonin 5HT2 than dopamine D2 receptors and greater 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 (10mg) 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 10mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

In a second 12-month recurrence prevention study in manic episode patients who achieved remission with a combination of olanzapine and lithium and were then randomised to olanzapine or lithium alone, olanzapine was statistically non-inferior to lithium on the primary endpoint of bipolar recurrence (olanzapine 30.0%, lithium 38.3%; p = 0.055).
In an 18-month co-therapy study in manic or mixed episode patients stabilised with olanzapine plus a mood stabiliser (lithium or valproate), long-term olanzapine co-therapy with lithium or valproate was not statistically significantly superior to lithium or valproate alone in delaying bipolar recurrence, defined according to syndromic (diagnostic) criteria.

PAEDIATRIC POPULATION
The experience in adolescents (ages 13 to 17 years) is limited to short-term efficacy data in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20mg/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 20mg/day was not associated with any distinguishing profile of adverse events.

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

In renally impaired patients (creatinine clearance < 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 210mg/kg (mice) and 175mg/kg (rats). Dogs tolerated single oral doses up to 100mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, laboured respiration, miosis, and anorexia. In monkeys, single oral doses up to 100mg/kg resulted in prostration and, at higher doses, semi-consciousness.

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

HAEMATOLOGIC TOXICITY
Effects on haematology parameters were found in each species, including dose-related reductions in circulating 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 anaemia developed in a few dogs treated with 8 or 10mg/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 1.1mg/kg (3 times the maximum human dose) and reproduction parameters were influenced in rats given 3mg/kg (9 times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Tablet core
Lactose monohydrate
Hydroxypropylcellulose (E463)
Crospovidone (E1202)
Microcrystalline cellulose (E460)
Magnesium stearate (E572)

Tablet coat
Polyvinyl alcohol
Titanium dioxide (E171)
Talc (E553b)
Lactose monohydrate
Triacetin

6.2 INCOMPATIBILITIES
Not applicable.
6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER
Cold-formed aluminium blisters in cartons of 28, 50, 56, 60 or 70 tablets per carton.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Athlone Pharmaceuticals Limited
Ballymurray
Co. Roscommon
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 30464/0099

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/10/2011

10 DATE OF REVISION OF THE TEXT
11/10/2011
NAME OF THE MEDICINAL PRODUCT
Olanzapine 10mg Film-coated Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 10mg olanzapine.

Excipient: Each film-coated tablet contains 344mg lactose monohydrate.

For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Film-coated tablet
Off-white to pale yellow film-coated tablets debossed with “J” on one side and “10” on the other.

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 10mg/day.

Manic episode: The starting dose is 15mg 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 10mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

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

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

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

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

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

(See 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 4.4mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

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

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

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal product. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.
HYPERGLYCAEMIA AND DIABETES
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. 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 medicines. In the event of elevated ALT and/or AST during treatment, followup should be organised and dose reduction should be considered. In cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

NEUTROPENIA
Caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

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

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

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

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

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

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

USE IN CHILDREN AND ADOLESCENTS UNDER 18 YEARS OF AGE
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 medicine.

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).

4.6 PREGNANCY AND LACTATION

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

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

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

ADULTS

The most frequently (seen in ≥ 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic transaminases (see section 4.4), rash, asthenia, fatigue and oedema.

The following table lists the adverse reactions and laboratory investigations observed from spontaneous reporting and in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the data available).

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
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<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Eosinophilia</td>
<td>Leukopenia</td>
<td>Thrombocytopenia</td>
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<tr>
<td>Immune system disorders</td>
<td>Neutropenia</td>
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<td>Allergic reaction</td>
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<tr>
<td>Table: Metabolism and nutrition disorders</td>
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<td>------------------------------------------</td>
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<tr>
<td><strong>Weight gain</strong></td>
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<tr>
<td>Elevated cholesterol levels&lt;sup&gt;2,3&lt;/sup&gt;</td>
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<tr>
<td>Elevated glucose levels&lt;sup&gt;4&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Elevated triglyceride levels&lt;sup&gt;2,5&lt;/sup&gt;</td>
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<tr>
<td>Glucosuria</td>
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<tr>
<td>Increased appetite</td>
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<tr>
<td>Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4) Hypothermia</td>
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<th>Table: Nervous system disorders</th>
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<tr>
<td><strong>Somnolence</strong></td>
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<td>Dizziness</td>
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<tr>
<td>Akathisia&lt;sup&gt;6&lt;/sup&gt;</td>
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<tr>
<td>Parkinsonism&lt;sup&gt;6&lt;/sup&gt;</td>
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<tr>
<td>Dyskinesia&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Seizures where in most cases a history of seizures or risk factors for seizures were reported Neureleptic malignant syndrome (see section 4.4) Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms&lt;sup&gt;7&lt;/sup&gt;</td>
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<th>Table: Cardiac disorders</th>
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<tr>
<td>Bradycardia</td>
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<tr>
<td>QT&lt;sub&gt;c&lt;/sub&gt; prolongation</td>
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<tr>
<td>(see section 4.4)</td>
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<tr>
<td>Ventricular tachycardia/ fibrillation, sudden death (see section 4.4)</td>
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<th>Table: Vascular disorders</th>
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<tr>
<td>Orthostatic hypotension</td>
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<tr>
<td>Thromboembolism (including pulmonary embolism and deep vein thrombosis)</td>
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<th>Table: Gastrointestinal disorders</th>
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<tr>
<td>Mild, transient anticholinergic effects including constipation and dry mouth</td>
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<tr>
<td>Pancreatitis</td>
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<th>Table: Hepato-biliary disorders</th>
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<tr>
<td>Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment (see section 4.4)</td>
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<tr>
<td>Hepatitis (including hepatocellular, cholestatic or mixed liver injury)</td>
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<th>Table: Skin and subcutaneous tissue disorders</th>
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<tr>
<td>Rash</td>
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<td>Photosensitivity reaction</td>
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<td>Alopecia</td>
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<th>Table: Musculoskeletal and connective tissue disorders</th>
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<tr>
<td>Rhabdomyolysis</td>
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<th>Table: Renal and urinary disorders</th>
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<tr>
<td>Urinary hesitation</td>
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<th>Table: Reproductive system and breast disorders</th>
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<tr>
<td>Priapism</td>
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<th>Table: General disorders and administration site conditions</th>
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<tr>
<td>Asthenia</td>
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Investigations

<table>
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<tr>
<th>Elevated plasma prolactin levels&lt;sup&gt;8&lt;/sup&gt;</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. Following short-term treatment (median duration 47 days), weight gain ≥ 7% of baseline body weight was very common (22.2 %), ≥ 15% was common (4.2 %) and 25% was uncommon (0.8 %). Patients gaining ≥ 7 %, ≥ 15 % and ≥ 25% of their baseline body weight with long-term exposure (at least 48 weeks) were very common (64.4 %, 31.7 % and 12.3 % respectively).

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

3 Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol) 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 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, erythaema, visual hallucinations and urinary incontinence were observed commonly.

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

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

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

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

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

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

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

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

<table>
<thead>
<tr>
<th>Hepato-biliary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very common:</strong> 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><strong>Very common:</strong> Decreased total bilirubin, increased GGT, elevated plasma prolactin levels(^12).</td>
</tr>
</tbody>
</table>

\(^9\) Following short-term treatment (median duration 22 days), weight gain ≥ 7% of baseline body weight (kg) was very common (40.6 %), ≥ 15% of baseline body weight was common (7.1 %) and ≥ 25 % was common (2.5 %). With long-term exposure (at least 24 weeks), 89.4 % gained ≥ 7 %, 55.3 % gained ≥ 15 % and 29.1 % gained ≥ 25 % of their baseline body weight.

\(^10\) Observed for fasting normal levels at baseline (< 1.016 mmol/l) which increased to high (≥ 1.467 mmol/l) and changes in fasting triglycerides from borderline at baseline (≥ 1.016 mmol/l - < 1.467 mmol/l) to high (≥ 1.467 mmol/l). 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.

\(^11\) Elevated plasma prolactin levels were reported in 47.4% of adolescent patients.

4.9 OVERDOSE

**SIGNS AND SYMPTOMS**

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

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

**MANAGEMENT OF OVERDOSE**

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

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

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: 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 behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater in vitro affinity for serotonin 5HT2 than dopamine D2 receptors and greater 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 (10mg) 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 10mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

In a second 12-month recurrence prevention study in manic episode patients who achieved remission with a combination of olanzapine and lithium and were then randomised to olanzapine or lithium alone, olanzapine was statistically non-inferior to lithium on the primary endpoint of bipolar recurrence (olanzapine 30.0%, lithium 38.3%; p = 0.055).
In an 18-month co-therapy study in manic or mixed episode patients stabilised with olanzapine plus a mood stabiliser (lithium or valproate), long-term olanzapine co-therapy with lithium or valproate was not statistically significantly superior to lithium or valproate alone in delaying bipolar recurrence, defined according to syndromic (diagnostic) criteria.

PAEDIATRIC POPULATION
The experience in adolescents (ages 13 to 17 years) is limited to short-term efficacy data in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20mg/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 20mg/day was not associated with any distinguishing profile of adverse events.

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

In renally impaired patients (creatinine clearance < 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 (39.8 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 210mg/kg (mice) and 175mg/kg (rats). Dogs tolerated single oral doses up to 100mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, laboured respiration, miosis, and anorexia. In monkeys, single oral doses up to 100mg/kg resulted in prostration and, at higher doses, semi-consciousness.

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

**HAEMATOLOGIC TOXICITY**
Effects on haematology parameters were found in each species, including dose-related reductions in circulating 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 anaemia developed in a few dogs treated with 8 or 10mg/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 1.1mg/kg (3 times the maximum human dose) and reproduction parameters were influenced in rats given 3mg/kg (9 times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Tablet core
- Lactose monohydrate
- Hydroxypropylcellulose (E463)
- Crospovidone (E1202)
- Microcrystalline cellulose (E460)
- Magnesium stearate (E572)

Tablet coat
- Polyvinyl alcohol
- Titanium dioxide (E171)
- Talc (E553b)
- Lactose monohydrate
- Triacetin

6.2 INCOMPATIBILITIES
Not applicable.
6.3 **SHELF LIFE**
2 years.

6.4 **SPECIAL PRECAUTIONS FOR STORAGE**
This medicinal product does not require any special storage conditions.

6.5 **NATURE AND CONTENTS OF CONTAINER**
Cold-formed aluminium blisters in cartons of 28, 50, 56, 60 or 70 tablets per carton. Not all pack sizes may be marketed.

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Athlone Pharmaceuticals Limited
Ballymurray
Co. Roscommon
Ireland

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 30464/0100

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
11/10/2011

10 **DATE OF REVISION OF THE TEXT**
11/10/2011
1 NAME OF THE MEDICINAL PRODUCT
Olanzapine 15mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 15mg olanzapine.
Excipient: Each film coated tablet contains 339mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Off-white to pale yellow film-coated tablets debossed with “J” on one side and “15” on the other.

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 10mg/day.
Manic episode: The starting dose is 15mg 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 10mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.
During treatment for schizophrenia, manic episode and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours. Olanzapine can be given without 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 (5mg/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 (5mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5mg and only increased with caution.
**GENDER**
The starting dose and dose range need not be routinely altered for female patients relative to male patients.

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

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

(See 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 4.4mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

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

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

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

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. 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 medicines. In the event of elevated ALT and/or AST during treatment, followup should be organised and dose reduction should be considered. In cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

NEUTROPENIA

Caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

DISCONTINUATION OF TREATMENT

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

QT INTERVAL

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

THROMBOEMBOLISM

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

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

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

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

USE IN CHILDREN AND ADOLESCENTS UNDER 18 YEARS OF AGE
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 medicine.

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).

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

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

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

**4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**
No studies on the effects on the ability to drive and use machines have been performed. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

**4.8 UNDESIRABLE EFFECTS**

**ADULTS**
The most frequently (seen in ≥ 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic transaminases (see section 4.4), rash, asthenia, fatigue and oedema.

The following table lists the adverse reactions and laboratory investigations observed from spontaneous reporting and in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the data available).

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and the lymphatic system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Leukopenia</td>
<td>Neutropenia</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
<td></td>
<td>Allergic reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Nervous system disorders</td>
<td>Cardiac disorders</td>
<td>Vascular disorders</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------------</td>
<td>-------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Weight gain&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Elevated cholesterol levels&lt;sup&gt;2,3&lt;/sup&gt; Elevated glucose levels&lt;sup&gt;4&lt;/sup&gt; Elevated triglyceride levels&lt;sup&gt;2,5&lt;/sup&gt; Glucosuria Increased appetite</td>
<td>Dizziness</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>
Investigations

<table>
<thead>
<tr>
<th>Elevated plasma prolactin levels⁸</th>
<th>High creatine phosphokinase</th>
<th>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. Following short-term treatment (median duration 47 days), weight gain ≥ 7% of baseline body weight was very common (22.2%), ≥ 15% was common (4.2%) and 25% was uncommon (0.8%). Patients gaining ≥ 7%, ≥ 15% and ≥ 25% of their baseline body weight with long-term exposure (at least 48 weeks) were very common (64.4%, 31.7% and 12.3% respectively).

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

³ Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol) 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 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 (≥ 10%), common (≥ 1% and < 10%).

| Metabolism and nutrition disorders | Very common: Weight gain9, elevated triglyceride levels10, increased appetite. |
| Nervous system disorders           | Very common: Sedation (including: hypersonnia, lethargy, somnolence). |
| Gastrointestinal disorders        | Common: Dry mouth |
| Hepato-biliary disorders          | Very common: Elevations of hepatic transaminases (ALT/AST; see section 4.4). |
| Investigations                   | Very common: Decreased total bilirubin, increased GGT, elevated plasma prolactin levels12. |

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

10 Observed for fasting normal levels at baseline (< 1.016 mmol/l) which increased to high (≥ 1.467 mmol/l) and changes in fasting triglycerides from borderline at baseline (≥ 1.016 mmol/l - < 1.467 mmol/l) to high (≥ 1.467 mmol/l).

11 Changes in total fasting cholesterol levels from normal at baseline (< 4.39 mmol/l) to high (≥ 5.17 mmol/l) were observed commonly. Changes in total fasting cholesterol levels from borderline at baseline (≥ 4.39 - < 5.17 mmol/l) to high (≥ 5.17 mmol/l) were very common.

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

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

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

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

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

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: 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 behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater in vitro affinity for serotonin 5HT2 than dopamine D2 receptors and greater 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 (10mg) 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 10mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

In a second 12-month recurrence prevention study in manic episode patients who achieved remission with a combination of olanzapine and lithium and were then randomised to olanzapine or lithium alone, olanzapine was statistically non-inferior to lithium on the primary endpoint of bipolar recurrence (olanzapine 30.0%, lithium 38.3%; p = 0.055).
In an 18-month co-therapy study in manic or mixed episode patients stabilised with olanzapine plus a mood stabiliser (lithium or valproate), long-term olanzapine co-therapy with lithium or valproate was not statistically significantly superior to lithium or valproate alone in delaying bipolar recurrence, defined according to syndromic (diagnostic) criteria.

**PAEDIATRIC POPULATION**

The experience in adolescents (ages 13 to 17 years) is limited to short-term efficacy data in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20mg/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 20mg/day was not associated with any distinguishing profile of adverse events.

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

In 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 (39.8 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 210mg/kg (mice) and 175mg/kg (rats). Dogs tolerated single oral doses up to 100mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, laboured respiration, miosis, and anorexia. In monkeys, single oral doses up to 100mg/kg resulted in prostration and, at higher doses, semi-consciousness.

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

HAEMATOLOGIC TOXICITY
Effects on haematology parameters were found in each species, including dose-related reductions in circulating 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 anaemia developed in a few dogs treated with 8 or 10mg/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 1.1mg/kg (3 times the maximum human dose) and reproduction parameters were influenced in rats given 3mg/kg (9 times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Tablet core
Lactose monohydrate
Hydroxypropylcellulose (E463)
Crospovidone (E1202)
Microcrystalline cellulose (E460)
Magnesium stearate (E572)

Tablet coat
Polyvinyl alcohol
Titanium dioxide (E171)
Talc (E553b)
Lactose monohydrate
Triacetin

6.2 INCOMPATIBILITIES
Not applicable.
6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER
Cold-formed aluminium blisters in cartons of 28, 50, 56, 60 or 70 tablets per carton. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORITY/PHARMACEUTICALS LIMITED
Athlone Pharmaceuticals Limited
Ballymurray
Co. Roscommon
Ireland

8 MARKETING AUTHORITY NUMBER(S)
PL 30464/0101

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
11/10/2011

10 DATE OF REVISION OF THE TEXT
11/10/2011
1 NAME OF THE MEDICINAL PRODUCT
Olanzapine 20mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 20mg olanzapine.

Excipient: Each film-coated tablet contains 334mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Off-white to pale yellow film-coated tablets debossed with “J” on one side and “20” on the other.

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 10mg/day.

Manic episode: The starting dose is 15mg 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 10mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

During treatment for schizophrenia, manic episode and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours. Olanzapine can be given without 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 (5mg/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 (5mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5mg and only increased with caution.
GENDER
The starting dose and dose range need not be routinely altered for female patients relative to male patients.

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

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

(See 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 4.4mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

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

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

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal product. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.
HYPERGLYCAEMIA AND DIABETES
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. 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 medicines. In the event of elevated ALT and/or AST during treatment, follow-up should be organised and dose reduction should be considered. In cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

NEUTROPENIA
Caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

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

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

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

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

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

POSTURAL HYPOPOTENSION
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 medicine.

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).

4.6 PREGNANCY AND LACTATION

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

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

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

ADULTS

The most frequently (seen in ≥ 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic transaminases (see section 4.4), rash, asthenia, fatigue and oedema.

The following table lists the adverse reactions and laboratory investigations observed from spontaneous reporting and in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the data available).

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
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<tbody>
<tr>
<td><strong>Blood and the lymphatic system disorders</strong></td>
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<tr>
<td>Eosinophilia</td>
<td>Leukopenia</td>
<td>Neutropenia</td>
<td>Thrombocytopenia</td>
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<td><strong>Immune system disorders</strong></td>
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<tr>
<td>Allergic reaction</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Nervous system disorders</td>
<td>Cardiac disorders</td>
<td>Vascular disorders</td>
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<tr>
<td>Weight gain&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Elevated cholesterol</td>
<td>Dizziness</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>levels&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>Elevated glucose</td>
<td>Akathisia&lt;sup&gt;6&lt;/sup&gt;</td>
<td>QT&lt;sub&gt;c&lt;/sub&gt; prolongation (see section 4.4)</td>
</tr>
<tr>
<td>levels&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Elevated triglyceride</td>
<td>Parkinsonism&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Ventricular tachycardia/ fibrillation, sudden death (see section 4.4)</td>
</tr>
<tr>
<td>levels&lt;sup&gt;2,5&lt;/sup&gt;</td>
<td>Glucosuria</td>
<td>Dyskinesia&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Increased appetitie</td>
<td></td>
<td></td>
<td>Orthostatic hypotension</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Thromboembolism (including pulmonary embolism and deep vein thrombosis)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Nervous system disorders</td>
<td>Cardiac disorders</td>
<td>Vascular disorders</td>
</tr>
<tr>
<td>Weight gain&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Elevated cholesterol</td>
<td>Dizziness</td>
<td>Bradycardia</td>
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<tr>
<td>levels&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>Elevated glucose</td>
<td>Akathisia&lt;sup&gt;6&lt;/sup&gt;</td>
<td>QT&lt;sub&gt;c&lt;/sub&gt; prolongation (see section 4.4)</td>
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<td>levels&lt;sup&gt;4&lt;/sup&gt;</td>
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<tr>
<td>levels&lt;sup&gt;2,5&lt;/sup&gt;</td>
<td>Glucosuria</td>
<td>Dyskinesia&lt;sup&gt;6&lt;/sup&gt;</td>
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<td>Thromboembolism (including pulmonary embolism and deep vein thrombosis)</td>
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<td>Gastrointestinal disorders</td>
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<td></td>
<td>Mild, transient anticholinergic effects including constipation and dry mouth</td>
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<td>Pancreatitis</td>
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<td>Hepato-biliary disorders</td>
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<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></td>
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<td>Hepatitis (including hepatocellular, cholestatic or mixed liver injury)</td>
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<td>Skin and subcutaneous tissue disorders</td>
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<td>Photosensitivity reaction Alopecia</td>
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<td>Musculoskeletal and connective tissue disorders</td>
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<td>Renal and urinary disorders</td>
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<td>Reproductive system and breast disorders</td>
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<tr>
<td>General disorders and administration site conditions</td>
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<tr>
<td>Asthenia</td>
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<tr>
<td>Investigations</td>
<td>Fatigue</td>
<td>Oedema</td>
<td>High creatine phosphokinase</td>
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<tr>
<td>Elevated plasma prolactin levels(^8)</td>
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</tbody>
</table>

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

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

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

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

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

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

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

8 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 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 \( \geq 7\% \) from baseline body weight occurred in 17.4\% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of \( \geq 7\% \) from baseline body weight in 39.9\% of patients.

**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 (\( \geq 7\% \)) 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 (\( \geq 10\% \)), common (\( \geq 1\% \) and < 10\%).

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

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

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

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

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

\(^9\) Following short-term treatment (median duration 22 days), weight gain \( \geq 7\% \) of baseline body weight (kg) was very common (40.6\%), \( \geq 15\% \) of baseline body weight was common (7.1\%) and \( \geq 25\% \) was common (2.5\%). With long-term exposure (at least 24 weeks), 89.4\% gained \( \geq 7\% \), 55.3\% gained \( \geq 15\% \) and 29.1\% gained \( \geq 25\% \) of their baseline body weight.

\(^{10}\) Observed for fasting normal levels at baseline (< 1.016 mmol/l) which increased to high (\( \geq 1.467 \) mmol/l) and changes in fasting triglycerides from borderline at baseline (\( \geq 1.016 \) mmol/l - < 1.467 mmol/l) to high (\( \geq 1.467 \) mmol/l).

\(^{11}\) Changes in total fasting cholesterol levels from normal at baseline (< 4.39 mmol/l) to high (\( \geq 5.17 \) mmol/l) were observed commonly. Changes in total fasting cholesterol levels from borderline at baseline (\( \geq 4.39 \) - < 5.17 mmol/l) to high (\( \geq 5.17 \) 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, dysartrhia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

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

**MANAGEMENT OF OVERDOSE**

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

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

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: 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 behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater in vitro affinity for serotonin 5HT2 than dopamine D2 receptors and greater 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 (10mg) 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 10mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

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

In a second 12-month recurrence prevention study in manic episode patients who achieved remission with a combination of olanzapine and lithium and were then randomised to olanzapine or lithium alone, olanzapine was statistically non-inferior to lithium on the primary endpoint of bipolar recurrence (olanzapine 30.0%, lithium 38.3%; p = 0.055).
In an 18-month co-therapy study in manic or mixed episode patients stabilised with olanzapine plus a mood stabiliser (lithium or valproate), long-term olanzapine co-therapy with lithium or valproate was not statistically significantly superior to lithium or valproate alone in delaying bipolar recurrence, defined according to syndromic (diagnostic) criteria.

**PAEDIATRIC POPULATION**

The experience in adolescents (ages 13 to 17 years) is limited to short-term efficacy data in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20mg/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 20mg/day was not associated with any distinguishing profile of adverse events.

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

In renally impaired patients (creatinine clearance < 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 210mg/kg (mice) and 175mg/kg (rats). Dogs tolerated single oral doses up to 100mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, laboured respiration, miosis, and anorexia. In monkeys, single oral doses up to 100mg/kg resulted in prostration and, at higher doses, semi-consciousness.

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

HAEMATOLOGIC TOXICITY
Effects on haematology parameters were found in each species, including dose-related reductions in circulating 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 anaemia developed in a few dogs treated with 8 or 10mg/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 1.1mg/kg (3 times the maximum human dose) and reproduction parameters were influenced in rats given 3mg/kg (9 times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Tablet core
Lactose monohydrate
Hydroxypropylcellulose (E463)
Crospovidone (E1202)
Microcrystalline cellulose (E460)
Magnesium stearate (E572)

Tablet coat
Polyvinyl alcohol
Titanium dioxide (E171)
Talc (E553b)
Lactose monohydrate
Triacetin

6.2 INCOMPATIBILITIES
Not applicable.
6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER
Cold-formed aluminium blisters in cartons of 28 tablets per carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Athlone Pharmaceuticals Limited
Ballymurray
Co. Roscommon
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 30464/0102

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/10/2011

10 DATE OF REVISION OF THE TEXT
11/10/2011
UKPAR Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg Film-Coated Tablets PL 30464/0097-0102

PATIENT INFORMATION LEAFLET

OLANZAPINE
2.5mg, 5mg, 7.5mg, 10mg, 15mg AND 20mg
FILM-COATED TABLETS

olanzapine

Read all of this leaflet carefully before you start taking this medicine.

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

IN THIS LEAFLET

1. What Olanzapine film-coated tablets are and what they are used for
2. Before you take Olanzapine film-coated tablets
3. How to take Olanzapine film-coated tablets
4. Possible side effects
5. How to store Olanzapine film-coated tablets
6. Further information

1. WHAT OLANZAPINE FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

Olanzapine film-coated tablets belong to a group of medicines called antipsychotics.

Olanzapine film-coated tablets are 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 film-coated tablets are 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 FILM-COATED TABLETS

Do not take Olanzapine film-coated tablets:
- If you are allergic (hypersensitive) to olanzapine or any of the other ingredients of Olanzapine film-coated tablets.

An allergic reaction may be recognised as a rash, itching, a swollen face, swollen lips or shortness of breath. If this has happened to you, tell your doctor.
- If you have been previously diagnosed with eye problems such as certain kinds of glaucoma (increased pressure in the eye).

Take special care with Olanzapine film-coated tablets:
- Medicines of this type may cause unusual movements mainly of the face or tongue. If this happens after you have been given Olanzapine film-coated tablets 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 film-coated tablets 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)

See also section 4. “Possible side effects”.

If you suffer from dementia, your carer or 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 film-coated tablets are not suitable for patients who are under 18 years.

3. HOW TO TAKE OLANZAPINE FILM-COATED TABLETS

Always take Olanzapine film-coated tablets 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 film-coated tablets to take and how long you should continue to take them. The daily dose of Olanzapine film-coated tablets is between 5 and 20mg. Consult your doctor if your symptoms return but do not stop taking Olanzapine film-coated tablets unless your doctor tells you to.

You should take your Olanzapine film-coated tablets once a day following the advice of your doctor. Try to take your tablets at the same time each day. It does not matter whether you take them with or without food.

Olanzapine film-coated tablets are for oral use. You should swallow the Olanzapine film-coated tablets whole with water.

If you take more Olanzapine film-coated tablets than you should

Patients who have taken more Olanzapine film-coated tablets 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, slowness 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 film-coated tablets

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

If you stop taking Olanzapine film-coated tablets

Do not stop taking your tablets just because you feel better. It is important that you carry on taking Olanzapine film-coated tablets for as long as your doctor tells you.
UKPAR Olanzapine 2.5mg, 5mg, 7.5mg, 10mg, 15mg and 20mg Film-Coated Tablets PL 30464/0097-0102

If you suddenly stop taking Olanzapine film-coated tablets, 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 film-coated tablets can cause side effects, although not everybody gets them.

Tell your doctor immediately if you experience any of these symptoms:
- Allergic reaction (e.g. swelling in the mouth and throat, itching, rash)
- Combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness
- Unusual movement (especially of the face or tongue)

Tell your doctor if any of the below side effects starts bothering you:

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
- 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
- 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
- Diabetes or the worsening of diabetes, occasionally associated with ketoadosis (ketones in the blood and urine) or coma
- Lowering of normal body temperature
- Seizures, usually associated with a history of seizures (epilepsy)
- 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 film-coated tablets 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 film-coated tablets in the last stage of pregnancy (3rd trimester) may have tremors, be sleepy or droopy.

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 FILM-COATED TABLETS

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Do not use Olanzapine film-coated tablets after the expiry date, which is stated on the blister and carton. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

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 film-coated tablets contain
- The active substance is Olanzapine.
- Each Olanzapine film-coated tablet contains either 2.5mg, 5mg, 7.5mg, 10mg, 15mg or 20mg of the active substance.
- The exact amount is shown on your Olanzapine tablet pack.
- The other ingredients are (tablet core) lactose monohydrate, hypromellose (E463), crospovidone (E1202), microcrystalline cellulose (E460), magnesium stearate (E572) and tablet coating polyvinyl alcohol, talc (E553b), titanium dioxide (E171), lactose monohydrate and triacetin.

What Olanzapine film-coated tablets look like and contents of the pack
- Olanzapine 2.5mg film-coated tablets are off-white to pale yellow and debossed with "J" on one side and "2.5" on the other.
- Olanzapine 5mg film-coated tablets are off-white to pale yellow and debossed with "J" on one side and "5" on the other.
- Olanzapine 7.5mg film-coated tablets are off-white to pale yellow and debossed with "J" on one side and "7.5" on the other.

This leaflet was last revised in June 2011.