AUSTRALIAN PRODUCT INFORMATION

ZYPREXA IM (OLANZAPINE) POWDER FOR INJECTION

1. NAME OF THE MEDICINE

ZYPREXA IM® (olanzapine).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Olanzapine 10 mg

The active ingredient in ZYPREXA IM is olanzapine 10 mg. ZYPREXA IM also contains excipients: lactose monohydrate and tartaric acid. Hydrochloride acid and/or sodium hydroxide may have been added during manufacture to adjust pH.

3. PHARMACEUTICAL FORM

ZYPREXA IM 10mg is yellow lyophilised powder in a clear glass vial. It is intended for intramuscular use only.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZYPREXA IM is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia and related psychoses and in patients with acute mania associated with Bipolar 1 Disorder, when oral therapy is not appropriate.

4.2 DOSE AND METHOD OF ADMINISTRATION

ZYPREXA IM is for intramuscular use. Do not administer intravenously or subcutaneously.

ZYPREXA IM is intended for short-term use only.

Agitated patients with schizophrenia or bipolar mania

The recommended dose for ZYPREXA IM is 10 mg, administered as a single intramuscular injection. In clinical trials, ZYPREXA IM was effective following a dose of 5 to 10 mg. Therefore, a lower dose may be given, on the basis of individual clinical status. A second injection, up to 10 mg, may be administered as early as 2 hours after the first injection on the basis of individual clinical status. A third injection, up to 10 mg may be administered as early as 4 hours after the second injection. In clinical trials, 30 mg olanzapine was the maximum dose administered intramuscularly in any 24-hour period. There is limited information on the safety and efficacy of higher doses of ZYPREXA IM, as less than 10% of agitated clinical trial patients received doses higher than 20 mg in any 24-hour period. Vital signs should be closely monitored in patient who receive the maximum dose of 30 mg within the specified

minimum time period of 6 hours in order to detect adverse cardiovascular effects, such as hypotension.

The maximum daily dose of ZYPREXA IM is 30 mg, not more than 3 injections in any 24-hour period.

The efficacy and safety of the use of ZYPREXA IM for longer than 24 hours has not been systematically studied.

Treatment with ZYPREXA IM should be discontinued and the use of oral ZYPREXA should be initiated as soon as clinically appropriate.

For further information on continued treatment with oral ZYPREXA (5 to 20 mg daily), see the Product Information for ZYPREXA tablets and ZYPREXA ZYDIS® wafers.

Elderly patients

A low starting dose of 5 mg per injection should be considered for those patients 65 and over when clinical factors warrant.

Patients with hepatic and/or renal impairment

Small single-dose clinical pharmacology studies did not reveal any major alterations in olanzapine pharmacokinetics in subjects with renal or hepatic impairment. However, as clinical experience is limited in these patients, a lower starting dose (5 mg/day) should be considered. Further dose adjustments, when indicated, should be conservative in these patients.

Female compared with male patients

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

Non-smoking patients compared with smoking patients

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

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 **4.4 Special warnings and precautions for use** and **5.1 Pharmacodynamic properties**).

Instructions for use/handling – ZYPREXA IM vial

- ZYPREXA IM should be reconstituted only with sterile water for injection.
- ZYPREXA IM should not be combined in a syringe nor should be used simultaneously with parenteral benzodiazepines (see **4.4 Special warnings and precautions for use**).
- ZYPREXA IM should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.
- Reconstitute using standard aseptic techniques for reconstitution of parenteral products.

- Use immediately within 1 hour after reconstitution.
- Discard any unused portion.
- Following reconstitution, the resulting solution should be clear and yellow in colour.
- Parenteral drug products should be inspected visually for particulate matter prior to administration whenever solution and container permit.

Reconstitution of ZYPREXA IM with sterile water for injection

1. Reconstitute using 2.1 mL of Sterile Water for Injection.
2. Rotate the vial until the contents have completely dissolved, giving a yellow coloured solution. The table below indicates the volume required to deliver the desired dose of olanzapine.

Table 1. Volume required per dose

Dose, mg ZYPREXA	Volume of Injection, mL
10.0	2.0
7.5	1.5
5.0	1.0

3. Administer the solution intramuscularly. Do not administer intravenously or subcutaneously.

4.3 CONTRAINDICATIONS

ZYPREXA IM is contraindicated in those patients with a known hypersensitivity to any ingredient of the product.

Simultaneous administration of ZYPREXA IM and parenteral benzodiazepines is not recommended due to the potential for excessive sedation, cardiorespiratory depression and, in very rare cases, death (see **4.4 Special warnings and precautions for use**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypotension and/or bradycardia have been observed during intramuscular administration of ZYPREXA IM (see **4.8 Adverse effects (Undesirable Effects)**). Patients should remain recumbent if drowsy or dizzy after injection, until examination has indicated that they are not experiencing hypotension, postural hypotension, bradycardia and/or hypoventilation.

In view of the possibility of bradycardia and/or hypotension with ZYPREXA IM, caution should be considered in patients with serious cardiovascular disease where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression. Simultaneous administration of ZYPREXA IM and parenteral benzodiazepines is not recommended due to the potential for excessive sedation, cardiorespiratory depression and, in very rare cases, death. In the event of use of a parenteral benzodiazepine with ZYPREXA IM, whether intentional or inadvertent, the patient should be closely monitored for excessive sedation and cardiorespiratory depression.

Concomitant illnesses

While ZYPREXA demonstrated anticholinergic activity *in vitro*, experience during clinical trials revealed a low incidence of related events. As clinical experience with ZYPREXA in patients with concomitant illness is limited, caution is advised when prescribing for patients with prostatic hypertrophy, narrow-angle glaucoma or paralytic ileus and related conditions.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including ZYPREXA. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Lipid alterations

Undesirable alterations in lipids have been observed in ZYPREXA-treated patients in placebo-controlled trials. ZYPREXA-treated patients had a greater mean increase in fasting total cholesterol, LDL cholesterol, and triglycerides compared to placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline. Appropriate clinical monitoring is recommended (see **4.8 Adverse effects (Undesirable Effects)**).

Weight gain

Potential consequences of weight gain should be considered prior to starting ZYPREXA. As with all antipsychotics, patients receiving ZYPREXA should receive regular monitoring of weight. In clinical trials significant weight gain was observed across all baseline Body Mass Index (BMI) categories in ZYPREXA treated patients (see **4.8 Adverse effects (Undesirable Effects)**).

Blood

As with other neuroleptic drugs, caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, 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. Thirty-two patients with clozapine-related neutropenia or agranulocytosis histories received ZYPREXA without decreases in baseline neutrophil counts.

In animal studies, dose-related reductions in circulating leucocytes were observed in mice and rats at oral doses greater than 3 to 4 mg/kg/day; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia or anaemia developed in a few dogs treated with 8 or 10 mg/kg/day. In cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow. No haematologic effects were seen in dogs receiving 5 mg/kg/day. In clinical trials, there were no data to suggest ZYPREXA adversely affected bone marrow function, even in patients with a history of drug-associated neutropenia or leucopenia (see **4.8 Adverse effects (Undesirable Effects)**).

Neuroleptic malignant syndrome (NMS)

NMS, a potentially fatal symptom complex, is associated with antipsychotic drugs, including olanzapine (see **4.8 Adverse effects (Undesirable Effects)**). 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 kinase, myoglobinuria (rhabdomyolysis) and acute renal failure. In such an event or with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs, including ZYPREXA should be discontinued.

Seizures

ZYPREXA 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 such patients when treated with ZYPREXA (see **4.8 Adverse effects (Undesirable Effects)**).

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. Discontinue olanzapine if DRESS is suspected.

Tardive dyskinesia

In comparator studies of one year or less duration, ZYPREXA was associated with a statistically significantly 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 ZYPREXA, a dose reduction or drug discontinuation should be considered. These symptoms can temporarily deteriorate or even arise after discontinuation of treatment.

Akathisia

The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move, and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular

attention should be paid to monitoring for such signs and symptoms as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

Cardiac

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

In clinical trials, ZYPREXA was not associated with a persistent increase in absolute QT intervals. Only 8 of 1,685 subjects had an increase in the corrected QT interval (QTc) on multiple occasions. As with other antipsychotics, caution should be exercised when ZYPREXA is prescribed with drugs known to increase QTc interval, especially in elderly patients.

Sudden cardiac death

In a retrospective observational study, patients treated with atypical antipsychotics (including olanzapine) or typical antipsychotics had a similar dose-related increase of presumed sudden cardiac death compared to non-users of antipsychotics, with almost twice the risk than that for non-users. In post-marketing reports with olanzapine, the event of sudden cardiac death has been reported very rarely.

Safety experience in elderly patients with dementia-related psychosis

In elderly patients with dementia-related psychosis, the efficacy of olanzapine has not been established. In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively). Risk factors that may predispose this patient population to increased mortality when treated with olanzapine include age >80 years, sedation, concomitant use of benzodiazepines, or presence of pulmonary conditions (eg, pneumonia, with or without aspiration).

Cerebrovascular adverse events (CVAE), including stroke, in elderly patients with dementia

Cerebrovascular adverse events (eg, stroke, transient ischaemic attack), including fatalities, were reported in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled studies, there was a higher incidence of CVAE in patients treated with olanzapine compared to patients treated with placebo (1.3% vs 0.4%, respectively). All patients who experienced a cerebrovascular event had pre-existing risk factors known to be associated with an increased risk for a CVAE (eg, history of previous CVAE or transient ischaemic attack, hypertension, cigarette smoking) and presented with concurrent medical conditions and/or concomitant medications having a temporal association with CVAE. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

There are insufficient data to determine if any differences exist in the incidence of cerebrovascular accidents and/or mortality between oral olanzapine and olanzapine for injection in elderly patients with dementia. In this patient population, the increased incidence of cerebrovascular accidents and/or mortality compared to placebo, and the risk factors identified for oral olanzapine, cannot be excluded for olanzapine for injection.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ZYPREXA for patients who will be experiencing conditions which may contribute to an elevation in core body

temperature, eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic drug use. ZYPREXA and other antipsychotic agents should be used cautiously in patients at risk for aspiration pneumonia.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany therapy. Prescriptions for olanzapine should be written for the smallest quantity possible, consistent with good patient management, in order to reduce the risk of overdose.

Sleep apnoea

Sleep apnoea and related disorders have been reported in patients treated with olanzapine, with or without prior history of sleep apnoea, and with or without concomitant weight-gain. Olanzapine should be used with caution in patients who have sleep apnoea or risk factors for developing sleep apnoea, and also in patients who are concomitantly using central nervous system depressants.

Use in hepatic impairment

Transient, asymptomatic elevations of hepatic transaminases, alanine transferase (ALT), aspartate transferase (AST) have been seen occasionally, especially in early treatment. Rare postmarketing reports of hepatitis have been received. Very rare cases of jaundice, cholestatic or mixed liver injury have also been reported in the postmarketing period (see **4.8 Adverse effects (Undesirable Effects)**). 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 drugs.

Use in the elderly

Caution should be used when ZYPREXA is administered to the elderly, especially if there are other factors that may influence drug metabolism and/or pharmacodynamic parameters.

Paediatric use

The safety and efficacy of ZYPREXA have not been established in patients under 18 years of age.

Effects on laboratory tests

No information is available on the effect of ZYPREXA on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Administration of intramuscular lorazepam (2 mg) one hour after intramuscular olanzapine (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this coadministration of intramuscular lorazepam and intramuscular olanzapine added to the somnolence observedwith either drug alone.

Simultaneous use of ZYPREXA IM and parenteral benzodiazepines is not recommended (see **4.4 Special warnings and precautions for use**).

Hypotension and/or bradycardia have been observed during intramuscular administration of ZYPREXA IM. Olanzapine has alpha-1 adrenergic antagonist activity. Caution should be exercised in patients who receive treatment with medicinal products that can lower blood pressure by mechanisms other than alpha-1 adrenergic antagonism.

Given the primary central nervous system effects of ZYPREXA, caution should be used when it is taken in combination with other centrally acting drugs and alcohol. As it exhibits *in vitro* dopamine antagonism, ZYPREXA may antagonise the effects of direct and indirect dopamine agonists.

Caution should be exercised when ZYPREXA is used concomitantly with medicines known to cause electrolyte imbalance or to increase QT interval (see **4.4 Special warnings and precautions for use, Cardiac**).

Potential for other medicines to affect ZYPREXA

Single-doses of antacids (containing aluminium and magnesium) or cimetidine do not affect the oral bioavailability of ZYPREXA. The concomitant administration of activated charcoal reduces the oral bioavailability of ZYPREXA by 50% to 60%.

Fluoxetine (60-mg single dose or 60 mg daily for 8 days) caused a 16% increase in the maximum plasma concentration of olanzapine and a 16% decrease in olanzapine clearance. The magnitude of this is small in comparison to the overall variability between individuals and therefore dose modification is not routinely recommended.

The metabolism of ZYPREXA may be induced by concomitant smoking (the clearance of ZYPREXA is 33% lower and the terminal elimination half-life is 21% longer in non-smokers compared to smokers) or carbamazepine therapy (clearance is increased 44% and the terminal elimination half-life is reduced by 20% when administered with carbamazepine). Smoking and carbamazepine therapy induce P450-1A2 activity. The pharmacokinetics of theophylline, which is metabolised by P450-1A2, is not altered by ZYPREXA.

Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine C_{max} following fluvoxamine of 54% in female non-smokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine or any other P450-1A2 inhibitor, such as ciprofloxacin.

Potential for ZYPREXA to affect other medicines

In clinical trials with single doses of ZYPREXA, no inhibition of the metabolism of imipramine/desipramine (P450-2D6, P450-3A or P450-1A2), warfarin (P450-2C19), theophylline (P450-1A2) or diazepam (P450-3A4 and P450-2C19) was evident. ZYPREXA showed no interaction when coadministered with lithium or biperiden. The *in vitro* ability of ZYPREXA to inhibit metabolism by five principle cytochromes has been examined. These studies found inhibitory constants for 3A4 (491 mcM), 2C9 (751 mcM), 1A2 (36 mcM), 2C19 (920 mcM), 2D6 (89 mcM) that compared to ZYPREXA plasma concentrations of approximately 0.2 mcM, would mean maximum inhibition of these P450 systems by ZYPREXA would be less than 0.7%. The clinical relevance of these findings is unknown.

Steady state concentrations of olanzapine had no effect on the pharmacokinetics of ethanol (45 mg/70 kg). However, additive pharmacological effects such as increased sedation may occur when ethanol is ingested together with olanzapine.

Studies *in vitro* using human liver microsomes showed that olanzapine has little potential to inhibit the major metabolic pathway of valproate, which is glucuronidation. Further, valproate was found to have little effect on the oxidative metabolism of olanzapine *in vitro*. Daily concomitant *in vivo* administration of 10 mg olanzapine for 2 weeks did not affect steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In male rats dosed orally with olanzapine at 22.5 mg/kg/day, mating performance was impaired as a result of the drug's sedative activity, but fertility was normal 10 days after stopping treatment. In male dogs, hypospermatogenesis was seen at oral doses greater than 5 mg/kg/day. In female rats, oestrous cycles were disrupted at oral doses greater than 0.25 mg/kg/day and fertility was impaired at dose levels greater than 1 mg/kg/day.

Use in pregnancy

Category C. 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 ZYPREXA.

Neonates exposed to antipsychotic drugs (including ZYPREXA) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required additional medical treatment or monitoring.

ZYPREXA should be used during pregnancy only if the anticipated benefit outweighs the risk, and the administered dose and duration of treatment should be as low and as short as possible.

Olanzapine had no teratogenic effects in rats or rabbits at oral dose levels up to 18 and 30 mg/kg/day, respectively. However, resorptions were increased in rats at oral doses greater than 4 mg/kg/day. Foetal weight was decreased in both species at oral doses greater than 1 and 8 mg/kg/day, respectively, and foetal development was retarded in rats at doses greater than 4 mg/kg/day. Oral administration of olanzapine to pregnant rats resulted in prolonged gestation and an increased incidence of stillbirths at doses greater than 5 mg/kg/day. Oral administration of olanzapine to rats prior to mating and throughout mating, gestation and lactation was associated with transient decreases in offspring activity levels at doses of 0.25 mg/kg/day or greater.

Labour and delivery

In rats, oral administration of olanzapine to pregnant rats resulted in prolonged gestation and an increased incidence of stillbirths at doses greater than 5 mg/kg/day.

Use in lactation

In a study in lactating, 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 if they are receiving ZYPREXA.

Hyperprolactinaemia

When prescribing ZYPREXA, there is the possibility of secondary amenorrhoea and hypoestrogenism arising from treatment (see **4.8 Adverse effects (Undesirable Effects)**). Premenopausal women should be questioned regarding menstrual irregularities and those who experience secondary amenorrhoea for longer than six months duration while taking ZYPREXA, should be appropriately investigated and offered appropriate therapy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be cautioned about operating hazardous machinery, including motor vehicles because ZYPREXA may cause somnolence.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Additional adverse events identified from clinical trials with ZYPREXA IM rather than oral ZYPREXA were as follows:

Cardiovascular system – Common (≥1% and <10%): hypotension; bradycardia with or without hypotension or syncope; tachycardia.

The adverse events listed below have been observed following administration of oral ZYPREXA, but may also occur following administration of ZYPREXA IM.

Adverse events identified from clinical trials with oral olanzapine

Body as a whole – Very common (≥10%): weight gain, weight gain ≥7% baseline body weight. Common (≥1% and <10%): asthenia, fatigue, weight gain ≥15% of baseline body weight, pyrexia. Uncommon (≥0.1% and <1%): photosensitivity reaction.

Weight – In an analysis of 13 placebo-controlled olanzapine monotherapy studies, ZYPREXA-treated patients gained an average of 2.6 kg compared to an average 0.3 kg weight loss in placebo-treated patients with a median exposure of 6 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of ZYPREXA-treated patients and 0% of placebo-treated patients.

In long-term studies (at least 48 weeks) the mean weight gain was 5.6 kg. Both the magnitude of weight gain and the proportion of ZYPREXA-treated patients who had a clinically significant weight gain were greater than in the short term studies. Gain of ≥25% of baseline body weight was very common with long term exposure to ZYPREXA. Discontinuation due to weight gain occurred in 0.4% of ZYPREXA-treated patients following at least 48 weeks of exposure.

Cardiovascular system – Very Common (≥10%): orthostatic hypotension. Uncommon (≥0.1% and <1%): bradycardia.

Digestive system – Common (≥1% and <10%): constipation; dry mouth; increased appetite. Uncommon (≥0.1% and <1%): abdominal distension.

Metabolic – Common (≥1% and <10%): peripheral oedema. Rare (<0.1% and ≥0.01%): elevated creatine kinase levels.

Musculoskeletal system – Common (≥1% and <10%): arthralgia.

Nervous system – Very common (≥10%): somnolence. Common (≥1% and <10%): dizziness; akathisia. Uncommon (≥0.1% and <1%): amnesia; Restless Legs Syndrome.

In active-controlled studies, ZYPREXA-treated patients had a lower incidence of Parkinsonism, akathisia, dyskinesia 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 cannot be concluded at present that ZYPREXA produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

Clinical chemistry - Very common (≥10%): prolactin-increased, cholesterol-total (fasting borderline to high), triglycerides (fasting borderline to high), glucose (fasting borderline to high). Common (≥1% and <10%): alanine transferase (ALT)-increased; aspartate transferase (AST)-increased, cholesterol-total (fasting normal to high), triglycerides (fasting normal to high), glucose (fasting normal to high), glycosuria , alkaline phosphatase increased, gamma glutamyl transferase (GGT) high, uric acid high.

Glucose – In adult clinical trials (up to 52 weeks) ZYPREXA was associated with a greater mean increase in both non-fasting and fasting blood glucose concentrations than placebo. In patients with baseline glucose dysregulation (including those with diabetes mellitus or who met criteria suggestive of hyperglycaemia) the mean increase in the non-fasting blood glucose concentration was significantly greater in those treated with ZYPREXA compared to placebo. A smaller between-treatment difference was also seen in fasting blood glucose concentrations in patients with baseline glucose dysregulation. ZYPREXA was also associated with a greater increase in HbA1c concentration than placebo in patients with baseline glucose dysregulation.

The proportion of patients who had a change in glucose level from normal or borderline at baseline to high increased over time. In patients who had at least 48 weeks exposure to olanzapine, 12.8% of patients who had normal baseline fasting glucose levels experienced high glucose levels at least once. For patients with borderline baseline fasting glucose levels, 26.0% experienced high glucose levels at least once. In an analysis of patients who completed 9 to 12 months of ZYPREXA therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Hepatic Transaminases – Transient, asymptomatic elevations of hepatic transaminases, ALT and AST, have been seen occasionally.

Lipids –In an analysis of five placebo-controlled clinical trials of up to 12 weeks in duration, ZYPREXA-treated adult patients had a greater mean increase in fasting total cholesterol, LDL cholesterol, and triglycerides compared to placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline. For fasting HDL cholesterol, no statistically significant differences were observed between ZYPREXA-treated patients and placebo-treated patients.

The proportion of patients who had changes in total cholesterol, LDL cholesterol or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal

or borderline to low, was greater in long term studies (at least 48 weeks) than in short term studies. In long term studies the proportion of patients who had normal or borderline baseline levels of fasting triglycerides and experienced high levels was 32.4% and 70.7%, respectively. In long term studies the proportion of patients who had normal or borderline baseline levels of fasting total cholesterol and experienced high levels was 14.8% and 55.2%, respectively. In long term studies the proportion of patients who had normal or borderline baseline levels of fasting LDL cholesterol and experienced high levels was 7.3% and 31.0%, respectively. In an analysis of patients who completed 12 months of therapy, the mean non-fasting total cholesterol did not increase further after approximately 4 to 6 months.

Prolactin – In clinical trials of olanzapine in schizophrenia and other psychiatric indications of up to 12 weeks duration, plasma prolactin levels were elevated from normal at baseline to high in approximately 30% of olanzapine-treated patients compared with 10.5% of placebo-treated patients. In the majority of patients these elevations were mild. Across all indications, potentially associated clinical manifestations included sexual function-related events such as erectile dysfunction in males and decreased libido in both genders (commonly observed), menstrual-related events such as amenorrhoea (uncommonly observed), and breast-related events such as breast enlargement and galactorrhoea in females and gynaecomastia and breast enlargement in males (uncommonly observed).

Haematology – Common (≥1% and <10%): eosinophilia; leucopenia including neutropenia.

Eosinophilia – Asymptomatic eosinophilia was occasionally seen.

Respiratory – Uncommon (≥0.1% and <1%): epistaxis.

Undesirable effects for special populations

Undesirable effects associated with the use of olanzapine in clinical trials with elderly patients with dementia-related psychosis:

Body as a whole – Very common (≥10%): falls.

Nervous system – Very common (≥10%): abnormal gait.

Urogenital system – Common (≥1% and <10%): urinary incontinence.

Respiratory system – Common (≥1% and <10%): pneumonia.

Undesirable effects associated with the use of olanzapine in clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease:

Nervous system – Very common (≥10%): Hallucinations and worsening of Parkinsonian symptomatology. In these trials, patients were required to be stable on the lowest effective dose of anti-Parkinsonian medications (dopamine agonist) prior to the beginning of the study and to remain on the same anti-Parkinsonian medications and dosages throughout the study. Olanzapine was started at 2.5 mg/day and titrated up to a maximum of 15 mg/day based on investigator judgement.

In clinical trials in patients with bipolar mania, 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 (1% to 10%).

Adolescents (ages 13 to 17 years)

The types of undesirable effects observed in adolescent patients treated with olanzapine were similar to those seen in adult patients. Although no clinical trials designed to compare adolescents to adults were conducted, the data from the adolescent trials were compared to those of the adult trials.

Mean increases in weight in adolescents (4.6 kg over 3 weeks' median duration of exposure) were greater than in adults (2.6 kg over 7 weeks' median duration of exposure). In four placebo-controlled trials, discontinuation due to weight gain occurred in 1% of ZYPREXA-treated adolescent patients compared to 0% of placebo-treated adolescent patients.

In long term studies (at least 24 weeks), both the magnitude of weight gain and the proportion of adolescent patients treated with ZYPREXA who had clinically significant weight gain were greater than in short term studies, and were greater than in adult patients with comparable exposure. The mean weight gain in adolescent patients in long term studies was 11.2 kg. With long term exposure, approximately half of adolescent patients gained ≥15% and almost a third gained ≥25% of their baseline body weight. Among adolescent patients, mean weight gain was greatest in patients who were overweight or obese at baseline. Discontinuation due to weight gain occurred in 2.2% of ZYPREXA-treated adolescent patients following at least 24 weeks of exposure.

Increases in fasting glucose were similar in adolescents and adults treated with ZYPREXA, however the difference between ZYPREXA and placebo groups was greater in adolescents compared to adults.

In long term studies (at least 24 weeks), changes in fasting glucose from normal at baseline to high in adolescents were uncommon. Changes from borderline at baseline to high were very common.

Increases in fasting total cholesterol, LDL cholesterol, and triglycerides were generally greater in adolescents than in adults treated with ZYPREXA. However, in short term studies the differences between ZYPREXA and placebo were similar for adolescents and adults.

Adolescents treated with olanzapine experienced a significantly higher incidence of elevated prolactin levels and significantly higher mean increases in prolactin levels compared with adults. In adolescents elevated plasma prolactin levels were reported in approximately 47% of olanzapine-treated patients and 7% of placebo-treated patients.

The information below summarises core adverse drug reaction terms and their frequencies identified only during clinical trials in adolescent patients (ages 13 to 17 years). Actual percentages are provided for aggregate data from up to four separate studies of olanzapine in adolescent patients:

Body as a whole – Very common (≥10%): weight gain ≥7% of baseline body weight – 40.6%. Common (≥1% and <10%): weight gain ≥15% of baseline body weight – 7.1%.

Digestive system – Very common (≥10%): increased appetite – 24.0%. Common (≥1% and <10%): dry mouth – 6.1%.

Nervous system – Very common (≥10%): sedation (including hypersomnia, lethargy, sedation, somnolence) – 44.1%.

Clinical chemistry – Very common (≥10%): ALT >3 x ULN (all randomised patients with ALT baseline ≤3 x ULN) – 12.1%, AST-increased – 27.6%, total bilirubin-decreased – 22.1%, GGT-increased – 10.1%, prolactin increased – 47.4%, cholesterol-total (fasting borderline to high) – 38.9%, triglycerides (fasting normal to high) – 26.9%, triglycerides (fasting borderline to high) – 59.5%, glucose (fasting borderline to high) – 14.3%. Common (≥1% and <10%): cholesterol-total (fasting normal to high) – 6.9%. Very rare (<0.01%): glucose (fasting normal to high).

Adverse events based on post marketing spontaneous reports with oral olanzapine

Body as a whole – Very rare (<0.01%): allergic reaction (eg, anaphylactoid reaction, angioedema, pruritus or urticaria); discontinuation reaction (acute symptoms such as sweating, insomnia, tremor, anxiety, nausea or vomiting have been reported very rarely when ZYPREXA is stopped suddenly).

Digestive system – Very rare (<0.01%): pancreatitis.

Hepatobiliary disorders – Rare (<0.1% and ≥0.01%): hepatitis. Very rare (<0.01%): jaundice.

Metabolic – Rare (<0.1% and ≥0.01%): hyperglycaemia. Very rare (<0.01%): diabetic coma; diabetic ketoacidosis; exacerbation of pre-existing diabetes; hypertriglyceridemia (random triglyceride levels of ≥11.29 mmol/L); hypercholesterolaemia (random cholesterol levels of ≥6.21 mmol/L).

Nervous system – Uncommon (<1% and ≥0.1%): stuttering. Rare (<0.1% and ≥0.01%): seizures. Very rare (<0.01%): neuroleptic malignant syndrome.

Skin and appendages – Rare (<0.1% and ≥0.01%): rash. Very rare (<0.01%): alopecia, Drug Reaction with Eosinophilia and Systemic Symptom (DRESS).

Urogenital system – Very rare (<0.01%): priapism; urinary hesitation, urinary retention, urinary incontinence.

Haematology – Very rare (<0.01%): thrombocytopenia.

Cardiovascular – Very rare (<0.01%): venous thromboembolism, including pulmonary embolism and deep vein thrombosis.

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported very rarely with the use of neuroleptics and may be considered a class effect.

Musculoskeletal system – Very rare (<0.01%): rhabdomyolysis.

Clinical chemistry – Very rare (<0.01%): total bilirubin increased, creatine kinase increased.

Adverse events based on post marketing spontaneous reports with olanzapine

Digestive system – Uncommon (<1% and ≥0.1%): salivary hypersecretion.

Respiratory - Sleep apnoea syndrome. A causal association between olanzapine and sleep apnoea syndrome is suspected but has not been definitively established.

Psychiatric disorders – Somnambulism (sleepwalking) and sleep-related eating disorder have been reported with the use of atypical antipsychotic medicines, including olanzapine.

Frequency: Not known

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs of oral toxicity in rodents were characteristic of potent neuroleptic compounds: hypoactivity, coma, tremors, clonic convulsions and salivation. In dogs, olanzapine caused sedation, ataxia, tremors, tachycardia, laboured respiration, miosis and anorexia. In monkeys, prostration and semi-consciousness were observed.

Signs and symptoms

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

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

Management of overdose

There is no specific antidote to ZYPREXA. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated. The possibility of multiple drug involvement should be considered.

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. The use of activated charcoal for overdose should be considered because the concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50% to 60%. In patients who are not fully conscious or who have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Olanzapine is not substantially removed by haemodialysis.

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. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents such as noradrenaline. Adrenaline, dopamine or other sympathomimetic agents should not be used since beta stimulation may worsen hypotension in the setting of alpha blockade induced by ZYPREXA. Cardiovascular monitoring should be considered to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

Contact the Poisons Information Centre in Australia (telephone 13 11 26) or the National Poisons Centre in New Zealand (telephone 0800 POISON or 0800 764 766) for advice on management of overdose with ZYPREXA.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki; <100 nmol) for serotonin $5HT_{2A/2C}$, $5HT_3$, $5HT_6$; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors m_1-m_5; α_1 adrenergic; and histamine H_1 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 $5HT_2$ than dopamine D_2 receptors and in *in-vivo* models, greater $5HT_2$ than D_2 activity. 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 increased responding in an 'anxiolytic' test.

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

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

Clinical trials

Schizophrenia and related disorders

The efficacy of ZYPREXA in the reduction of and maintenance of the reduction of the manifestations of schizophrenia and related psychotic disorders was established in 3 well-controlled clinical trials of psychotic inpatients who, at entry met the DSM-III-R criteria for schizophrenia (most with a course at entry of "chronic with acute exacerbation") and 1 well-controlled clinical trial of psychotic inpatients and outpatients who, at entry, met the DSM-III-R criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. The age range of patients in these pivotal efficacy studies were 18 to 86 years. The results of the trials follow:

1. A 6-week, placebo-controlled trial (n=335) compared 3 fixed dosage ranges of ZYPREXA [5 ± 2.5, 10 ± 2.5 and 15 ± 2.5 mg/day (once daily)], 1 dosage range of haloperidol (15 ± 5 mg/day BID) and placebo. The 2 higher dosage ranges of ZYPREXA

were statistically significantly superior to placebo on the Brief Psychiatric Rating Scale (BPRS) total, the Clinical Global Impressions - Severity of Illness (CGI-S) scale, and the BPRS positive psychosis cluster. The highest dosage range of ZYPREXA was statistically significantly superior to placebo and to haloperidol on the Scale for the Assessment of Negative Symptoms (SANS). Efficacy of ZYPREXA generally increased with dose.

2. A 6-week, placebo-controlled trial (n=152) compared 2 fixed doses of ZYPREXA [1 or 10 mg/day (once daily)] and placebo. ZYPREXA, 10 mg/day, was statistically significantly superior to placebo on the BPRS total, the BPRS positive psychosis cluster, the CGI-S scale, the Positive and Negative Syndrome Scale (PANSS) total, the PANSS positive subscale and the PANSS negative subscale.

3. A 6-week, dose comparison trial (n=431) compared 3 fixed dosage ranges of ZYPREXA (5 ± 2.5, 10 ± 2.5 and 15 ± 2.5 mg/day (once daily)], ZYPREXA [1 mg/day (once daily)] and haloperidol (15 ± 5 mg/day BD). There were no statistically significant differences between groups on efficacy measures except for the highest dosage range of ZYPREXA, which was statistically significantly superior to ZYPREXA, 1 mg, on the BPRS positive psychosis cluster, PANSS positive subscale and the CGI-S scale.

4. A 6-week comparator-controlled trial (n=1,996, 2:1 randomisation, ZYPREXA:haloperidol) compared 1 dosage range of ZYPREXA [5 to 20 mg/day (once daily)] and 1 dosage range of haloperidol [5 to 20 mg/day (once daily)]. The acute mean maintenance modal doses (for those patients with at least 3 weeks of treatment) were 13.2 mg/day for ZYPREXA and 11.8 mg/day for haloperidol. ZYPREXA was statistically significantly superior to haloperidol on the BPRS total, the BPRS negative psychosis cluster, the PANSS negative subscale and the CGI-S scale. ZYPREXA was also statistically significantly superior to haloperidol on the Montgomery-Asberg Depression Rating Scale (MADRS).

5. The effectiveness of ZYPREXA in long-term therapy, ie, >6 weeks, was evaluated in 3 double-blind, controlled extension maintenance trials (of acute trials 1, 3 and 4 above). Patients who showed adequate clinical improvement following double-blind acute therapy were allowed to continue on their acute dosage regime in a double-blind, long-term extension maintenance phase. Long-term maintenance of response (ie, continued reduction in signs and symptoms sufficient to not require hospitalisation for psychosis) was compared over time and the percentage of patients completing one year of treatment was compared. ZYPREXA was statistically significantly superior to placebo in the one placebo-controlled trial and was comparable or statistically significantly superior to haloperidol in 3 active comparator-controlled trials.

The above trials (including open-label extension) and an additional trial comprising geriatric patients with primary degenerative dementia of the Alzheimer's type constitute the integrated primary database (n=2500 patients treated with ZYPREXA, corresponding to 1,122.2 patient-years; n=810 patients treated with haloperidol, corresponding to 193.0 patient-years; n=236 patients treated with placebo, corresponding to 27.1 patient-years).

Acute mania associated with bipolar disorder

The efficacy of olanzapine in the treatment of acute manic episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials and one 6-week

comparator-controlled trial, comparing olanzapine to placebo when each was added to lithium or valproate, in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid cycling course.

Several instruments were used for assessing manic symptoms in these trials. The Young Mania Rating Scale (Y-MRS) is an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). A second assessment, the Clinical Global Impression-Bipolar Version (CGI-BP), reflects the clinician's impression of the severity of the patient's mania and overall bipolar illness in a range from 1 (normal, not ill) to 7 (very severely ill). Additional secondary assessments in the comparator-controlled trial included the Positive and Negative Symptom Scale (PANSS) (total, positive and negative) and the Hamilton Depression Rating Scale-21 (HAMD-21). The results of the trials follow:

1. In a 3-week placebo controlled trial (n=139) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score, the PANSS total score, the PANSS positive subscale and the CGI-BP severity of mania score.

2. In a 4 week placebo controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score, the PANSS total score, the PANSS positive subscale, the CGI-BP severity of mania score and the CGI-BP severity of overall bipolar illness score.

3. In a 6-week co-therapy study (n=344) of patients treated with lithium or valproate for a minimum of 2 weeks, the addition of olanzapine 10 mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania (Y-MRS total score) than lithium or valproate monotherapy after 6 weeks.
   In patients with a manic or mixed episode of bipolar disorder, olanzapine demonstrated superior efficacy to valproate semisodium (divalproex) in reduction of manic symptoms over 3 weeks.

Preventing recurrence in bipolar disorder

In a 12-month recurrence prevention study, patients (n=361), who met DSM-IV criteria for Bipolar I Disorder and who were in symptomatic remission following a 6- to 12-week period of olanzapine treatment, were randomised to continuation of their current olanzapine doses (ranging from 5 to 20 mg) or placebo for up to 12 months. Olanzapine demonstrated statistically significant superiority over placebo in delaying time to symptomatic bipolar recurrence (174 days until 50% of olanzapine patients experienced recurrence vs 22 days for placebo). Olanzapine also showed a statistically significant advantage over placebo in terms of either recurrence into mania or recurrence into depression, although a greater advantage was seen in preventing recurrence into mania. The criteria for recurrence were hospitalisation for relapse or worsening in total scores of Young Mania Rating Scale (Y-MRS) or Hamilton Psychiatric Rating Scale for Depression-21 Items (HAMD-21). In a second 12-month recurrence prevention study in manic episode patients stabilised with a combination of olanzapine and lithium and then randomised to olanzapine or lithium alone, olanzapine was numerically but not statistically superior to lithium in rate of symptomatic bipolar recurrence (30.0% vs 38.8%, respectively; p=0.055). Olanzapine showed a statistically significant advantage over lithium on recurrence into mania and was not statistically significantly different from lithium on recurrence into depression.

In an 18-month co-therapy recurrence prevention study in manic episode patients stabilised with olanzapine plus mood stabilisers (lithium or valproate), olanzapine co-therapy was numerically but not statistically superior to mood stabiliser alone in delaying time to syndromic bipolar recurrence (119 days until 25% of olanzapine patients experienced recurrence vs 29 days for placebo). The incidence of recurrence of mania was statistically significantly less for olanzapine co-therapy than for patients receiving placebo plus mood stabiliser.

Agitation and disturbed behaviour in schizophrenia and related psychoses, in acute mania associated with bipolar I disorder

The efficacy of intramuscular olanzapine for injection for the rapid control of agitation was established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated inpatients with schizophrenia, schizophreniform disorder, schizoaffective disorder or Bipolar I Disorder (manic or mixed episodes).

The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component (PANSS-EC) at 2 hours post-injection. The PANSS-EC consists of 5 items which rate poor impulse control, tension, hostility, uncooperativeness and excitement. Several additional efficacy measures including the Agitation Calmness Evaluation Scale (ACES) and the Corrigan Agitated Behaviour Scale (CABS; used in schizophrenia and bipolar mania studies only) were also utilised. Patients could receive up to three injections during the 24-hour IM treatment periods; however, patients could not receive the second injection until after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

1. In a placebo controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder, 270 patients were randomised to olanzapine IM at doses of 2.5 mg, 5 mg, 7.5 mg, 10 mg or haloperidol 7.5 mg IM or placebo IM.
   As defined *a priori* in the protocol, patients with a reduction of ≥40% in the PANSS-EC at 2-hours post first IM injection compared to baseline were classified as responders. Numerically, the number and percentage of responders increased with increasing doses of olanzapine, ranging from 50.0% responders in the IM olanzapine 2.5 mg treatment group to 80.4% responders in the IM olanzapine 10 mg treatment group. In the IM haloperidol 7.5 mg and IM placebo treatment groups, 60.0% and 20.0%, respectively, were responders.
   From the pairwise comparisons, statistically significantly greater response rates were observed in each IM olanzapine treatment group compared with IM placebo ($p=0.004$ for the IM olanzapine 2.5 mg treatment group and $p<0.001$ for the 5, 7.5 and 10 mg IM olanzapine treatment groups). The IM olanzapine 7.5 and 10 mg treatment groups also demonstrated significantly greater response rates compared with the IM olanzapine 2.5 mg treatment group ($p=0.021$ and $p=0.002$, respectively). There were no statistically significant differences between the IM haloperidol 7.5 mg treatment group and any of the IM olanzapine treatment groups, although a trend toward significance was observed in favour of the IM olanzapine 10 mg treatment group ($p=0.056$).

2. In a second placebo controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder, 311 patients were randomised to olanzapine 10 mg IM, haloperidol 7.5 mg IM or placebo IM. The 24-hour IM period was followed by a 4 day treatment period in which patients who had received either olanzapine IM or placebo were treated with oral olanzapine

5-20 mg/day, while patients who had received haloperidol IM were treated with oral haloperidol 5-20 mg/day.
As defined *a priori* in the protocol, patients with a reduction of ≥40% in the PANSS-EC at 2 hours post first IM injection compared to baseline were classified as responders. Ninety-six (73.3%) IM olanzapine-treated patients were responders compared to 87 (69.0%) IM haloperidol-treated patients and 18 (33.3%) IM placebo-treated patients. Using a Fisher's exact test, both the IM olanzapine and IM haloperidol treatment groups demonstrated significantly greater response rates compared with the IM placebo treatment group ($p<0.001$ in both cases), but did not differentiate between themselves ($p=0.492$).

3. In a placebo controlled trial in agitated inpatients meeting DSM-IV criteria for Bipolar I Disorder (and currently displaying an acute manic or mixed episode with or without psychotic features), 201 patients were randomised to olanzapine 10 mg IM, lorazepam 2 mg IM or placebo IM.
As defined *a priori* in the protocol, patients with a reduction of ≥40% in the PANSS-EC at 2 hours post first IM injection compared to baseline were classified as responders. There were 79 (80.6%) IM olanzapine-treated patients classified as responders compared to 33 (64.7%) IM lorazepam-treated patients and 22 (44.0%) IM placebo-treated patients. Using a Fisher's exact test, both the IM olanzapine and IM lorazepam treatment groups demonstrated significantly greater response rates compared with the IM placebo treatment group ($p<0.001$ and $p=0.046$, respectively). The IM olanzapine treatment group also showed a significantly greater response rate compared with the IM lorazepam treatment group ($p=0.045$).

5.2 PHARMACOKINETIC PROPERTIES

ZYPREXA IM results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. The Cmax occurs earlier after intramuscular use compared to oral use (15 to 45 minutes versus 5 to 8 hours). Based upon a pharmacokinetic study in healthy subjects, a 5 mg intramuscular dose of olanzapine for injection produces, on average, a maximum plasma concentration which is approximately 5 times higher than the maximum plasma concentration produced by a 5 mg oral dose. The area under the olanzapine plasma concentration time curve attained after intramuscular injection is essentially equivalent to the area under the curve achieved when the same amount is administered orally. A crossover study in healthy subjects comparing 5 mg IM and 5 mg oral olanzapine showed that the geometric mean AUC IM/oral ratio was 1.23 with a 90% confidence interval of 1.15 to 1.31. These results provide an estimate that the AUC for the IM product is on average about 23% larger than the AUC produced by the same amount of olanzapine administered orally, a difference which does not require dose adjustments. As with oral use, Cmax and area under the curve after intramuscular use are directly proportional to the dose administered. For the same dose of olanzapine administered intramuscularly and orally, the half-life, clearance and volume of distribution are very similar. After IM administration, olanzapine exhibits linear pharmacokinetics over the dose range of 0.1 to 12.5 mg. Metabolic profiles after intramuscular administration are quantitatively similar and qualitatively identical to metabolic profiles after oral administration.

Table 2. Mean and range of olanzapine pharmacokinetic variables for a single dose of olanzapine as 10 mg orally versus 10 mg intramuscularly administered as two 5 mg doses 4 hours apart.

Pharmacokinetic Variable		Orally Administered Olanzapine 10 mg		Intramuscularly Administered Olanzapine 2x5 mg 4 hrs Apart	
	(units)	Mean	(range)	Mean	(range)
C_{max}	(ng/mL)	15.1	(6.6 to 22.4)	23.7[a]	(13.1 to 43.2)[a]
$AUC_{0-\infty}$	(hr)	499	(287 to 838)	522	(353 to 792)
CLp	(L/hr)	22.1	(11.9 to 34.8)	20.2	(12.6 to 28.3)
$t_{1/2}$	(hr)	31.0	(20.0 to 44.2)	30.4	(20.4 to 39.1)

[a] The C_{max} values in this table for olanzapine IM cannot be directly compared to those for the 10 mg oral dose. The IM dose was divided into two 5 mg doses 4 hours apart and the C_{max} values generally reflect the second IM 5 mg dose.

Additional pharmacokinetic data following administration of oral olanzapine are described below.

Absorption

Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. Absorption is not affected by food. Plasma concentrations of olanzapine after oral administration were linear and dose proportional in trials studying doses from 1 to 20 mg.

Distribution

The plasma protein binding of olanzapine is about 93% over the concentration range of about 7 to about 1,000 ng/mL. Olanzapine is bound to albumin and α1 acid glycoprotein.

Metabolism

Olanzapine is metabolised in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxy-methyl metabolites, both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine.

Excretion

After oral administration to healthy subjects, the mean terminal elimination half-life was 33 hours (21 to 54 hours for 5th to 95th percentile) and the mean olanzapine plasma clearance was 26 L/hr (12 to 47 L/hr for the 5th to 95th percentile). Olanzapine pharmacokinetics varied on the basis of smoking status, gender and age.

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

In female versus male subjects, the mean elimination half-life was somewhat prolonged (36.7 hr vs 32.3 hr) and the clearance was reduced (18.9 L/hr vs 27.3 L/hr). However,

ZYPREXA (5-20 mg) demonstrated a comparable safety profile in female (n=467) as in male patients (n=869).

Smoking induces the CYP1A2 metabolism of olanzapine. Therefore, in smokers the clearance of olanzapine is higher, on average, than the clearance in non-smokers.

The plasma clearance of olanzapine is lower in elderly versus non-elderly subjects and in females versus males. 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.Approximately 57% of radiolabelled olanzapine is excreted in urine, principally as metabolites, approximately 7% is excreted unchanged in the urine after a single oral dose and approximately 30% is excreted in the faeces.

Renal impairment

Only incomplete information is available on excretion in renal-impaired patients (creatinine clearance <10 mL/min) versus healthy subjects, suggesting there was no significant difference in mean elimination half-life (37.7 hr vs 32.4 hr) or drug clearance (21.2 L/hr vs 25.0 L/hr). The available data indicate a trend for decreased clearance and increased half-life with renal-impairment. Consequently, caution should be exercised in prescribing olanzapine for patients with renal impairment and particularly in those with severe renal disease and in the elderly. Olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic impairment

Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in male subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine in the dose range 2.5 to 7.5 mg daily. Consequently, dosage adjustment may not be necessary if hepatic impairment is the sole consideration.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Olanzapine was not mutagenic or clastogenic in a full range of standard tests, which included bacterial mutation tests and *in vitro* and *in vivo* tests, indicating that it is not a genotoxic carcinogen.

Carcinogenicity

Carcinogenicity studies in mice and rats showed the development of mammary adenocarcinomas at oral doses greater than 0.5 and 0.1 mg/kg/day respectively.

The increased incidence of mammary tumours may be due to an endocrine mechanism, possibly involving elevation of circulating prolactin levels in response to the dopamine D_2 receptor antagonistic activity of olanzapine. Mammary tumours are known to occur in rats and mice treated with other drugs that antagonise dopamine D_2 receptors. Neither clinical studies nor epidemiological studies, conducted to date, have shown an association between these drugs and carcinogenesis, but the available evidence is considered too limited to be conclusive at this time. The use of ZYPREXA in patients with familial history or previously detected breast cancer should be avoided. Caution should also be exercised when considering ZYPREXA treatment in patients with pituitary tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

For full list of excipients, see **2 Qualitative and Quantitative Composition.**

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Solution following reconstitution of the vial can be stored for 1 hour. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

ZYPREXA IM 10 mg is available in a Type 1 glass flint vial. One carton contains 1 vial or 10 vials.

(Cartons containing 10 vials are not marketed in Australia or New Zealand).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

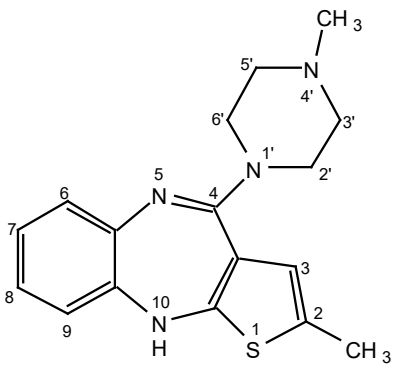
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Chemically, olanzapine is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thienol[2,3-*b*] [1,5]benzodiazepine and its empirical formula is $C_{17}H_{20}N_4S$. Olanzapine is a yellow crystalline solid, practically insoluble in water with a molecular weight of 312.44.

Olanzapine has the following structural formula:



CAS number

The CAS number for olanzapine is 132539-06-1.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription only Medicine

8. SPONSOR

Pharmaco (Australia) Ltd
Level 9, Tower A
Zenith Towers
821 Pacific Highway
Chatswood, NSW 2067
Australia

Phone: 1800 201 564

Under license of CHEPLAPHARM Schweiz GmbH, Switzerland

9. DATE OF FIRST APPROVAL

12 July 2001

10. DATE OF REVISION

06 February 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Sponsor update