

AUSTRALIAN PRODUCT INFORMATION

ZYPREXA RELPREVV (OLANZAPINE PAMOATE MONOHYDRATE) POWDER FOR INJECTION

WARNING: The potential for signs and symptoms of sedation and/or delirium consistent with olanzapine overdose exists after every injection of ZYPREXA RELPREVV. ZYPREXA RELPREVV should be administered by appropriately qualified health professionals in a healthcare facility with access to emergency services for management of olanzapine overdose. Healthcare professionals who prescribe or administer ZYPREXA RELPREVV should be aware of this potential risk and the consequent need to monitor patients for at least two hours after each injection. The two hour period should be extended as clinically appropriate for patients who exhibit any potential signs or symptoms of a post-injection syndrome event. See **4.4 Special warnings and precautions for use, Post-injection syndrome**.

1. NAME OF THE MEDICINE

ZYPREXA RELPREVV® (olanzapine pamoate monohydrate – alternatively named olanzapine embonate monohydrate).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Olanzapine pamoate monohydrate, equivalent to olanzapine 210 mg.

Olanzapine pamoate monohydrate, equivalent to olanzapine 300 mg.

Olanzapine pamoate monohydrate, equivalent to olanzapine 405 mg.

For the full list of excipients, see **6.1 List of excipients**.

3. PHARMACEUTICAL FORM

ZYPREXA RELPREVV 210 mg, 300 mg and 405 mg is available in a Type I cerium oxide vial. One carton provides a kit containing 1 vial of olanzapine pamoate monohydrate, one vial of sterile diluent, one 3 mL syringe with pre-attached 19-gauge 38 mm Hypodermic Needle-Pro® safety needle, one 19-gauge 38 mm Hypodermic Needle-Pro® safety needle and two 19-gauge 50 mm Hypodermic Needle-Pro® safety needles.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZYPREXA RELPREVV is a long-acting injectable formulation of olanzapine indicated for maintenance treatment of schizophrenia in adult patients sufficiently stabilised during acute treatment with oral olanzapine.

The effectiveness of ZYPREXA RELPREVV is consistent with the established effectiveness of orally administered olanzapine for acute or maintenance treatment of schizophrenia.

4.2 DOSE AND METHOD OF ADMINISTRATION

Do not confuse ZYPREXA RELPREVV 210 mg, 300 mg or 405 mg powder and sterile diluent for injection with any other forms of olanzapine, including ZYPREXA IM 10 mg powder for solution for injection.

ZYPREXA RELPREVV is for deep intramuscular gluteal use. Do not administer intravascularly or subcutaneously. (See **4.4 Special warnings and precautions for use, Post-injection syndrome**).

ZYPREXA RELPREVV is for single use in one patient only. Discard any residue.

Schizophrenia

The efficacy of ZYPREXA RELPREVV has been demonstrated within the range 150 to 300 mg administered every 2 weeks and with 405 mg administered every four weeks.

Olanzapine-naïve patients

For olanzapine-naïve patients it is recommended to establish tolerability with immediate release oral olanzapine tablets or wafers prior to starting treatment with ZYPREXA RELPREVV.

Previously stabilised with olanzapine

Based on the recommended dose range of 10 to 20 mg/day of oral olanzapine, the following table outlines the dose recommendations considering oral olanzapine and olanzapine pamoate.

Table 1. Recommended Dose Scheme between oral olanzapine and ZYPREXA RELPREVV

| Target Oral Olanzapine Dose | Recommended Starting Dose of ZYPREXA RELPREVV | Maintenance Dose after 2 Months of ZYPREXA RELPREVV Treatment |
|-----------------------------|---|---|
| 10 mg/day | 210 mg / 2 weeks or 405 mg / 4 weeks | 150 mg / 2 weeks or 300 mg / 4 weeks |
| 15 mg/day | 300 mg / 2 weeks | 210 mg / 2 weeks or 405 mg / 4 weeks |
| 20 mg/day | 300 mg / 2 weeks | 300 mg / 2 weeks |

Supplementation with oral olanzapine is not required at the start of treatment with ZYPREXA RELPREVV. Supplementation using doses of up to 20 mg per day oral olanzapine was allowed in an open label ZYPREXA RELPREVV clinical trial but has not been systematically studied in clinical trials (see **5.1 Pharmacodynamic properties, Clinical trials**).

ZYPREXA RELPREVV doses greater than 405 mg every 4 weeks or 300 mg every 2 weeks have not been studied in clinical trials.

ZYPREXA RELPREVV has not been systematically studied in elderly patients (65 years and over), hepatically or renally impaired patients. Unless a well-tolerated and effective dosage regimen using oral olanzapine has been established in such patients, ZYPREXA RELPREVV should not be used.

Elderly patients

A low starting dose of 150 mg of ZYPREXA RELPREVV every 4 weeks 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 of ZYPREXA RELPREVV (150 mg every 4 weeks) 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 RELPREVV

ZYPREXA RELPREVV must be suspended only with the diluent provided with the product in order to ensure adequate suspension and injectability. Use standard aseptic techniques for the reconstitution of parenteral products. It is recommended that gloves are worn when reconstituting ZYPREXA RELPREVV, as olanzapine pamoate may be irritating to the skin. Flush with water if contact is made with the skin.

Each ZYPREXA RELPREVV pack is provided with a card that fully describes the reconstitution and administration instructions. Please refer to the card for instructions on how to reconstitute and administer this product.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Post-injection syndrome

ZYPREXA RELPREVV is for deep intramuscular gluteal use. Do not administer intravascularly or subcutaneously.

During premarketing clinical studies of ZYPREXA RELPREVV involving 59,482 injections given to 2054 patients events that presented with signs and symptoms consistent with olanzapine overdose occurred in approximately 0.07% of injections and in 1.85% of patients. Most of these patients have developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, agitation, anxiety and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension or possible convulsions (see 4.9 Overdose). In most cases, initial signs and symptoms related to this event have appeared within one hour following injection, and in all cases full recovery was reported to have occurred within 24 to 72 hours after injection.

Based on data from clinical trials of ZYPREXA RELPREVV, the potential for onset of an event is greatest within the first hour, as shown in the following table.

Table 2. Time to onset of post-injection syndrome event

| Time period post injection | Frequency of post injection syndrome event | Frequency category |
|----------------------------|--|--------------------|
| ≤1 hour | 0.05% of injections | Rare |
| >1 hour and ≤2 hours | <0.01% of injections | Very rare |
| >2 hours | <0.01% of injections | Very rare |

Healthcare providers are advised to discuss this potential risk with patients each time they prescribe and administer ZYPREXA RELPREVV.

ZYPREXA RELPREVV should be administered by appropriately qualified health professionals in a healthcare facility with access to emergency services for management of olanzapine overdose. After each injection, patients should be observed by appropriately trained personnel for at least 2 hours and actively monitored for alertness every 30 minutes. Immediately prior to leaving the facility, it should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose. The two hour observation period should be extended as clinically appropriate for patients who exhibit any potential signs or symptoms of a post-injection syndrome event.

For the remainder of the day after injection, patients should be advised to be vigilant for symptoms of post-injection adverse reactions, should be able to obtain medical assistance if needed, and should not drive or operate heavy machinery.

If an overdose is suspected at any time, close medical supervision and monitoring should be instituted until examination indicates that signs and symptoms have resolved.

If parenteral benzodiazepines are required for management of post injection adverse reactions, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

Concomitant illnesses

While olanzapine 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.

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.

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 RELPREVV. As with all antipsychotics, patients receiving ZYPREXA RELPREVV 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 RELPREVV should be discontinued.

Seizures

ZYPREXA RELPREVV 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 RELPREVV, 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 RELPREVV 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 RELPREVV 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 RELPREVV 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 close supervision of high-risk patients should accompany therapy.

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 RELPREVV is administered to the elderly, especially if there are other factors that may influence drug metabolism and/or pharmacodynamic parameters.

Paediatric use

ZYPREXA RELPREVV has not been studied in patients under 18 years of age. 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 RELPREVV on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No specific interaction studies with ZYPREXA RELPREVV have been conducted. The following information refers to data obtained with other formulations of olanzapine.

Administration of intramuscular lorazepam (2 mg) one hour after intramuscular olanzapine (5 mg ZYPREXA IM) 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 observed with either drug alone.

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. Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression.

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

Caution should be exercised when ZYPREXA RELPREVV 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

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 olanzapine may be induced by concomitant smoking (the clearance of olanzapine 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 olanzapine.

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 olanzapine 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 olanzapine plasma concentrations of approximately 0.2 mcM, would mean maximum inhibition of these P450 systems by olanzapine 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

Fertility studies with ZYPREXA RELPREVV were not conducted. In male rats dosed orally with olanzapine at 22.5 mg/kg/day (11 times the maximum recommended oral clinical dose, based on mg/m²), 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 of 10 mg/kg/day (7 times greater than the AUC-based maximum clinical exposure for an oral dose). In female rats, oestrous cycles were disrupted at oral doses of 1 mg/kg/day or greater (but not 0.25 mg/kg/day) and fertility was impaired at 3 (but not 1) mg/kg/day. The oral dose in rats equivalent to the maximum clinical dose on a mg/m² basis is 2.2 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 RELPREVV.

Neonates exposed to antipsychotic drugs (including ZYPREXA RELPREVV) 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 RELPREVV 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.

In rats or rabbits, there was no evidence of teratogenicity following oral administration of olanzapine during the period of organogenesis at respective doses up to 18 and 30 mg/kg/day (9- and 30-fold the maximum clinical oral dose, based on mg/m²), or following an intramuscular injection of 75 mg/kg olanzapine pamoate monohydrate to rats at the beginning of organogenesis (similar to clinical exposure, based on plasma AUC). In rats, resorptions were increased and foetal development was retarded at an oral olanzapine dose of 18 (but not 4) mg/kg/day. Foetal weight was decreased in both species at oral doses of 4 (but not 1) and 30 (but not 8) mg/kg/day. Oral administration of olanzapine to pregnant rats resulted in prolonged gestation and an increased incidence of stillbirths at a dose of 10 (but not 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 pregnant rats, prolonged gestation was found following oral administration of olanzapine at 10 mg/kg/day (5-fold the maximum clinical dose on a mg/m² basis) but not at 5 mg/kg/day, and following intramuscular administration of ZYPREXA RELPREVV at 75 mg/kg (exposure similar to clinical exposure, based on plasma AUC).

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 RELPREVV.

Hyperprolactinaemia

When prescribing ZYPREXA RELPREVV, 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 RELPREVV, should be appropriately investigated and offered appropriate therapy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients receiving an injection of ZYPREXA RELPREVV should be advised not to drive or operate heavy machinery for the remainder of the day after each injection (see **4.4 Special warnings and precautions for use, Post-injection syndrome**).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Potential inadvertent intravascular injection events have occurred with ZYPREXA RELPREVV leading to symptoms consistent with olanzapine overdose (see **4.4 Special warnings and precautions for use, Post-injection syndrome**). Clinical signs and symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, agitation, anxiety and other cognitive impairment). Other symptoms noted include extrapyramidal

symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension or possible convulsions.

Other adverse effects observed in patients treated with ZYPREXA RELPREVV were similar to those seen with oral olanzapine. In clinical trials with ZYPREXA RELPREVV, the only adverse event reported at a statistically significantly higher rate in the ZYPREXA RELPREVV group than in the placebo group was sedation (ZYPREXA RELPREVV 8.2%, placebo 2.0%). Among all ZYPREXA RELPREVV treated patients, sedation was reported by 4.7% of patients.

In a 24 week fixed dose study of ZYPREXA RELPREVV in patients with schizophrenia comparing 150 mg/2 weeks, 405 mg/4 weeks and 300 mg/2 weeks increases in fasting triglycerides from normal at baseline to high at any time were statistically different between different dose groups.

Injection site abscess has been observed as a rare adverse event following use of ZYPREXA RELPREVV.

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

Adverse events identified from clinical trials with olanzapine

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

Weight – In an analysis of 13 placebo-controlled olanzapine monotherapy studies, ZYPREXA-treated patients gained an average of 2.6kg compared to an average 0.3kg 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 $\geq 25\%$ 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 ($\geq 10\%$): orthostatic hypotension. Uncommon ($\geq 0.1\%$ and $< 1\%$): bradycardia.

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

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

Musculoskeletal system – Common ($\geq 1\%$ and $< 10\%$): arthralgia.

Nervous system – Very common ($\geq 10\%$): somnolence. Common ($\geq 1\%$ and $< 10\%$): dizziness; akathisia. Uncommon ($\geq 0.1\%$ 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 ($\geq 10\%$): prolactin-increased, cholesterol-total (fasting borderline to high), triglycerides (fasting borderline to high), glucose (fasting borderline to high). Common ($\geq 1\%$ 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 ($\geq 1\%$ and $< 10\%$): eosinophilia; leucopenia including neutropenia.

Eosinophilia – Asymptomatic eosinophilia was occasionally seen.

Respiratory – Uncommon ($\geq 0.1\%$ 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 ($\geq 10\%$): falls.

Nervous system – Very common ($\geq 10\%$): abnormal gait.

Urogenital system – Common ($\geq 1\%$ and $< 10\%$): urinary incontinence.

Respiratory system – Common ($\geq 1\%$ 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 ($\geq 10\%$): 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 ($\geq 10\%$) 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 $\geq 15\%$ and almost a third gained $\geq 25\%$ 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 ($\geq 10\%$): weight gain $\geq 7\%$ of baseline body weight – 40.6%. Common ($\geq 1\%$ and $< 10\%$): weight gain $\geq 15\%$ of baseline body weight – 7.1%.

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

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

Clinical chemistry – Very common ($\geq 10\%$): ALT $> 3 \times$ ULN (all randomised patients with ALT baseline $\leq 3 \times$ 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 ($\geq 1\%$ and $< 10\%$):

cholesterol-total (fasting normal to high) – 6.9%. Very rare (<0.01%): glucose (fasting normal to high) – 0.0%.

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

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

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 $\geq 0.01\%$): hepatitis. Very rare (<0.01%): jaundice.

Metabolic – Rare (<0.1% and $\geq 0.01\%$): 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 $\geq 0.1\%$): stuttering. Rare (<0.1% and $\geq 0.01\%$): seizures. Very rare (<0.01%): neuroleptic malignant syndrome.

Skin and appendages – Rare (<0.1% and $\geq 0.01\%$): 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 $\geq 0.1\%$): salivary hypersecretion.

Respiratory - Sleep apnoea syndrome. A casual 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

If signs and symptoms of overdose consistent with inadvertent intravascular administration are observed appropriate supportive measures should be instituted (see **4.4 Special warnings and precautions for use, Post-injection syndrome**). Although overdose is less likely with this parenteral preparation that is administered by a healthcare professional, reference information for oral olanzapine overdose is presented below.

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 ($\geq 10\%$ 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 or ZYPREXA RELPREVV.

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 (K_i ; <100 nmol) for serotonin 5HT_{2A/2C}, 5HT₃, 5HT₆; dopamine D₁, D₂, D₃, D₄, D₅; cholinergic muscarinic receptors m₁-m₅; α_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 *in-vitro* affinity for serotonin 5HT₂ than dopamine D₂ receptors and in *in-vivo* models, greater 5HT₂ than D₂ 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 D₂ receptor. A Single Photon Emission Computed Tomography (SPECT) imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D₂ occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

In a PET study in patients treated with ZYPREXA RELPREVV (300 mg/4 weeks), mean D₂ receptor occupancy was 60% or higher at the end of a 6 month period, a level consistent with that found during treatment with oral olanzapine.

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

ZYPREXA RELPREVV in schizophrenia

The effectiveness of ZYPREXA RELPREVV in the treatment and maintenance of schizophrenia is consistent with the established effectiveness of the oral formulation of olanzapine.

A total of 1469 patients with schizophrenia were included in two pivotal trials with ZYPREXA RELPREVV.

The first was an 8-week, placebo-controlled trial conducted in adult patients (n=404) who were experiencing acute psychotic symptoms. Patients were randomised to receive injections of ZYPREXA RELPREVV 405 mg every 4 weeks, 300 mg every 2 weeks, 210 mg every 2 weeks or placebo every 2 weeks. No oral antipsychotic supplementation was allowed. Total Positive and Negative Symptom Scores (PANSS) showed significant improvement from baseline (baseline mean Total PANSS score 101) to endpoint (mean changes -22.6, -26.3, -22.5, respectively) with each dose of ZYPREXA RELPREVV (405 mg every 4 weeks, 300 mg every 2 weeks and 210 mg every 2 weeks) compared to placebo (mean change -8.5). Visitwise mean change from baseline to endpoint in PANSS Total score indicated that by Day 3, patients in the 300 mg/2 weeks and 405 mg/4 weeks treatment groups had statistically significantly greater reductions in PANSS Total score compared to placebo (-8.6, -8.2 and -5.2, respectively). All three ZYPREXA RELPREVV treatment groups showed statistically significantly greater improvement than placebo beginning by end of Week 1. These results support efficacy for ZYPREXA RELPREVV over 8 weeks of treatment and a drug effect that was observed as early as one week after starting treatment with ZYPREXA RELPREVV, without the use of oral antipsychotic supplementation.

The second study was a long term study in clinically stable patients (n=1065, baseline mean Total PANSS score 54.3 to 57.8) who were initially treated with oral olanzapine for 4 to 8 weeks and then switched to continue on oral olanzapine or to ZYPREXA RELPREVV for 24 weeks. No oral antipsychotic supplementation was allowed. ZYPREXA RELPREVV treatment groups of 150 mg and 300 mg given every two weeks (doses pooled for analysis) and 405 mg given every 4 weeks were non-inferior to the combined doses of 10, 15 and 20 mg of oral olanzapine as measured by rates of exacerbation of symptoms of schizophrenia (respective exacerbation rates, 10%, 10%, 7%). Exacerbation was measured by worsening of items on the PANSS derived BPRS Positive scale and hospitalisation due to worsening of positive psychotic symptoms. The combined 150 mg and 300 mg/2 week treatment group was non inferior to the 405 mg/4 week treatment group (exacerbation rates 10% for each group) at 24 weeks after randomisation. A secondary analysis of this study showed that Total PANSS scores for ZYPREXA RELPREVV 150 mg/2 weeks, 300 mg/2 weeks and 405 mg/4 weeks remained stable for the duration of the 24 week study (Baseline mean Total PANSS Scores 55.9 with mean changes at the end of 24 weeks of +2.7, -2.2, -0.1 respectively) compared to the low dose of ZYPREXA RELPREVV 45 mg/ 4 weeks (Baseline mean Total PANSS Score of 58 with mean changes at the end of 24 weeks of +7.3). In addition, post-hoc analyses demonstrated that the 405 mg /4 weeks treatment group was non inferior to the combined oral olanzapine treatment group. ZYPREXA RELPREVV doses of 300 mg/2 weeks, 405 mg/4 weeks and 150 mg/2 weeks were superior to ZYPREXA RELPREVV 45 mg/4 weeks as measured by time to exacerbation (p values <0.01, <0.01 and 0.06, respectively).

Patients who had enrolled in short term studies of ZYPREXA RELPREVV were eligible to enrol in a long term open label extension study examining the long term safety and efficacy of ZYPREXA RELPREVV 45 to 405 mg administered on a flexible 2-, 3- or 4-week interval. This six year, open label, uncontrolled study enrolled 931 patients with a mean PANSS score at baseline of 54.54, indicating mild symptoms. 370 patients (39.7%) continued treatment until the end of the study. There was no significant change from baseline in mean PANSS score for

continuing patients, indicating that for those who continued treatment ZYPREXA RELPREVV was effective in long term maintenance of the treatment effect. Pharmacokinetic analyses revealed no indication of long term systemic accumulation of olanzapine.

The open label long term study permitted supplementation of ZYPREXA RELPREVV with up to 20 mg/day oral olanzapine when clinically necessary. In this study 31.6% of patients received supplemental oral olanzapine at some time during the study, but the mean modal dose was 0.66 mg/day in those who received supplementation, indicating that most patients who did supplement did not do so every day. Data from the primary efficacy studies indicate that additional use of oral antipsychotic medication to gain efficacy at the start of therapy with ZYPREXA RELPREVV is not necessary.

Oral olanzapine in 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 18-86 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).

5.2 PHARMACOKINETIC PROPERTIES

Olanzapine release from the ZYPREXA RELPREVV suspension is slow and the resulting prolonged administration sustains the systemic olanzapine plasma concentrations throughout the period of time between injections. Typical systemic concentrations reach a peak level within the first week after injection and are at the lowest trough level immediately prior to the next injection. Throughout an entire injection interval of 2 to 4 weeks, reasonably consistent olanzapine plasma concentrations are sustained. The olanzapine concentration fluctuation between the peak and the trough is comparable to the peak and trough fluctuations associated with once daily oral dosing.

Plasma concentrations remain measurable for several months after the last ZYPREXA RELPREVV injection. The half-life of olanzapine after ZYPREXA RELPREVV is 30 days, compared to 30 hours following oral administration. The elimination phase is complete approximately six to eight months after the last injection.

Dose proportionality and oral dose correspondence

ZYPREXA RELPREVV provides a dose of 150, 210, 300 or 405 mg olanzapine. Injection of a larger dose produces dose-proportional increases in the systemic exposure. Dose proportional exposure for ZYPREXA RELPREVV aligns with the corresponding exposure for an oral dose of olanzapine. A dose of 300 mg olanzapine pamoate depot injected every two weeks delivers approximately 20 mg olanzapine per day and a dose of 150 mg olanzapine injected every two weeks delivers approximately 10 mg per day. These doses of ZYPREXA RELPREVV have been shown to sustain steady state olanzapine concentrations over long periods of treatment that correspond to those maintained by an oral dose of 10 or 20 mg olanzapine administered once daily.

Pharmacokinetic impact of switching to ZYPREXA RELPREVV from oral olanzapine

The switch from oral olanzapine to ZYPREXA RELPREVV changes the pharmacokinetics from elimination-rate controlled to absorption-rate controlled. The switch to ZYPREXA RELPREVV may require treatment for a period of approximately 3 months to re-establish steady state conditions. Initial treatment with ZYPREXA RELPREVV is recommended at a dose that is based on the mg/day oral dose (see **4.2 Dose and method of administration**). Plasma concentrations of olanzapine during the first injection interval may be lower than those maintained by a corresponding oral dose. Even though the concentrations are lower, the olanzapine concentrations remained within a therapeutically effective range and supplementation with orally administered olanzapine was generally not necessary in clinical trials.

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

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.

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.

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 (≥ 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.

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 α_1 acid glycoprotein.

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 genotoxic in a full range of standard tests, which included bacterial mutation tests and *in vitro* and *in vivo* tests. Pamoic acid was positive in an *in vitro* chromosome aberration assay but negative in a range of other *in vitro* and *in vivo* tests, with the weight of evidence indicating that it does not represent a genotoxic liability at the proposed clinical dose.

Carcinogenicity

Carcinogenicity studies with olanzapine showed the development of mammary adenocarcinomas at oral doses of 2 mg/kg/day or greater in mice and 2.5 mg/kg/day or greater in rats (similar to or less than the maximum recommended clinical oral dose, based on mg/m². The respective no-effect doses were 0.5 and 1 mg/kg/day (less than the maximum recommended clinical oral dose). Monthly intramuscular administration of olanzapine pamoate monohydrate to rats at doses up to 20 mg/kg (males) or 50 mg/kg (females) for 2 years was not associated with tumour formation, although rat exposures (plasma AUC) to pamoic acid and olanzapine were similar to and less than the respective exposures to pamoic acid and olanzapine at the maximum recommended clinical dose of ZYPREXA RELPREVV.

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 D₂ receptor antagonistic activity of olanzapine. Mammary tumours are known to occur in rats and mice treated with other drugs that antagonise dopamine D₂ 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 RELPREVV in patients with familial history or previously detected breast cancer should be avoided. Caution should also be exercised when considering ZYPREXA RELPREVV treatment in patients with pituitary tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Carmellose sodium

Mannitol

Polysorbate 80

Water for injections

Hydrochloric acid and/or sodium hydroxide may have been added during manufacture to adjust pH

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

After reconstitution, chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. However, the product should be used as soon after reconstitution as possible. If necessary, the reconstituted product should be stored for not more than 6 hours at room temperature.

6.5 NATURE AND CONTENTS OF CONTAINER

ZYPREXA RELPREVV is supplied in a kit containing two vials, one containing powder and one containing a sterile diluent, one syringe with fixed needle and three needles. ZYPREXA RELPREVV is a yellow powder for suspension in a clear glass vial. The active ingredient in ZYPREXA RELPREVV is olanzapine pamoate monohydrate. The powder is suspended using the supplied sterile diluent. The sterile diluent is a clear, colourless to slightly yellow viscous liquid in a clear glass vial. When the product is reconstituted as instructed the resulting suspension contains 150 mg/mL olanzapine. The reconstituted suspension is intended for deep intramuscular gluteal use only. The sterile diluent for ZYPREXA RELPREVV also contains excipients: carmellose sodium, mannitol, polysorbate 80 and water for injections.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

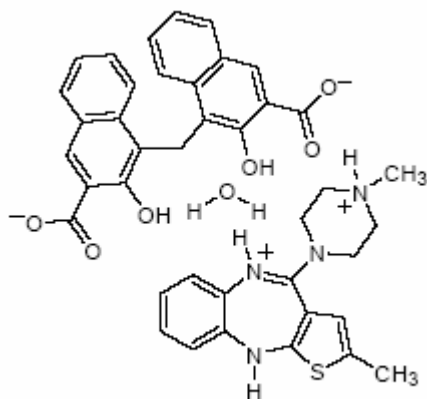
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Chemically, olanzapine pamoate monohydrate is 10*H*-thieno[2,3-*b*][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)-,4,4'-methylenebis[3-hydroxy-2-naphthalene-carboxylate] (1:1), monohydrate. The formula is C₁₇H₂₂N₄SC₂₃H₁₄O₆H₂O. Olanzapine pamoate monohydrate is a yellow solid that is practically insoluble in water with a molecular weight of 718.8.

Olanzapine pamoate monohydrate has the following structural formula:



CAS number

The CAS number for olanzapine pamoate monohydrate is 221373-18-8.

7. MEDICINE SCHEDULE

S4 – Prescription only Medicine

8. SPONSOR

Eli Lilly Australia Pty Ltd
Level 9, 60 Margaret Street, Sydney, NSW 2000
AUSTRALIA
1800 454 559

9. DATE OF FIRST APPROVAL

24 March 2009

10. DATE OF REVISION

19 January 2024

SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|-----------------|----------------------------|
| 8 | Sponsor address update |

ZYPREXA® RELPREVV® is a registered trademark of Eli Lilly and Company.