NEW ZEALAND DATA SHEET

ZYPINE ODT

1. Product Name

ZYPINE ODT, 5 mg and 10 mg, wafer.

2. Qualitative and Quantitative Composition

Each ZYPINE ODT wafer contains 5 mg or 10 mg of olanzapine.

Excipient with known effect: aspartame.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

5 mg wafer

Light yellow to yellow coloured, plain to mottled, round, flat faced, bevelled edged tablets debossed with “M” one side and “OE1” on the other side.

10 mg wafer

Light yellow to yellow coloured, plain to mottled, round, flat faced, bevelled edged tablets debossed with “M” one side and “OE2” on the other side.

4. Clinical Particulars

4.1 Therapeutic indications

ZYPINE ODT wafers are indicated in adults for the treatment of schizophrenia and related psychoses.

ZYPINE ODT wafers alone or in combination with lithium or valproate are indicated in adults for the short-term treatment of acute manic episodes associated with Bipolar I disorder.

ZYPINE ODT wafers are indicated in adults for preventing recurrence of manic, mixed or depressive episodes in Bipolar I disorder.

4.2 Dose and method of administration

Dose

Schizophrenia and related disorders

The recommended starting dose for ZYPINE ODT wafersis 5 to 10 mg/day, administered as a single daily dose without regard to meals. Daily dosage may subsequently be adjusted on the basis of individual clinical status within the range of 5 to 20 mg daily. An increase to a dose greater than the routine therapeutic dose of 10 mg/day is recommended only after appropriate clinical reassessment.

Acute mania associated with bipolar disorder

The recommended starting dose for ZYPINE ODT wafers is 10 or 15 mg administered once a day as monotherapy or 10 mg administered once daily in combination therapy with lithium or valproate. It may be given without regard to meals. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours. When dosage adjustments are necessary, dose increments/decrements of 5 mg daily are recommended. Antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Preventing recurrence in bipolar disorder

Patients who have been receiving olanzapine for the treatment of acute mania should initially continue therapy for preventing recurrence in bipolar disorder at the same dose. For patients already in remission, the suggested starting dose for ZYPINE ODT wafers is 10 mg once a day. Subsequent daily dosage should be adjusted on the basis of clinical status within a range of 5 mg to 20 mg per day. ZYPINE ODT wafers may be given without regard to meals, as its absorption is not affected by food.

Special populations

Paediatric

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

Elderly

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

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.

Gender differences

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

Smoking/non-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 sections 4.4 and 5.2).

Method of administration

Do not halve ZYPINE ODT wafers. Dose equivalence when a wafer is divided has not been established.

ZYPINE ODT wafers should be placed in the mouth and allowed to completely dissolve before swallowing the saliva. A glass of water may be taken following administration to assist with

swallowing the saliva. Alternatively, the ZYPINE ODT wafers may be dispersed in a full glass of water immediately before administration.

Bioequivalence with other olanzapine-containing products on the New Zealand market has not been established when ZYPINE ODT wafers are taken without water.

4.3 Contraindications

ZYPINE ODT wafers are contraindicated in patients with a known:

- hypersensitivity to olanzapine, or any of the excipients listed in section 6.1.
- risk of narrow-angle glaucoma.

4.4 Special warnings and precautions for use

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

Concomitant illnesses

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

Parkinson's disease

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

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 olanzapine. 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 (e.g. 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 olanzapine-treated patients in placebo-controlled trials. Olanzapine-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 section 4.8).

Weight gain

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

Hepatic

Transient, asymptomatic elevations of hepatic transaminases, alanine transferase (ALT), aspartate transferase (AST) have been seen occasionally, especially in early treatment. Rare post-marketing reports of hepatitis have been received. Very rare cases of jaundice, cholestatic or mixed liver injury have also been reported in the post-marketing period (see section 4.8). 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.

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 olanzapine 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 olanzapine adversely affected bone marrow function, even in patients with a history of drug-associated neutropenia or leucopenia (see section 4.8).

Neuroleptic malignant syndrome (NMS)

NMS, a potentially fatal symptom complex, is associated with antipsychotic drugs, including olanzapine (see section 4.8). 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 olanzapine should be discontinued.

Seizures

ZYPINE ODT wafers 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 olanzapine (see section 4.8).

Drug reaction with eosinophilia and systemic symptoms (DRESS)

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, olanzapine 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 ZYPINE ODT wafers, a dose reduction or drug discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

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, olanzapine was not associated with a persistent increase in absolute QT intervals. Only 8 of 1685 subjects had an increase in the corrected QT interval (QTc) on multiple occasions. As with other antipsychotics, caution should be exercised when ZYPINE ODT wafers are 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 (e.g. pneumonia, with or without aspiration).

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

Cerebrovascular adverse events (e.g. stroke, transient ischemic 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 (e.g. history of previous CVAE or transient ischemic 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.

Thromboembolism

Temporal association of olanzapine treatment and venous thromboembolism has been reported uncommonly (≥ 0.1% and < 1%). A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism, all possible risk factors for VTE, e.g. immobilisation of patients, should be identified and preventative measures undertaken.

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 olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g. 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. ZYPINE ODT wafers 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 of tablets 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.

Discontinuation of treatment

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

Hyperprolactinaemia

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

Special populations

Paediatric

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

Elderly

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

Effects on laboratory tests

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

4.5 Interaction with other medicines and other forms of interaction

Given the primary central nervous system effects of olanzapine, caution should be used when it is taken 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 olanzapine is used concomitantly with medicines known to cause electrolyte imbalance or to increase QT interval (see section 4.4).

Potential for other medicines to affect olanzapine

Single-doses of antacids (containing aluminium and magnesium) or cimetidine do not affect the oral bioavailability of olanzapine. The concomitant administration of activated charcoal reduces the oral bioavailability of olanzapine 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 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 olanzapine to affect other medicines

In clinical trials with single doses of olanzapine, 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. Olanzapine showed no interaction when co-administered 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

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 olanzapine.

Neonates exposed to antipsychotic drugs (including olanzapine) 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, 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.

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

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.

Breast-feeding

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 taking olanzapine.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥ 10%); common (≥ 1% to < 10%); uncommon (≥ 0.1% to < 1%); rare (≥ 0.01% to < 0.1%); very rare (< 0.01%).

Adverse events identified from clinical trials of olanzapine

Body as a whole

Very common:	weight gain: weight gain ≥ 7% baseline body weight.
Common:	asthenia, fatigue, weight gain ≥ 15% baseline body weight, pyrexia.
Uncommon:	photosensitivity reaction.

Weight

In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-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 olanzapine-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 olanzapine-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 olanzapine.

Discontinuation due to weight gain occurred in 0.4% of olanzapine-treated patients following at least 48 weeks of exposure.

Cardiovascular system

Very common:	orthostatic hypotension.
Uncommon:	bradycardia.

Digestive system

Common:	constipation, dry mouth, increased appetite.
Uncommon:	abdominal distension.

Metabolic

Common:	peripheral oedema.
Rare:	elevated creatine kinase levels.

Musculoskeletal system

Uncommon:	arthralgia.

Nervous system

Very common:	somnolence.
Common:	dizziness, akathisia.
Uncommon:	amnesia, restless legs syndrome.

In active-controlled studies, olanzapine -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 olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

Clinical chemistry

Very common:	prolactin-increased, cholesterol-total (fasting borderline to high), triglycerides (fasting borderline to high), glucose (fasting borderline to high).
Common:	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 (ALP) increased, gamma glutamyltransferase (GGT) high, uric acid high.

Glucose

In adult clinical trials (up to 52 weeks) olanzapine 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 olanzapine compared to placebo. A smaller between-treatment difference was also seen in fasting blood glucose concentrations in patients with baseline glucose dysregulation. Olanzapine 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 olanzapine 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, olanzapine-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 olanzapine-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: eosinophilia, leucopenia including neutropenia.

Eosinophilia

Asymptomatic eosinophilia was occasionally seen.

Respiratory

Uncommon: epistaxis.

Undesirable effects for special populations

Elderly patients

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

Body as a whole

Very common: falls.

Nervous system

Very common: abnormal gait.

Urogenital system

Common: urinary incontinence.

Respiratory system

Common: pneumonia.

Patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease

Nervous system

Very common: 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 olanzapine-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 olanzapine 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 olanzapine-treated adolescent patients following at least 24 weeks of exposure

Increases in fasting glucose were similar in adolescents and adults treated with olanzapine, however the difference between olanzapine 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 olanzapine. However, in short term studies the differences between olanzapine 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: weight gain ≥ 7% of baseline body weight (40.6%).
Common: weight gain ≥ 15% of baseline body weight (7.1%).

Digestive system

Very common: increased appetite (24.0%).
Common: dry mouth (6.1%).

Nervous system

Very common: sedation (including hypersomnia, lethargy, sedation, somnolence) (44.1%).

Clinical chemistry

Very common: ALT > 3xULN (all randomised patients with ALT baseline ≤ 3xULN) (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: cholesterol-total (fasting normal to high) (6.9%).
Very rare: glucose (fasting normal to high).

Adverse events based on post marketing spontaneous reports with oral olanzapine

Body as a whole

Very rare: allergic reaction (e.g. 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 olanzapine is stopped suddenly).

Digestive system

Uncommon: salivary hypersecretion.
Very rare: pancreatitis.

Hepatobiliary disorders

Rare: hepatitis.
Very rare: jaundice.

Metabolic

Rare: hyperglycaemia.
Very rare: 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: stuttering.
Rare: seizures.
Very rare: neuroleptic malignant syndrome.

Skin and appendages

Rare: rash.
Very rare: alopecia, Drug Reaction with Eosinophilia and Systemic Symptom (DRESS).

Urogenital system

Very rare: priapism, urinary hesitation, urinary retention, urinary incontinence.

Haematology

Very rare: thrombocytopenia.

Cardiovascular

Very rare: 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: rhabdomyolysis.

Psychiatric reactions

Rare: somnambulism and other related events.

Respiratory

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

Clinical chemistry

Very rare: total bilirubin increased, creatine kinase increased.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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 olanzapine overdose include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of olanzapine 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 2000 mg.

Management of overdose

There is no specific antidote to olanzapine. 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 olanzapine. Cardiovascular monitoring should be considered to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antipsychotics,

ATC code: N05AH03

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 nanomol) 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.

Clinical efficacy and safety

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 2900 schizophrenic patients, with both positive and negative symptoms, olanzapine was associated with statistically significantly greater improvements in negative as well as positive symptoms of schizophrenia.

Schizophrenia and related disorders

The efficacy of olanzapine in the reduction of and maintenance of the reduction of the manifestations of schizophrenia and related psychotic disorders has been 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 olanzapine [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 olanzapine 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 olanzapine was statistically significantly superior to placebo and to haloperidol on the Scale for the Assessment of Negative Symptoms (SANS). Efficacy of olanzapine generally increased with dose.

2. A 6-week, placebo-controlled trial (n = 152) compared 2 fixed doses of olanzapine [1 or 10 mg/day (once daily)] and placebo. Olanzapine, 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 olanzapine [5 ± 2.5, 10 ± 2.5 and 15 ± 2.5 mg/day (once daily)], olanzapine [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 olanzapine, which was statistically significantly superior to olanzapine, 1 mg, on the BPRS positive psychosis cluster, PANSS positive subscale and the CGI-S scale.

4. A 6-week comparator-controlled trial (n = 1996, 2:1 randomisation, olanzapine:haloperidol) compared 1 dosage range of olanzapine [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 olanzapine and 11.8 mg/day for haloperidol. Olanzapine was statistically significantly superior to haloperidol on the BPRS total, the BPRS negative psychosis cluster, the PANSS negative subscale and the CGI-S scale. Olanzapine was also statistically significantly superior to haloperidol on the Montgomery-Asberg Depression Rating Scale (MADRS).

5. The effectiveness of olanzapine in long-term therapy, i.e. > 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 (i.e. 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. Olanzapine 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 olanzapine, corresponding to 1122.2 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 to 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 to 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.

5.2 Pharmacokinetic properties

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 1000 nanogram/mL. Olanzapine is bound to albumin and α_1 acid glycoprotein.

Biotransformation

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.

Elimination

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

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.

Special populations

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.

Elderly

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.

The plasma clearance of olanzapine is lower in elderly versus non-elderly subjects and in females versus males.

Gender

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

Smoking

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

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 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 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 olanzapine in patients with familial history or previously detected breast cancer should be avoided. Caution should also be exercised when considering olanzapine treatment in patients with pituitary tumours.

Reproductive toxicity

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.

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.

6. Pharmaceutical Particulars

6.1 List of excipients

ZYPINE ODT wafers also contain:

- mannitol,
- microcrystalline cellulose,
- guar gum,
- crospovidone,
- magnesium stearate,
- anhydrous colloidal silica,
- aspartame (E951, source of phenylalanine),
- sodium lauryl sulfate.

ZYPINE ODT wafers are lactose and gluten free.

Sulfites may be present in this product in trace amounts.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25°C. Protect from light and moisture.

6.5 Nature and contents of container

Polyamide/Al/PVC/Al blister packs of 28, 56 and 84 wafers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

19 July 2012

10. Date of Revision of the Text

04 December 2019

Sections	Summary of changes
-	Minor editorial changes
4.4	Added information related to sleep apnoea
4.8	Added information related to sleep apnoea and salivary hypersecretion
6.1	