SCHEDULING STATUS S5

1. NAME OF THE MEDICINE

ZYPREXA IM (powder for solution for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZYPREXA IM vials contain 10,0 mg olanzapine.

After reconstitution each ml of the solution contains 5 mg olanzapine.

Excipient with known effect: ZYPREXA IM contains 50 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection

ZYPREXA IM contains a yellow, sterile, lyophilised plug.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

ZYPREXA IM injection is indicated for the control of agitation and disturbed behaviour in patients with schizophrenia and related psychoses and in patients with acute mania associated with Bipolar I disorder when oral therapy is not appropriate.

Treatment with ZYPREXA IM should be discontinued and replaced with oral therapy as soon as clinically appropriate.

4.2 Posology and method of administration

Posology

ZYPREXA IM is for intramuscular use only. **ZYPREXA IM should not be administered intravenously or subcutaneously.**

The recommended dose for ZYPREXA IM injection is 10 mg administered as a single intramuscular injection. On the basis of individual clinical status, a second injection of up to 10 mg may be administered as early as 2 hours after the first injection, and a third injection of up to 10 mg may be administered as early as 4 hours after the second injection. The safety of total daily doses greater than 30 mg has not been evaluated in clinical trials.

Treatment with ZYPREXA IM for injection should be discontinued and oral ZYPREXA therapy, in a range of 5 - 20 mg/day, should be initiated as soon as clinically appropriate.

Elderly patients:

A lower starting dose of 2,5 - 5 mg per injection should be considered for elderly patients.

Method of administration

Reconstitution of ZYPREXA IM (powder for injection) with sterile water for injection (see section 6.6):

• Reconstitute using 2,1 ml sterile water for injection.

• The following table provides injection volumes for delivering various doses of ZYPREXA IM:

Dose, mg ZYPREXA IM	Volume of Injection, ml
10,0	Withdraw total contents of vial
7,5	1,5
5,0	1,0
2,5	0,5

Major reconstitution incompatibilities:

- ZYPREXA IM should be reconstituted with sterile water for injection only.
- ZYPREXA IM should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed.
- Lorazepam injection should not be used to reconstitute ZYPREXA IM as this combination results in a delayed reconstitution time.
- ZYPREXA IM should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

4.3 Contraindications

ZYPREXA is contraindicated in:

- patients who are hypersensitive to the active substance, olanzapine, or to any of the excipients listed in section 6.1.
- patients with known risk of narrow-angle glaucoma.

Paediatric use*:* Safety and effectiveness in patients under 18 years of age have not been established.

4.4 Special warnings and precautions for use

The efficacy of ZYPREXA IM has not been established in patients with agitation and disturbed behaviours related to conditions other than schizophrenia or manic episode.

Unstable medical conditions

ZYPREXA IM should not be administered to patients with unstable medical conditions, such as acute myocardial infarction, unstable angina pectoris, severe hypotension and/or bradycardia, sick sinus syndrome, or following heart surgery. If the patient's medical history with regard to these unstable medical conditions cannot be determined, the risks and benefits of IM olanzapine should be considered in relation to other alternative treatments.

Concomitant use of benzodiazepines and other medicines

Special caution is necessary in patients who have received treatment with other medicines having haemodynamic properties similar to those of intramuscular olanzapine including other antipsychotics (oral and/or intramuscular) and benzodiazepines (see section 4.5).

Serious/severe bradycardia and syncope may occur. In clinical studies there were cases with serious symptomatic hypotension, apnoea, and ventricular tachydysrythmias including fatalities. In most of the serious cases, there was a temporal relationship with the use of benzodiazepines.

Simultaneous injection of intramuscular ZYPREXA IM and parenteral benzodiazepines has not been studied and is therefore not recommended (see section 4.5). If the patient is considered to need parenteral benzodiazepine treatment, this should not be given until at least 1 hour after ZYPREXA IM administration. If the patient has received

parenteral benzodiazepines, ZYPREXA IM administration should only be considered after careful evaluation of clinical status and the patient should be closely monitored for excessive sedation and cardiorespiratory depression.

Hypotension

Hypotension and/or bradycardia after ZYPREXA IM administration may occur and patients should be closely observed, particularly for the first 4 hours following injection, and close observation after that if clinically indicated. Blood pressure, pulse, respiratory rate and level of consciousness should be observed regularly, and remedial treatment provided if required. Patients should remain recumbent if drowsy or dizzy after injection, until examination has indicated that they are not experiencing hypotension, postural hypotension, bradycardia and/or hypoventilation. In view of the possibility of bradycardia and/or hypotension with ZYPREXA IM caution should be considered in patients with serious cardiovascular disease where the occurrence of syncope or hypotension and/or bradycardia might put the patient at increased medical risk.

Discontinuation of treatment

Discontinuation reactions may occur, usually within a week of discontinuing ZYPREXA. These reactions may consist of a cholinergic syndrome (diaphoresis, diarrhoea, sialorrhoea, nausea and vomiting, anxiety, agitation, insomnia and tremor). ZYPREXA should therefore be gradually discontinued.

Hyperprolactinaemia

ZYPREXA elevates prolactin levels and elevation persists during chronic administration.

Neuroleptic malignant syndrome (NMS)

NMS has occurred in association with ZYPREXA. NMS is a potentially fatal symptom complex.

Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. ZYPREXA should be discontinued, as well as all antipsychotic medicines, should any of the clinical manifestations of NMS or unexplained high fever without additional clinical manifestations of NMS be observed.

Seizures

ZYPREXA should be used cautiously in patients who have a history of seizures or are subject to factors which may lower seizure threshold as seizures have been reported to occur in patients treated with ZYPREXA.

Tardive dyskinesia

ZYPREXA was associated with dyskinesia. If signs or symptoms of tardive dyskinesia appear in a patient on ZYPREXA, a dose reduction or discontinuation of treatment should be considered. The risk of tardive dyskinesia increases with long-term exposure. Symptoms of tardive dyskinesia can temporarily deteriorate or even arise after discontinuation of treatment.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with ZYPREXA 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 ZYPREXA if DRESS is suspected.

Hepatic impairment

Transient, asymptomatic elevations of hepatic aminotransferases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve and in patients who are being treated with potentially hepatotoxic medicines. Periodic assessment of transaminases is recommended in patients with significant hepatic disease. A 5 mg starting dose should be considered for patients with moderate hepatic impairment. In cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, ZYPREXA treatment should be discontinued.

Safety experience in elderly patients with Dementia-related psychosis

In elderly patients with dementia-related psychosis, the efficacy of ZYPREXA has not been established. In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in ZYPREXA-treated patients was significantly greater than placebo-treated patients (3,5 % vs 1,5 % respectively). Abnormal gait and falls were very common (> 10 %), urinary incontinence and respiratory infection were common, and there was an increased incidence in cerebrovascular incidents, including stroke. Risk factors that may predispose this patient population to increased mortality when treated with ZYPREXA include age ≥ 65 years, dysphagia, sedation, malnutrition and dehydration, concomitant use of benzodiazepines, or presence of pulmonary conditions (e.g. pneumonia, with or without aspiration).

ZYPREXA is not indicated for the treatment of patients with dementia-related psychosis.

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 ZYPREXA in elderly patients with dementia-related psychosis. In placebo-controlled studies, there was a higher incidence of CVAE in patients treated with ZYPREXA 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.

Parkinson's disease

The use of ZYPREXA in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended. In clinical trials, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo (see section 4.8), and olanzapine was not more effective than placebo in the treatment of psychotic symptoms. In these trials, patients were initially required to be stable on the lowest effective dose of anti-Parkinsonian medicines (dopamine agonist) and to remain on the same anti-Parkinsonian medicines and dosages throughout the study. Olanzapine was started at 2,5 mg/day and titrated to a maximum of 15 mg/day based on investigator judgement.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia and diabetes mellitus, which may be associated with ketoacidosis or hyperosmolar coma or death due to exacerbation of pre-existing diabetes, have been reported in patients treated with ZYPREXA.

Patients with an established diagnosis of diabetes mellitus who are started on ZYPREXA should be monitored regularly for worsening of glucose control (measuring of blood glucose at baseline, 12 weeks after starting olanzapine treatment and annually thereafter). Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes), who are starting treatment with ZYPREXA should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with ZYPREXA should undergo fasting blood glucose testing. Weight should be monitored regularly, e.g. at baseline, 4, 8 and 12 weeks after starting ZYPREXA treatment and quarterly thereafter. Continuation of anti-diabetic treatment may be needed even after discontinuation of ZYPREXA.

Anticholinergic activity

Clinical experience with ZYPREXA in patients with concomitant illness is limited. ZYPREXA demonstrated anticholinergic activity *in vitro.* Caution is advised when prescribing for patients with symptomatic prostatic enlargement, narrow-angle glaucoma or paralytic ileus and related conditions (see section 4.3).

Lipid Alterations

Increases in total cholesterol, LDL cholesterol and triglycerides are very common in patients treated with ZYPREXA. Appropriate clinical monitoring is recommended. Patients treated with any antipsychotic medicines, including ZYPREXA, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines, e.g. at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter.

QT interval

In clinical trials with oral administration, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥ 500 milliseconds [msec] at any time post baseline in patients with baseline QTcF < 500 msec) were uncommon (0,1 % to 1 %) in patients treated with ZYPREXA, with no significant differences in associated cardiac events compared to placebo. However, caution should be exercised when ZYPREXA is prescribed with medicines known

to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Thromboembolism

Temporal association of ZYPREXA treatment and venous thromboembolism has been reported uncommonly (≥ 0,1 % and < 1 %). A causal relationship between the occurrence of venous thromboembolism and treatment with ZYPREXA has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

General CNS activity

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

Sudden cardiac death

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

Geriatric use

Caution should be exercised in dosing the elderly, especially if there are other factors that might additively influence medicine metabolism and/or pharmacodynamic sensitivity. A lower starting dose of ZYPREXA should be used in the elderly. As postural hypotension may occur especially in the elderly, it is recommended that blood pressure is measured periodically in patients over 65 years.

Smokers

Plasma clearance of ZYPREXA is higher in smokers. The combined effects of age, smoking and gender could lead to substantial pharmacokinetic differences in population. The clearance in young smoking males is 3 times higher than that in elderly non-smoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of ZYPREXA.

Orthostatic hypotension

ZYPREXA may induce orthostatic hypotension associated with dizziness, tachycardia, and syncope.

ZYPREXA has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from pre-marketing clinical studies. Because of the risk of orthostatic hypotension with ZYPREXA, caution should be observed in cardiac patients.

Neutropenia

Caution should be exercised when using ZYPREXA in the following types of patients:

- In patients with low leucocyte and/or neutrophil counts due to any reason.
- In patients with a history of medicine-induced bone marrow depression/toxicity.
- In patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy.
- In patients with hypereosinophilic conditions or with myeloproliferative disease.
- In patients using concomitant valproate (see section 4.8).

Body temperature regulation

Disruption of the body's ability to reduce core body temperature, pyrexia and malignant hyperpyrexia may occur during ZYPREXA therapy.

Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic medicines such as ZYPREXA. ZYPREXA should be used with caution in patients at risk for aspiration pneumonia.

Suicide

The possibility of suicide attempt is inherent in schizophrenia and close supervision of patients at risk should accompany ZYPREXA treatment.

ZYPREXA IM contains lactose

Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ZYPREXA IM.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Caution should be exercised when ZYPREXA is taken in combination with other centrally acting medicines (especially those that can cause CNS depression) and alcohol. ZYPREXA may antagonise the effects of levodopa and dopamine agonists. Because of the potential for inducing hypotension, ZYPREXA may enhance the effects of certain antihypertensive medicines.

Hypotension and/or bradycardia have been observed after administration of ZYPREXA for injection. ZYPREXA has α-1 adrenergic antagonist activity. Caution should be exercised in patients who receive treatment with other medicines that can lower blood pressure.

Potential for other medicines to affect ZYPREXA

Administration of intramuscular lorazepam (2 mg) one hour after intramuscular ZYPREXA IM (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular ZYPREXA IM increased the somnolence observed with either medicine alone and is associated with hypotension, which may be symptomatic and severe. Temporal association of treatment with ZYPREXA IM with hypotension, bradycardia, respiratory depression and death has

been very rarely (< 0,01 %) reported particularly in patients who have received benzodiazepines and/or other antipsychotics.

Simultaneous injection of intramuscular ZYPREXA IM and parenteral benzodiazepine is not recommended due to the potential for excessive sedation, cardiorespiratory depression and in very rare cases, death (see sections 4.2 and 4.4). If the patient is considered to need parenteral benzodiazepine treatment, this should not be given until at least one hour after ZYPREXA IM administration. If the patient has received parenteral benzodiazepine, ZYPREXA IM administration should only be considered after careful evaluation of clinical status and the patient should be closely monitored for excessive sedation and cardiorespiratory depression.

Potential interactions affecting ZYPREXA

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

Induction of CYP1A2

The metabolism of olanzapine may be induced by concomitant smoking or carbamazepine therapy causing subsequent lower olanzapine plasma levels. Clinical monitoring is recommended and an increase of the ZYPREXA dose may be considered.

Inhibition of CYP1A2

Known potent inhibitors of CYP1A2 activity may decrease ZYPREXA clearance. Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of ZYPREXA. The mean increase in olanzapine C_{max} following fluvoxamine was 54 % in female non-smokers and 77 % in male smokers. The mean increase in olanzapine AUC was 52 % and 108 % respectively. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin or ketoconazole. A decrease in the dose of ZYPREXA should be considered if treatment with an inhibitor of CYP1A2 is initiated.

Potential for ZYPREXA to affect other medicines

Olanzapine may antagonise the effects of direct and indirect dopamine agonists. In clinical trials with single doses of ZYPREXA, no inhibition of the metabolism of imipramine/desipramine (P450-CYP2D6 or P450-CYP3A/1A2), warfarin (P450-CYP2C9), theophylline (P450-CYP1A2) or diazepam (P450-CYP3A4 and P450-CYP2C19) was evident.

ZYPREXA showed no interaction when co-administered with lithium or biperiden.

In *in vitro* studies with human liver microsomes, olanzapine showed little potential to inhibit cytochromes P450-CYP1A2, -CYP2C9, -CYP2C19, -CYP2D6, and -CYP3A4.

Studies *in vitro* using human liver microsomes, determined that ZYPREXA has little potential to inhibit the glucuronidation of valproate, which is the major pathway for valproate metabolism. Further, valproate was found to have little effect on the metabolism of ZYPREXA *in vitro*.

Daily concomitant *in vivo* administration of 10 mg ZYPREXA for 2 weeks did not affect steady state plasma concentrations of valproate. Therefore, with concomitant use of ZYPREXA and valproate administration, a dosage adjustment of valproate is not needed.

General CNS activity

Caution should be exercised in patients who consume alcohol or receive medicines that can cause central nervous system depression.

The concomitant use of ZYPREXA with anti-Parkinsonian medicines in patients with Parkinson's disease and dementia is not recommended (see section 4.4).

QTc interval

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

Major reconstitution incompatibilities: See section 4.2.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of ZYPREXA during pregnancy has not been established. 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.

New born infants exposed to antipsychotics (including ZYPREXA) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, new borns should be monitored carefully.

Breastfeeding

Safety of ZYPREXA during lactation has not been established.

In a study in breastfeeding, healthy women, ZYPREXA was excreted in breast milk. Mean infant exposure (mg/kg) at steady state was estimated to be 1,8 % of the maternal olanzapine dose (mg/kg). Patients should be advised not to breast feed an infant if they are taking ZYPREXA.

Fertility

Effects on fertility are unknown (see section 5.3 for preclinical information).

4.7 Effects on ability to drive and use machines

ZYPREXA may cause somnolence. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that ZYPREXA therapy does not affect them adversely.

4.8 Undesirable effects

Summary of the safety profile

A common (≥ 1/100 to < 1/10) undesirable effect associated with the use of intramuscular olanzapine in clinical trials was somnolence.

In post marketing reports, temporal association of treatment with IM olanzapine with cases of respiratory depression, hypotension or bradycardia and death have been very rarely reported, mostly in patients who concomitantly received benzodiazepines, and/or other antipsychotic medicines or who were treated in excess of olanzapine recommended daily doses (see sections 4.4 and 4.5).

The following table is based on the undesirable effects and laboratory investigations from clinical trials with ZYPREXA IM powder for solution for injection rather than oral olanzapine.

Cardiac disorders *Common (≥ 1/100 to < 1/10):* Bradycardia with or without hypotension or syncope, tachycardia. *Uncommon (≥ 1/1 000 to < 1/100):* Sinus pause.
Vascular Disorders *Common (≥ 1/100 to < 1/10):* Postural hypotension, hypotension.
Respiratory disorders *Uncommon (≥ 1/1 000 to < 1/100):* Hypoventilation.
General disorders and administration site conditions *Common (≥ 1/100 to < 1/10):* Injection site discomfort.

The undesirable effects listed below have been observed following administration of oral and prolonged release intramuscular injection olanzapine, but may also occur following administration of ZYPREXA IM powder for solution for injection.

Adults

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

hepatic aminotransferases (see section 4.4), rash, asthenia, fatigue, pyrexia, arthralgia, increased alkaline phosphatase, high gamma glutamyltransferase, high uric acid, high creatine phosphokinase and oedema.

Tabulated list of adverse reactions

The following table lists the adverse reactions and laboratory investigations observed from spontaneous reporting and in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the data available).

Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and the lymphatic system disorders				
	Eosinophilia Leukopenia[10] Neutropenia[10]		Thrombocytopenia[11]	
Immune system disorders				
		Hypersensitivity[11]		
Metabolism and nutrition disorders				
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5] Glucosuria Increased appetite	Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4) [11]	Hypothermia[12]	
Nervous system disorders				

Somnolence	Dizziness Akathisia[6] Parkinsonism[6] Dyskinesia[6]	Seizures where in most cases a history of seizures or risk factors for seizures were reported [11] Dystonia (including oculogyration) [11] Tardive dyskinesia[11] Amnesia [9] Dysarthria Stuttering[11] Restless Legs Syndrome[11]	Neuroleptic malignant syndrome (see section 4.4)[12] Discontinuation symptoms[7, 12]	
Cardiac disorders				
		Bradycardia QT_c prolongation (see section 4.4)	Ventricular tachycardia/fibrillation, sudden death (see section 4.4)[11]	
Vascular disorders				
Orthostatic hypotension[10]		Thromboembolism (including pulmonary embolism and deep vein thrombosis) (see section 4.4)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry	Abdominal distension[9] Salivary hypersecretion[11]	Pancreatitis[11]	

	mouth			
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury) [11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	
Renal and urinary disorders				
		Urinary incontinence, urinary retention Urinary hesitation[11]		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders				

	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhoea in females Gynaecomastia/breast enlargement in males	Priapism[12]	
General disorders and administration site conditions				
	Asthenia Fatigue Oedema Pyrexia[10]			
Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase[10] High uric acid [10]	Increased total bilirubin		

[1] Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Following short term treatment (median duration 47 days), weight gain ≥ 7 % of baseline body weight was very common (22,2 %), ≥ 15 % was common (4,2 %) and ≥ 25 % was uncommon (0,8 %). Patients gaining ≥ 7 %, ≥ 15 % and ≥ 25 % of their baseline body weight with long-term exposure (at least 48 weeks) were very common (64,4 %, 31,7 % and 12,3 % respectively).

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

[3] Observed for fasting normal levels at baseline (< 5,17 mmol/l) which increased to high (≥ 6,2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5,17 to < 6,2 mmol/l) to high (≥ 6,2 mmol/l) were very common.

[4] Observed for fasting normal levels at baseline (< 5,56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 5,56 to < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5] Observed for fasting normal levels at baseline (< 1,69 mmol/l) which increased to high (≥ 2,26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥ 1,69 mmol/l - < 2,26 mmol/l) to high (≥ 2,26 mmol/l) were very common.

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

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

[8] In clinical trials of up to 12 weeks, plasma prolactin concentrations exceeded the upper limit of normal range in approximately 30 % of olanzapine treated patients with normal baseline prolactin value. In the majority of these patients the elevations were generally mild, and remained below two times the upper limit of normal range.

[9] Adverse event identified from clinical trials in the Olanzapine Integrated Database.

[10] As assessed by measured values from clinical trials in the Olanzapine Integrated Database.

[11] Adverse event identified from spontaneous post-marketing reporting with frequency determined utilising the Olanzapine Integrated Database.

[12] Adverse event identified from spontaneous post-marketing reporting with frequency estimated at the upper limit of the 95 % confidence interval utilising the Olanzapine Integrated Database.

Long-term exposure (at least 48 weeks)

The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9 to 12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Additional information on special populations

In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo (see section 4.4). Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.

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

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4,1 %; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥ 10 %) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥ 7 % from baseline body weight occurred in 17,4 % of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥ 7 % from baseline body weight in 39,9 % of patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications – https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Signs and symptoms

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

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

Treatment

The possibility of multiple medicine involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose, may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to ZYPREXA; therefore appropriate symptomatic and supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic medicines. Induction of emesis is not recommended. Do not use epinephrine, dopamine or other sympathomimetics with β-agonist activity, since β-stimulation may worsen hypotension in the setting of ZYPREXA-induced α-blockade. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

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

5.1 Pharmacodynamic properties

Olanzapine is an atypical antipsychotic, antimanic and mood stabilizing medicine, with affinity for serotonin $5HT_{2A/2C}$, $5HT_3$, $5HT_6$, dopamine D_4, D_3, D_1, D_2, cholinergic muscarinic receptors (m_1 - m_5), α_1-adrenergic and histamine H_1 receptors. Olanzapine demonstrated a greater *in vitro* affinity for serotonin 5HT2 than dopamine D2 receptors and greater 5 HT2 than D2 activity *in vivo* models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects.

In a single dose (10 mg) PET study in healthy volunteers, olanzapine produced higher $5HT_{2A}$ than dopamine D_2 receptor occupancy.

5.2 Pharmacokinetic properties

Absorption

Intramuscularly administered olanzapine results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. The peak concentration is about five fold higher than an equivalent oral dose. Area under the curve achieved after an intramuscular dose is equivalent to that achieved after oral administration of the same dose.

The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are quantitatively similar and qualitatively identical to metabolic profiles after oral administration.

Distribution

The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1 000 ng/ml. Olanzapine is bound predominantly 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. Other metabolites include the N-desmethyl and 2-hydroxymethyl metabolites, neither of which have *in vivo* pharmacological activity. The predominant pharmacologic activity is from the parent compound.

Elimination

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/h (12 to 47 L/hr for the 5th to 95th percentile). Olanzapine pharmacokinetics varied on the basis of smoking status, gender and age. The following table summarises these effects:

Patient Characteristics	Half-Life (hours)	Plasma Clearance (L/hr)
Non smoking	38,6	18,6
Smoking	30,4	27,7
Female	36,7	18,9
Male	32,3	27,3
Elderly (65 and older)	51,8	17,5
Nonelderly	33,8	18,2

Renal impairment

The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment (creatinine clearance < 10 ml/min) and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. Olanzapine is not removed by haemodialysis. 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 subjects (n=6) with clinically significant (Childs Pugh Classifications A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Smoking

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

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

5.3 Preclinical safety data

Acute (single-dose) toxicity

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

Repeated-dose toxicity

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

Haematologic toxicity

Effects on haematology parameters were found in each species, including dose-related reductions in circulating leukocytes in mice and non-specific reductions of circulating leukocytes in rats; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia, or anaemia developed in a few dogs treated with 8 or 10 mg/kg/day (total olanzapine exposure [AUC] is 12- to 15-fold greater than that of a man given a 12 mg dose). In cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

Reproductive toxicity

Olanzapine had no teratogenic effects. Sedation affected mating performance of male rats. Oestrous cycles were affected at doses of 1,1 mg/kg (3 times the maximum human dose) and reproduction parameters were influenced in rats given 3 mg/kg (9 times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

Mutagenicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Tartaric acid

Water for injection

Hydrochloric acid solution

Sodium hydroxide solution

6.2 Incompatibilities

ZYPREXA IM must not be mixed with other medicines except those mentioned in section 6.6.

ZYPREXA IM should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed.

Lorazepam injection should not be used to reconstitute ZYPREXA IM as this combination results in a delayed reconstitution time.

ZYPREXA IM should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

6.3 Shelf-life

Powder: 36 months

Reconstituted solution: Not more than one hour at room temperature. Do not freeze.

6.4 Special precautions for storage

Powder for injection vial:

Store at or below 25 ºC. Do not freeze. Protect from light and moisture.

After reconstitution with sterile water for injection:

Stable for one hour when stored at or below 25 ºC (see section 4.2).

6.5 Nature and contents of container

ZYPREXA IM (powder for solution for injection) vial, is a 5 ml size Type I flint glass vial closed with a rubber stopper and sealed with an aluminium crimp seal combined with a polypropylene flip top cap.

ZYPREXA IM (powder for solution for injection) vials are supplied as singles.

6.6 Special precautions for disposal and other handling

Reconstitute ZYPREXA IM only with water for injections using standard aseptic techniques for reconstitution of parenteral products. No other solutions should be used for reconstitution (see section 6.2).

Withdraw 2,1 ml of water for injection into a sterile syringe. Inject into a vial of ZYPREXA IM.

Rotate the vial until the contents have completely dissolved, giving a yellow coloured solution. The vial contains 11,0 mg olanzapine as a solution of 5 mg/ml (1 mg olanzapine is retained in the vial and syringe, thus allowing delivery of 10 mg olanzapine).

The following table provides injection volumes for delivering various doses of olanzapine:

Dose (mg)	Volume of injection (ml)
10,0	2,0
7,5	1,5
5,0	1,0
2,5	0,5

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

Discard the syringe and any unused solution in accordance with appropriate clinical procedures.

Use the solution immediately within 1 hour of reconstitution.

Parenteral medicines should be inspected visually for particulate matter prior to administration.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

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8. REGISTRATION NUMBER(S)

35/2.6.5/0307

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 July 2003

10. DATE OF REVISION OF THE TEXT

1 February 2022