SCHEDULING STATUS: S5

PROPRIETARY NAME AND DOSAGE FORMS:

ZYPREXA 2,5 (Tablets)

ZYPREXA 5 (Tablets)

ZYPREXA 10 (Tablets)

ZYPREXA VELOTAB 5 (Tablets)

ZYPREXA VELOTAB 10 (Tablets)

ZYPREXA IM (Powder for Injection)

COMPOSITION:

ZYPREXA is provided for oral administration as tablets containing olanzapine 2,5 mg; 5,0 mg or 10,0 mg.

ZYPREXA is also provided for oral administration as orally disintegrating tablets (ZYPREXA VELOTABS) containing olanzapine 5,0 mg or 10,0 mg. This is a freeze dried, rapid-dispersing preparation to be placed in the mouth or alternatively to be dispersed in water or other suitable beverage for administration. The 5 mg tablets contain sodium methyl parahydroxybenzoate 0,7 % m/m and sodium propyl parahydroxybenzoate 0,2 % m/m as preservatives. The 10 mg tablets contain sodium methyl parahydroxybenzoate 0,6 % m/m and sodium propyl parahydroxybenzoate 0,2 % m/m as preservatives.

ZYPREXA IM vials are provided for intramuscular administration as a powder for injection containing olanzapine 10,0 mg.

PHARMACOLOGICAL CLASSIFICATION:

A 2.6.5 Tranquillisers - miscellaneous structures.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties: Olanzapine is an atypical antipsychotic, antimanic and mood-stabilising agent having affinity for $5HT_{2A/2C}$, $5HT_3$, $5HT_6$, dopamine D_4, D_3, D_1, D_2, cholinergic muscarinic receptors (m_1 - m_5), α_1-adrenergic and histamine H_1 receptors. Further studies also demonstrate that olanzapine selectively interacts with the mesolimbic system without significantly interacting with the extrapyramidal system. In experimental animals, olanzapine reduces a conditioned avoidance response, a test predictive of antipsychotic activity, at doses below those required to produce catalepsy, a test predictive of motor side effects. Olanzapine increases response in an 'anxiolytic' test. In a single dose (10 mg) PET study in healthy volunteers, olanzapine produced higher $5HT_{2A}$ than dopamine D_2 receptor occupancy.

Olanzapine's antagonism of muscarinic receptors (m_1 - m_5) may explain its anticholinergic effects. Olanzapine's antagonism of histamine H_1 receptors may explain the somnolence observed with this medicine. Olanzapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this medicine.

Pharmacokinetic properties: Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food.

Pharmacokinetic studies showed that ZYPREXA film-coated tablets and ZYPREXA VELOTAB orally disintegrating tablets are bioequivalent.

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. After oral administration, the elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender:

	< 65 years	**≥ 65 years**
Men	29 hours	49 hours

Women	39 hours	55 hours

In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1,5 times greater in the elderly (≥ 65 years) than in non-elderly subjects (< 65 years). Caution should be exercised in dosing the elderly, especially if there are other factors that might additively influence medicine metabolism and/or pharmacodynamic sensitivity.

Plasma clearance of olanzapine 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, for example, may be 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 olanzapine.

The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by haemodialysis. The effect of renal impairment on metabolite elimination has not been studied.

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.

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.

INDICATIONS:

Oral olanzapine: ZYPREXA and ZYPREXA VELOTAB tablets are indicated for the management of the manifestations of psychotic disorders.

The antipsychotic efficacy of ZYPREXA was established in controlled trials of schizophrenic inpatients in the treatment of positive symptoms (such as delusions, hallucinations, disordered thinking, hostility and suspiciousness) and negative symptoms (such as blunted effect, emotional and social withdrawal, poverty of speech).

It is recommended that responding patients be continued on ZYPREXA at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

ZYPREXA is also indicated for the treatment of an acute episode of moderate to severe mania and for preventing recurrence of manic or depressive episodes of bipolar disorder.

Intramuscular olanzapine: 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 the use of ZYPREXA or ZYPREXA VELOTAB tablets should be initiated as soon as clinically appropriate.

CONTRA-INDICATIONS:

ZYPREXA is contra-indicated in patients who are hypersensitive to the product. It is also contra-indicated in patients with known risk of narrow-angle glaucoma.

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

WARNINGS:

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.

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

Hyperprolactinaemia: ZYPREXA elevates prolactin levels and a modest elevation persists during chronic administration. An increase in mammary gland neoplasms has been found in rodents after chronic administration of antipsychotic medicines and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumours in rodents is unknown.

Neuroleptic malignant syndrome (NMS): NMS has occurred infrequently in association with ZYPREXA. NMS is a potentially fatal symptom complex. 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 creatinine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. ZYPREXA should be discontinued should any of the clinical manifestations of NMS or 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. Seizures have been reported to occur infrequently in patients treated with olanzapine. In most of these cases, a history of seizures or risk factor for seizures was reported.

Tardive dyskinesia: ZYPREXA was associated with a low incidence of treatment emergent dyskinesia. If signs or symptoms of tardive dyskinesia appear in a patient on ZYPREXA, a dose reduction or discontinuation of treatment should be considered. However, some patients may benefit from continued treatment with ZYPREXA despite the presence of the syndrome. The risk of tardive dyskinesia increases with long-term exposure and symptoms can temporarily deteriorate or even arise after discontinuation of treatment.

Hepatic impairment: 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.

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 olanzapine-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 ≥ 80 years, sedation, concominant use of benzodiazepines, or presence of pulmonary conditions (e.g. pneumonia, with or without aspiration).

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 ZYPREXA.

Patients with an established diagnosis of diabetes mellitus who are started on ZYPREXA 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 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. In some cases, hyperglycaemia has resolved when ZYPREXA was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

INTERACTIONS:

Given the primary CNS effects of olanzapine, caution should be exercised when ZYPREXA is taken in combination with other centrally acting agents (especially those that can cause CNS depression) and alcohol. As it exhibits *in vitro* dopamine antagonism, 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 agents.

In clinical trials with ZYPREXA IM, olanzapine was not associated with a persistent increase in absolute QT or in QTc intervals. In clinical trials with oral administration, olanzapine was not associated with a persistent increase in absolute QT intervals. Only 8 of 1 685 subjects had increased QTc intervals on multiple occasions. However, as with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicines known to increase QTc intervals, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesemia.

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

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

Potential for other medicines to affect ZYPREXA: Single doses of antacid (aluminium, magnesium) or cimetidine did not affect the oral bioavailability of olanzapine. However, the concomitant administration of activated charcoal reduced the bioavailability of oral olanzapine by 50 to 60% and should be taken at least 2 hours before or after olanzapine.

Fluoxetine (60 mg single dose or 60 mg daily for 8 days) in combination with olanzapine (5 mg single dose), causes a mean 16 % increase in the maximum concentration of olanzapine and a mean 16 % decrease in olanzapine clearance. The effect of repeat dosage of ZYPREXA and higher dosages has not been evaluated. Combination therapy is not advised.

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

Induction of CYP1A2: The metabolism of olanzapine may be induced by concomitant smoking or carbamazepine therapy causing subsequent slightly to moderately lower olanzapine plasma levels. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine may be considered if necessary.

Inhibition of CYP1A2: Known potent inhibitors of CYP1A2 activity may decrease olanzapine clearance. Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. 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 olanzapine 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 coadministered with lithium or biperiden. Also, in *in vitro* studies with human liver microsomes, olanzapine showed little potential to inhibit cytochromes P450-CYP1A2, -CYP2C9, -CYP2C19, -CYP2D6, and -CYP3A4. Given the extensive clinical and *in vitro* studies, ZYPREXA would not be expected to interfere with the metabolism of most medicines.

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

Major reconstitution incompatibilities: See 'DOSAGE AND DIRECTIONS FOR USE – Reconstitution'

PREGNANCY AND LACTATION:

Safety of ZYPREXA during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Oral dosing:

Psychotic Disorders: ZYPREXA and ZYPREXA VELOTAB tablets should be administered on a once-a-

day schedule without regard to meals, generally beginning with an initial dose of 5 to 10 mg/day, with a target dose of 10 mg/day within several days.

In order to evaluate efficacy and guard against side effects, dosage increases should not be considered before one week, since steady state for olanzapine would not be achieved for approximately one week. The dose range is from 5 mg to 20 mg per day. Increasing the dose over the routine daily dose of 10 mg is advised only after appropriate clinical assessment.

Acute mania in bipolar disorder: ZYPREXA should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 mg. Dosage adjustments within the dose range of 5 mg to 20 mg per day, if indicated, should generally occur at intervals of not less than 24 hours.

Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg per day. For patients who have been receiving ZYPREXA for treatment of manic epispode, continue therapy for preventing recurrence at the same dose.

An increase to a dose greater than the recommended starting dose, within the range of 5 mg to 20 mg per day, is advised only after appropriate clinical assessment and should generally occur at intervals of not less than 24 hours.

The safety of doses above 20 mg/day has not been evaluated in clinical trials.

Gradual tapering of the dose should be considered when discontinuing ZYPREXA. (See 'Warnings').

ZYPREXA VELOTABS are bioequivalent to ZYPREXA coated tablets, with a similar rate and extent of absorption. They have the same dosage and frequency of administration as olanzapine coated tablets. ZYPREXA VELOTABS may be used as an alternative to ZYPREXA coated tablets.

ZYPREXA VELOTABS should be placed in the mouth, where they will rapidly disperse in the saliva, so they can be easily swallowed. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or suitable beverage (orange juice, apple juice, milk or coffee) immediately before administration.

Intramuscular dosing:

ZYPREXA IM is for intramuscular use only. Do not administer intravenously or subcutaneously. The recommended dose for olanzapine 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 olanzapine for injection should be discontinued and oral olanzapine 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.

Reconstitution:

Reconstitution of ZYPREXA IM (Powder for Injection) with sterile water for injection:

- Reconstitute using 2,1 ml sterile water for injection.
- The following table provides injection volumes for delivering various doses of olanzapine:

Dose, mg Olanzapine	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.**

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

The following table summarizes the core side effects identified with ZYPREXA during oral and intramuscular clinical trials and/or during postmarketing experience:

Body System/Adverse Reaction Terms	**Frequency**				
Events	≥ 10 %	< 10 % and ≥ 1 %	< 1 % and ≥ 0,1 %	< 0,1 % and ≥ 0,01 %	< 0,01 %
	Very Common	Common	Uncommon	Rare	Very Rare
Body as a Whole					
Allergic reaction					X
Asthenia		X			
Discontinuation reaction					X
Photosensitivity reaction			X		
Weight gain	X				

Cardiovascular					
Bradycardia			X		
Orthostatic hypotension		X			
Venous thromboembolism					X
Digestive System					
Constipation		X			
Dry mouth		X			
Hepatitis					X
Increased Appetite		X			
Pancreatitis					X
Haematologic					
Leucopenia				X	
Thrombocytopenia					X
Metabolic					
Diabetic coma					X
Diabetic ketoacidosis					X
Hypercholesterolaemia[1]					X
Hyperglycaemia					X
Hypertriglyceridaemia[1]					X
Peripheral oedema		X			
Musculoskeletal					
Rhabdomyolysis					X
Nervous System					
Akathisia		X			
Dizziness		X			
Seizures				X	
Somnolence	X				
Urogenital System					
Priapism					X
Skin and Appendages					

Rash				X	
Laboratory Analytes					
Clinical chemistry					
ALT/SGPT - Increased		X			
AST/SGOT - Increased		X			
Prolactin - Increased	X				
Haematology					
Eosinophilia		X			

[1] **Random cholesterol levels of greater than or equal to 240 mg/dL and random triglyceride levels of greater than or equal to 1000 mg/dL have been very rarely reported**

Common (< 10 % and ≥ 1%) undesirable effects associated specifically with use of intramuscular olanzapine in clinical trials included hypotension, tachycardia, and bradycardia.

The following table summarizes additional core side effects identified only during the intramuscular clinical trials:

Body System/Adverse Reaction Terms	**Frequency**				
Events	≥ 10 %	< 10 % and ≥ 1 %	<1 % and ≥ 0,1 %	< 0,1 % and ≥ 0,01 %	< 0,01 %
	Very Common	Common	Uncommon	Rare	Very Rare
Cardiovascular					
Hypotension		X			
Tachycardia		X			
Bradycardia		X			

The following table summarizes additional core side effects identified only during clinical trials in patients with dementia of the Alzheimer's type:

Body System/Adverse Reaction	**Frequency**

Terms					
Events	≥ 10 %	< 10 % and ≥ 1 %	< 1 % and ≥ 0,1 %	< 0,1 % and ≥ 0,01 %	< 0,01 %
	Very Common	Common	Uncommon	Rare	Very Rare
Nervous System					
Abnormal gait	X				
Falls	X				
Urogenital System					
Urinary incontinence		X			
Respiratory System					
Pneumonia		X			

The following table summarizes additional core side effects identified only during clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease:

Body System/Adverse Reaction Terms	**Frequency**				
Events	≥ 10 %	< 10 % and ≥ 1 %	< 1 % and ≥ 0,1 %	< 0,1 % and ≥ 0,01 %	< 0,01 %
	Very Common	Common	Uncommon	Rare	Very Rare
Nervous System					
Hallucinations	X				
Parkinsonian symptomatology	X				

The following table summarizes additional core side effects identified only during bipolar mania clinical trials in patients receiving olanzapine in combination with lithium or valproate:

Body System/Adverse Reaction	**Frequency**

Terms					
Events	≥ 10 %	< 10 % and ≥ 1 %	< 1 % and ≥ 0,1 %	< 0,1 % and ≥ 0,01 %	< 0,01 %
	Very Common	Common	Uncommon	Rare	Very Rare
Body as a whole					
Weight gain	X				
Digestive system					
Dry mouth	X				
Increased appetite	X				
Nervous System					
Speech disorder		X			
Tremor	X				

Special precautions:

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.

Hypotension and/or bradycardia have been observed during ZYPREXA IM administration. 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 IM olanzapine, 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.

Simultaneous injection of intramuscular olanzapine and parenteral benzodiazepines has not been studied and is therefore not recommended. (See also 'Interactions'). If the patient is considered to need parenteral benzodiazepine treatment, this should not be given until at least 1 hour after IM

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

Concomitant illnesses: Clinical experience with ZYPREXA in patients with concomitant illness is limited. As 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.

ZYPREXA has not been evaluated or used to any appreciable extent 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.

There is an increased prevalence of diabetes amongst patients with schizophrenia. As with other antipsychotics, hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during ZYPREXA treatment. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for developing diabetes mellitus.

Renal and hepatic impairment: See 'Pharmacokinetic properties'.

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

Phenylalanine: ZYPREXA VELOTAB tablets contain aspartame, which is a source of phenylalanine.

Effects on ability to drive and use of 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.

Geriatric use: In clinical studies, in general, there was no indication of any different tolerability of ZYPREXA in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, or increase the pharmacodynamic response to ZYPREXA, should lead to consideration of a lower starting dose. As postural hypotension was infrequently observed in the elderly in clinical trials, it is recommended that blood pressure is measured periodically in patients over 65 years.

Orthostatic hypotension: ZYPREXA may induce orthostatic hypotension associated with dizziness, tachycardia and in some patients, syncope, especially during the initial treatment period.

Hyperprolactinaemia: See 'Warnings'.

Transaminase elevations: Transient elevations of liver transaminases (ALT, AST) have been observed. Caution should therefore 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 agents. In the event of elevated ALT and/or AST during treatment, follow-up should be organised and dose reduction should be considered. In cases where hepatitis has been diagnosed, olanzapine treatment should be discontinued.

Haematology: Caution should be exercised when using olanzapine 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.

Thirty-two patients with clozapine-related neutropenia or agranulocytosis histories received olanzapine without decreases in baseline neutrophil counts.

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

Dysphagia: Oesophageal dysmotility and aspiration have been associated with antipsychotic medicines. 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 high risk patients should accompany ZYPREXA treatment.

Carcinogenesis: Based on the results of studies in mice and rats, it was concluded that olanzapine is not carcinogenic. Prolactin mediated tumours: see 'Hyperprolactinaemia' under WARNINGS.

Mutagenesis: 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.

Impairment of fertility: In rats, male mating, but not fertility, was impaired. Discontinuance of olanzapine treatment reversed the effect on mating performance. In female rats, oestrus cycles and reproduction parameters were influenced at doses higher than the maximum human dose.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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, 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 1 500 mg.

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 agents. 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 olanzapine-induced α-blockade. Close medical supervision and monitoring should continue until the patient recovers.

IDENTIFICATION:

ZYPREXA 2,5 (Tablets), TA 4112, are round, white, film-coated tablets, imprinted with "LILLY" and "4112" in blue ink.

ZYPREXA 5 (Tablets), TA 4115, are round, white, film-coated tablets, imprinted with "LILLY" and "4115" in blue ink.

ZYPREXA 10 (Tablets), TA 4117, are round, white, film-coated tablets, imprinted with "LILLY" and "4117" in blue ink.

ZYPREXA VELOTAB 5 (Tablets), TA4453, are yellow, round, freeze-dried tablets.

ZYPREXA VELOTAB 10 (Tablets), TA 4454, are yellow, round, freeze-dried tablets.

ZYPREXA IM (Powder for Injection) vial, VL 7597, is a 5 ml size Type I flint glass vial closed with a rubber stopper and sealed with an aluminium cap. It contains a yellow, sterile, lyophilised plug.

PRESENTATION:

ZYPREXA tablets are supplied in blister packs of 28.

ZYPREXA VELOTAB tablets are supplied in blister strips of 28. The blisters consist of aluminium-plastic web film sealed with an aluminium foil lid.

ZYPREXA IM (Powder for Injection) vials are supplied as singles.

STORAGE INSTRUCTIONS:

ZYPREXA tablets: Store below 30 ºC in blister packs. Protect from light and moisture.

ZYPREXA VELOTAB tablets: Store below 30 ºC in blister packs. Protect from light and moisture.

DO NOT REMOVE FROM BLISTER UNTIL READY FOR ADMINISTRATION.

Powder for injection vial: Store below 25 ºC. Do not freeze. Protect from light and moisture.

After reconstitution with sterile water for injection: Stable for one hour when stored below 25 ºC (see 'Dosage and directions for use').

Keep out of reach of children.

REGISTRATION NUMBERS:

32/2.6.5/0685 for ZYPREXA 2,5 tablets

31/2.6.5/0058 for ZYPREXA 5 tablets

31/2.6.5/0060 for ZYPREXA 10 tablets

38/2.6.5/0030 for ZYPREXA VELOTAB 5 tablets

38/2.6.5/0073 for ZYPREXA VELOTAB 10 tablets

35/2.6.5/0307 for ZYPREXA IM (Powder for Injection)

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Equity Pharmaceuticals (Pty) Ltd.

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