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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	

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
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 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					
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 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					
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:

Eli Lilly (S.A.) (Pty) Limited

1 Petunia Street, Private Bag X119

Bryanston, 2021

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

01 Dec 2006

BOTSWANA REGISTRATION DETAILS	REGISTRATION NUMBER
ZYPREXA 2.5 Tablets	R9800327 (S2)
ZYPREXA 5 Tablets	R9800186 (S2)
ZYPREXA 10 Tablets	R9800188 (S2)
ZYPREXA IM 10 mg	BOT 0300572 (S2)

ZIMBABWE REGISTRATION DETAILS	REGISTRATION NUMBER
ZYPREXA 2.5 Tablets	99/13.2.3/3513 (PP)
ZYPREXA 5 Tablets	99/13.2.3/3510 (PP)
ZYPREXA 10 Tablets	99/13.2.3/3512 (PP)
ZYPREXA IM 10 mg	2005/13.2.3/4392 (PP)

NAMIBIA REGISTRATION DETAILS

Namibian Schedule: NS3	REGISTRATION NUMBER
ZYPREXA 2.5 Tablets	04/2.6.5/0668
ZYPREXA 5 Tablets	04/2.6.5/0669
ZYPREXA 10 Tablets	04/2.6.5/0670
ZYPREXA IM 10 mg	05/2.6.5/0309
ZYPREXA VELOTAB 5	06/2.6/0220
ZYPREXA VELOTAB 10	06/2.6/0221

APPROVAL FOR SUBMISSION TO REGULATORY AUTHORITY:		
Title:	**Signature**	**Date:**
Affiliate Labelling Responsible Person	_____	_____
Registration Pharmacist/ Associate	_____	_____
Medical	_____	_____
Marketing	_____	_____
Accuracy of Afrikaans Translation verified by:		
Title:	**Signature:**	**Date:**
_____	_____	_____
APPROVAL FOR DEVELOPMENT OF PROOF:		
Title:	**Signature:**	**Date:**
Affiliate Labelling Responsible Person	_____	_____

SKEDULERINGSTATUS: S5

EIENDOMSNAME EN DOSEERVORME:

ZYPREXA 2,5 (Tablette)

ZYPREXA 5 (Tablette)

ZYPREXA 10 (Tablette)

ZYPREXA VELOTAB 5 (Tablette)

ZYPREXA VELOTAB 10 (Tablette)

ZYPREXA IM (Poeier vir Inspuiting)

SAMESTELLING:

ZYPREXA word voorsien vir mondelike toediening as tablette wat olansapien 2,5 mg; 5,0 mg of 10,0 mg bevat.

ZYPREXA word ook voorsien vir mondelike toediening as oplosbare tablette (ZYPREXA VELOTABS) wat olansapien 5,0 mg of 10,0 mg bevat. Dit is ’n vriesgedroogde, vinnig oplosbare preparaat wat in die mond of alternatiewelik in water of ’n toepaslike vloeistofmiddel opgelos kan word vir toediening. Die 5 mg tablette bevat natrium metiel parahidroksiebensoaat 0,7 % m/m en natrium propiel parahidroksiebensoaat 0,2 % m/m as preserveermiddels. Die 10 mg tablette bevat natrium metiel parahidroksiebensoaat 0,6 % m/m en natrium propiel parahidroksiebensoaat 0,2 % m/m as preserveermiddels.

ZYPREXA IM flessies word voorsien vir intramuskulêre toediening, as 'n poeier vir inspuiting wat olansapien 10,0 mg bevat.

FARMAKOLOGIESE KLASSIFIKASIE:

A 2.6.5 Bedaarmiddels - diverse strukture

FARMAKOLOGIESE WERKING:

Farmakodinamiese eienskappe: Olansapien is 'n atipiese anti-psigotiese, anti-maniese en gemoedstemming stabiliserende middel wat 'n affiniteit het vir $5HT_{2A/2C}$, $5HT_3$, $5HT_6$, dopamien D_4, D_3, D_1, D_2, cholinergiese muskarienreseptore (m_1 - m_5), α_1-adrenergiese en histamien H_1-reseptore. Verdere studies toon ook dat daar selektiewe wisselwerking tussen olansapien en die mesolimbiese stelsel plaasvind, sonder beduidende wisselwerking met die ekstrapiramidale stelsel. By eksperimentele diere verminder olansapien 'n gekondisioneerde ontwykingsreaksie, 'n toets wat gebruik word om moontlike antipsigotiese aktiwiteit te voorspel, teen dosisse wat laer is as dié wat nodig is om katalepsie, 'n toets waarmee motoriese newe-effekte voorspel kan word, te

bewerkstellig. Olansapien verhoog die reaksie op 'n 'anksiolitiese' toets. In 'n enkeldosis (10 mg) foton-emissie tomografie-studie by gesonde vrywilligers, het olansapien hoër $5HT_{2A}$- as dopamien D_2-reseptorbesetting teweeggebring.

Antagonisme van muskarienreseptore (m_1-m_5) deur olansapien kan die anticholinergiese effekte daarvan verklaar. Antagonisme van histamien H_1-reseptore deur olansapien kan die slaperigheid wat met die geneesmiddel waargeneem is, verklaar. Antagonisme van adrenergiese α_1-reseptore deur olansapien kan die ortostatiese hipotensie wat met die geneesmiddel waargeneem is, verklaar.

Farmakokinetiese eienskappe: Olansapien word goed geabsorbeer na mondelike toediening en bereik piekplasmakonsentrasies binne 5 tot 8 uur. Absorpsie word nie deur voedsel beïnvloed nie.

Farmakokinetiese studies het getoon dat ZYPREXA film-bedekte tablette en ZYPREXA VELOTAB orale oplosbare tablette bio-ekwivalent is.

Olansapien word in die lewer gemetaboliseer deur middel van konjugasie en oksidasie. Die hoof sirkulerende metaboliet is die 10-N-glukuronied, wat nie deur die bloedbreinskans gaan nie. Ander metaboliete sluit die N-desmetiel- en die 2-hidroksimetielmetaboliete, waarvan nie een *in vivo* farmakologies aktief is nie, in. Die moederverbinding is verantwoordelik vir die oorheersende farmakologiese aktiwiteit. Na mondelike toediening het die eliminasie-halfleeftyd van olansapien by gesonde persone gewissel volgens ouderdom en geslag:

	< 65 jaar	**≥ 65 jaar**
Mans	29 uur	49 uur
Vrouens	39 uur	55 uur

Tydens 'n studie met 24 gesonde proefpersone, was die gemiddelde eliminasie-halfleeftyd van olansapien ongeveer 1,5 keer langer by bejaarde persone (≥ 65 jaar) as by jonger persone (< 65 jaar). Dosering van bejaarde persone moet met omsigtigheid gedoen word, veral as ander faktore, wat 'n bydraende invloed op die geneesmiddelmetabolisme en/of farmakodinamiese sensitiwiteit kan hê, teenwoordig is.

Plasma-opruiming van olansapien is hoër by rokers.

Die gesamentlike invloed van ouderdom, rook en geslag kan tot aansienlike farmakokinetiese verskille in die populasie aanleiding gee. By jong, rokende mans, kan die olansapien-opruiming byvoorbeeld 3 keer hoër wees as by bejaarde, nie-rokende vrouens. Dosisaanpassing kan nodig

wees by pasiënte met 'n kombinasie van faktore, wat tot stadiger metabolisme van olansapien aanleiding kan gee.

Die farmakokinetiese eienskappe van olansapien was soortgelyk by pasiënte met erge nierontoereikendheid en normale proefpersone, wat daarop dui dat dosisaanpassing, gebaseer op die graad van nierontoereikendheid, nie nodig is nie. Daarbenewens word olansapien nie deur dialise verwyder nie. Die effek van nierontoereikendheid op metaboliet-eliminasie is nie nagevors nie.

Die plasmaproteïenbinding van olansapien was ongeveer 93 % oor die konsentrasiereikwydte van ongeveer 7 tot ongeveer 1 000 ng/ml. Olansapien is hoofsaaklik aan albumien en α_1-suurglikoproteïen gebonde.

Wanneer intramuskulêr toegedien, word olanzapien vinnig opgeneem en piekkonsentrasies word binne 15 tot 45 minute waargeneem. Die piekkonsentrasie is ongeveer vyf keer hoër as 'n ekwivalente mondelike dosis. Die halfleeftyd na binnespierse toediening is soortgelyk aan dié na mondelike toediening. Die farmakokinetika is reglynig oor die kliniese doseringsreikwydte. Die metaboliese profiel na binnespierse toediening is kwantitatief soortgelyk en kwalitatief identies aan die metaboliese profiel na mondelike toediening.

INDIKASIES:

Orale olansapien: ZYPREXA en ZYPREXA VELOTAB tablette word aangedui vir die beheer van manifestasies van psigotiese versteurings.

Die antipsigotiese doeltreffendheid van ZYPREXA is vasgestel in gekontroleerde proewe van skisofreniese binne-pasiënte, vir die behandeling van positiewe simptome (soos waandenkbeelde, hallusinasies, verwarde denke, vyandigheid en agterdogtigheid) en negatiewe simptome (soos afgestompte gemoed, emosionele en sosiale onttrekking en gebrekkige spraak).

Dit word aanbeveel dat pasiënte wat op die behandeling reageer, voortgaan met die laagste dosis ZYPREXA wat nodig is om remissie te handhaaf. Pasiënte moet periodiek geëvalueer word om die nodigheid van instandhoudingsbehandeling te bepaal.

ZYPREXA word ook aangedui vir die behandeling van ‘n akute episode van matige tot erge manie en vir die voorkoming van herhaling van maniese of depressiewe episodes in bipolêre versteurings.

Intramuskulêre olansapien: ZYPREXA IM inspuiting word aangedui vir die beheer van agitasie en versteurde gedrag by pasiënte met skisofrenie en verwante psigoses en by pasiënte met akute

manie wat met Bipolêre I afwyking verband hou, wanneer orale terapie nie toepaslik is nie. Behandeling met ZYPREXA IM moet gestaak en die gebruik van ZYPREXA of ZYPREXA VELOTAB tablette begin word sodra klinies van pas.

KONTRA-INDIKASIES:

ZYPREXA word teenaangedui by pasiënte wat daarvoor allergies is. Dit word ook teenaangedui by pasiënte met 'n bekende risiko van nouhoek-gloukoom.

Pediatriese gebruik: Veiligheid en doeltreffendheid by pasiënte onder die ouderdom van 18 jaar is nie vasgestel nie.

WAARSKUWINGS:

Diskontinuasie reaksies mag voorkom, gewoonlik binne ’n week nadat ZYPREXA gestaak is. Hierdie reaksies mag voorkom as cholinergiese sindroom (diaforese, diarree, sialoree, naarheid en braking, angstigheid, agitasie, insomnie en bewing). ZYPREXA moet om hierdie rede geleidelik verminder word.

Intramuskulêre gebruik: Ernstige/hewige bradikardie, sinkopee kan voorkom. Tydens kliniese proewe was daar gevalle van erge simptomatiese hipotensie, apnee en ventrikulêre tagidisritmieë, insluitend fataliteite. In meeste van die ernstige gevalle was daar ’n temporale verhouding met die gebruik van bensodiasepiene. Sien ‘Spesiale Voorsorgmaatreëls’.

Hiperprolaktinemie: ZYPREXA verhoog prolaktienvlakke en 'n matige verhoging duur voort tydens langdurige toediening. 'n Toename in borskliergewasse, wat as prolaktien-bemiddeld beskou word, is na langdurige toediening van antipsigotiese middels by knaagdiere gevind. Die toepaslikheid van die voorkoms van prolaktienbemiddelde endokriene gewasse by knaagdiere ten opsigte van risiko vir die mens is onbekend.

Neuroleptiese maligne sindroom (NMS): NMS het selde in assosiasie met ZYPREXA voorgekom. NMS is 'n potensieel noodlottige simptoomkompleks. Kliniese manifestasies van NMS is hiperpireksie, spierstyfheid, verandering in geestestoestand en tekens van outonome onstabiliteit (onreëlmatige pols of bloeddruk, tagikardie, sweettoename en hartdisritmieë). Addisionele tekens kan verhoogde kreatinienfosfokinase, mioglobinurie (rabdomiolise) en akute nierversaking insluit. ZYPREXA moet gestaak word indien enige van die kliniese manifestasies van NMS, of hoë koors sonder die addisionele kliniese manifestasies van NMS, waargeneem word.

Konvulsies: ZYPREXA moet met omsigtigheid gebruik word by pasiënte met 'n geskiedenis van konvulsies of wat onderhewig is aan faktore wat die drempelwaarde van konvulsies kan verlaag. Konvulsies is selde by pasiënte tydens behandeling met olansapien aangemeld. In meeste van die gevalle, is òf 'n geskiedenis van òf risikofaktore vir konvulsies aangemeld.

Vertraagde diskinesie: ZYPREXA is met 'n lae voorkoms van diskinesie tydens behandeling geassosieer. Indien tekens of simptome van vertraagde diskinesie voorkom by 'n pasiënt wat ZYPREXA ontvang, moet 'n dosisvermindering of staking van die behandeling oorweeg word. Sommige pasiënte kan egter baat vind by voortgesette behandeling met ZYPREXA ten spyte van die teenwoordigheid van hierdie sindroom. Die risiko van vertraagde diskinesie verhoog met langdurige blootstelling en simptome kan tydelik vererger of selfs ontstaan nadat behandeling gestaak is.

Lewerontoereikendheid: Olansapien moet met omsigtigheid gebruik word by pasiënte met tekens en simptome van lewerontoereikendheid, by pasiënte met voorafbestaande toestande wat met beperkte lewerfunksie-reserwe geassosieer word en by pasiënte wat met medisyne met moontlike lewertoksisiteit behandel word. Periodieke vasstelling van transaminases word aanbeveel by pasiënte met beduidende lewersiekte. 'n Aanvangsdosis van 5 mg moet oorweeg word by pasiënte met matige lewerontoereikendheid.

Kennis oor veiligheid in bejaarde pasiënte met demensie-verwante psigose:
Die effektiwiteit van ZYPREXA in bejaarde pasiënte met demensie-verwante psigose, is nog nie vasgestel nie. Tydens plasebo gekontroleerde kliniese studies van bejaarde pasiënte met demensie-verwante psigose, was die insidensie van sterftes statisties hoër in die olansapien behandelde pasiënte as in die plasebo behandelde pasiënte (3,5 % vs. 1,5 % onderskeidelik). Abnormale stap en val was baie algemeen (> 10 %), urinêre inkontinensie en respiratoriese infeksie was algemeen, en daar was ’n verhoogde insidensie van serebrovaskulêre insidente, insluitend beroerte. Risiko faktore wat hierdie pasiënte populasie se mortaliteit risiko verhoog wanneer hulle ZYPREXA behandeling ontvang, sluit in ouderdom ≥ 80 jaar, sedasie, gelyktydige gebruik met bensodiasepiene, of die teenwoordigheid van pulmonêre siekte (bv. pneumonie, met of sonder aspirasie).

Hiperglisemie en Diabetes Mellitus:
Hiperglisemie, in sekere gevalle van ernstige graad en geassosieer met ketoasidose of hiperosmolêre koma of sterfte, is aangemeld in pasiënte op ZYPREXA behandeling.

Pasiënte met ’n bestaande diagnose van diabetes mellitus wat met ZYPREXA behandeling begin word, moet gereeld gemoniteer word vir verswakking van glukose beheer. Pasiënte met risiko faktore van diabetes mellitus (bv. oorgewig, familie geskiedenis van diabetes), wat ZYPREXA behandeling begin, moet gemonitor word vir simptome van hiperglisemie insluitend, polidipsie, poliurie, polifagie en swakheid. Pasiënte wat hiperglisemiese simptome ontwikkel tydens ZYPREXA behandeling, moet vastende bloedglukose toetse laat doen. In sekere gevalle het die hiperglisemie opgeklaar met die staking van ZYPREXA, maar daar was ook gevalle waar pasiënte anti-diabetiese middel behandeling moes ontvang ten spyte daarvan dat ZYPREXA gestaak is.

INTERAKSIES:

Weens die primêre uitwerking van olansapien op die sentrale senuweestelsel, moet omsigtigheid aan die dag gelê word wanneer ZYPREXA saam met ander sentraalwerkende middels (veral dié wat SSS-onderdrukking kan veroorsaak) en alkohol geneem word. ZYPREXA kan die uitwerking van levodopa en dopamien-agoniste teenwerk aangesien dit *in vitro* dopamien-antagonisme toon. Weens die potensiaal om hipotensie te induseer, kan ZYPREXA die effek van sekere antihipertensiewe middels versterk.

Tydens kliniese proewe met ZYPREXA IM is olansapien nie geassosieer met ’n volgehoue toename in absolute QT- of QTc-intervalle nie. Tydens kliniese proewe met orale toediening is olansapien nie geassosieer met ’n volgehoue toename in absolute QT-intervalle nie. Slegs 8 van 1 685 persone het verhoogde QTc-intervalle met herhaalde geleenthede gehad. Versigtigheid moet egter aan die dag gelê word, soos met ander antipsigotiese middels, wanneer olansapien voorgeskryf word saam met ander medisyne waarvan dit bekend is dat hulle die QTc-interval verleng, veral by bejaardes, by pasiënte met kongenitale lang QT-sindroom, kongestiewe hartversaking, harthipertrofie, hipokalemie of hipomagnesemie.

Hipotensie en/of bradikardie is waargeneem tydens intramuskulêre toediening van olansapien vir inspuiting. Olansapien het α-1-adrenergiese aktiwiteit. Versigtigheid moet aan die dag gelê word by pasiënte wat behandeling met medisinale produkte ontvang wat bloeddruk kan verlaag deur meganismes anders as α-1-adrenergiese antagonisme.

Potensiële interaksies wat ’n uitwerking op olansapien kan hê: Aangesien olansapien deur CYP1A2 gemetaboliseer word, kan stowwe wat hierdie iso-ensiem spesifiek kan induseer of inhibeer, die farmakokinetika van olansapien beïnvloed.

Ander geneesmiddels se potensiaal om 'n uitwerking op ZYPREXA te hê: Enkeldosisse teensuurmiddel (aluminium, magnesium) of simetidien het nie die mondelike biobeskikbaarheid

van olansapien beïnvloed nie. Die gelyktydige toediening van geaktiveerde houtskool het egter die orale biobeskikbaarheid van olansapien met 50 tot 60 % verlaag en dit moet ten minste 2 uur voor of na olansapien geneem word.

Fluoksetien (60 mg enkeldosis of 60 mg daagliks vir 8 dae) in kombinasie met olansapien (5 mg enkeldosis), veroorsaak 'n gemiddelde toename van 16 % in die maksimum konsentrasie van olansapien en 'n gemiddelde afname van 16 % in olansapienopruiming. Die effek van herhaaldelike en hoër dosisse ZYPREXA is nie vasgestel nie. Kombinasie-behandeling word nie aanbeveel nie.

Die toediening van intramuskulêre lorasepam (2 mg) saam met intramuskulêre olansapien (5 mg) het nie die farmakokinetika van olansapien, ongekonjugeerde lorasepam of totale lorasepam beduidend beïnvloed nie. Toediening van intramuskulêre lorasepam saam met intramuskulêre olansapien het egter bygevoeg tot die slaperigheid wat met elke medisyne alleen waargeneem word.

Induksie van CYP1A2: Rook en gelyktydige karbamasepienbehandeling kan die metabolisme van olansapien induseer, wat effens tot taamlik verlaagde olansapienplasmavlakke kan veroorsaak. Die kliniese gevolge sal waarskynlik beperk wees, maar kliniese monitering word aanbeveel en ’n verhoging van olansapien kan oorweeg word, indien nodig.

Inhibisie van CYP1A2: Bekende kragtige inhibeerders van CYP1A2-aktiwiteit kan olansapien-opruiming verminder. Daar is gewys dat fluvoksamien, ’n spesifieke CYP1A2-inhibeerder, die metabolisme van olansapien beduidend inhibeer. Die gemiddelde toename in olansapien-C_{max} na fluvoksamien was 54 % by vroulike nie-rokers en 77 % by manlike rokers. Die gemiddelde toename in olansapien-AOK was 52 % en 108 % respektiewelik. ’n Laer begindosis van olansapien moet oorweeg word by pasiënte wat fluvoksamien of enige ander CYP1A2-inhibeerders gebruik, soos siprofloksasien of ketokonasool. ’n Verlaging in die dosis van olansapien moet oorweeg word as behandeling met ’n inhibeerder van CYP1A2 begin word.

ZYPREXA se potensiaal om 'n uitwerking op ander geneesmiddels te hê: Olansapien kan die uitwerking van direkte en indirekte dopamienagoniste antagoniseer. Tydens kliniese proewe met enkeldosisse van ZYPREXA, het daar geen onderdrukking van die metabolisme van imipramien/desipramien (P450-CYP2D6 of P450-CYP3A/1A2), warfarien (P450-CYP2C9), teofillien (P450-CYP1A2) of diasepam (P450-CYP3A4 en P450-CYP2C19) voorgekom nie. ZYPREXA het geen wisselwerking getoon wanneer dit gelyktydig met litium of biperideen toegedien is nie. Olansapien het ook, tydens *in vitro*-studies met menslike lewer mikrosome, min potensiaal getoon om die sitochrome P450-CYP1A2, -CYP2C9, -CYP2C19, -CYP2D6 en -

CYP3A4 te onderdruk. In die lig van die uitgebreide kliniese en *in vitro* studies, word nie verwag dat ZYPREXA met die metabolisme van die meeste geneesmiddels sal inmeng nie.

Tydens *in vitro* studies, waar van mens-lewermikrosome gebruik gemaak is, is vasgestel dat ZYPREXA min potensiaal het om die glukuronidasie van valproaat, die hoof metaboliese pad van valproaat, te inhibeer. Verder is daar ook *in vitro* vasgestel dat valproaat geringe invloed op die metabolisme van ZYPREXA het. Kliniese farmakokinetiese interaksie tussen ZYPREXA en valproaat is nie vasgestel nie.

Hoof hersamestelling onverenigbaarheid: Sien 'DOSIS EN GEBRUIKSAANWYSINGS' – 'Hersamestelling'

SWANGERSKAP EN LAKTASIE:
Veiligheid van ZYPREXA tydens swangerskap en borsvoeding is nog nie vasgestel nie.

DOSIS EN GEBRUIKSAANWYSINGS:
Orale dosering:
Psigotiese afwykings: ZYPREXA en ZYPREXA VELOTAB tablette moet as 'n daaglikse enkeldosis, sonder inagneming van maaltye, toegedien word. Oor die algemeen moet daar met 'n aanvangsdosis van 5 tot 10 mg per dag begin word, met 'n teikendosis van 10 mg/dag binne etlike dae.

Aangesien stabiele toestand van olansapienbloedvlakke eers na ongeveer een week bereik word en om die effektiwiteit te bepaal en te waak teen newe-effekte, moet verdere dosisaanpassings, indien aangedui, met tussenpose van nie minder as een week geskied nie. Die dosering reeks is van 5 mg tot 20 mg per dag. Verhoging van die dosis bo die aanbevolle daaglikse dosering van 10 mg word nie aanbeveel sonder toepaslike kliniese ondersoek nie.

Akute manie in bipolêre versteurings: ZYPREXA word gewoonlik begin as 'n daaglikse 10 mg enkeldosis, sonder inagneming van maaltye. Dosering aanpasssing binne die aanbevolle 5 mg tot 20 mg per dag, indien aangedui, moet oor teen intervalle van nie korter as 24 uur geskied nie.

Voorkoming van herhaling van episodes in bipolêre versteurings: Die aanbevolle begin dosering is 10 mg per dag. In pasiënte wat ZYPREXA ontvang vir die behandeling van maniese episodes, moet die terapie vir die voorkoming van herhaling van episodes volgehou word teen dieselfde dosering.

Verhoging van die dosering bo die roetine 10 mg daaglikse dosis, binne die reeks van 5 mg tot 20 mg per dag, word alleenlik aanbeveel na toepaslike kliniese ondersoek en nie teen intervalle van korter as 24 uur nie.

Die veiligheid van dosisse wat 20 mg/dag oorskry, is nie tydens kliniese proewe geëvalueer nie.

Geleidelike vermindering van die dosering moet oorweeg word wanneer ZYPREXA behandeling gestaak word. (Sien 'WAARSKUWINGS').

ZYPREXA VELOTAB is bio-ekwivalent aan ZYPREXA bedekte tablette, met 'n soortgelyke tempo en graad van absorpsie. Dit het dieselfde dosering en frekwensie van toediening as olansapien bedekte tablette. ZYPREXA VELOTABS mag gebruik word as 'n alternatief tot ZYPREXA bedekte tablette.

ZYPREXA VELOTABS moet in die mond geplaas word, waar dit vinnig kan oplos in die speeksel, sodat dit maklik ingesluk kan word. Verwydering van die heel oraal oplosbare tablet van die mond is moeilik. Die tablet moet dadelik geneem word wanneer dit uit die verpakking gehaal is, aangesien dit breekbaar is. Alternatiewelik kan dit in 'n glas vol water of 'n ander toepaslike vloeistof (lemoensap, appelsap, melk of koffie) direk voor toediening opgelos word.

Intramuskulêre dosis:
ZYPREXA IM is slegs vir intramuskulêre gebruik. Moenie intraveneus of subkutaan toedien nie. Die aanbevole dosis vir olansapieninspuiting is 10 mg, toegedien as 'n enkele intramuskulêre inspuiting. Op grond van individuele kliniese toestand kan 'n tweede inspuiting van tot 10 mg toegedien word reeds twee uur na die eerste inspuiting en 'n derde inspuiting van tot 10 mg kan toegedien word reeds vier uur na die tweede inspuiting. Die veiligheid van totale daaglikse dosisse groter as 30 mg is nie tydens kliniese proewe geëvalueer nie.

Behandeling met olansapien vir inspuiting moet gestaak word en met orale olansapien in 'n dosisreeks van 5 – 20 mg / dag begin word sodra klinies van pas.

Bejaarde pasiënte: 'n Kleiner begindosis van 2,5 - 5 mg per inspuiting moet oorweeg word vir bejaarde pasiënte.

Hersamestelling:

Hersamestelling van ZYPREXA IM (Poeier vir Inspuiting) met steriele water vir inspuiting:

- Gebruik 2,1 ml steriele water vir inspuiting vir hersamestelling.
- Inspuitingvolumes wat nodig is om verskillende dosisse van olansapien te lewer, word in die volgende tabel gegee:

Dosis, mg Olansapien	Volume van Inspuiting, ml
10,0	Onttrek totale inhoud van flessie
7,5	1,5
5,0	1,0
2,5	0,5

Hoof hersamestelling onverenigbaarheid:

- **ZYPREXA IM moet alleenlik met steriele water vir inspuiting gerekonstitueer word.**
- **ZYPREXA IM moet nie in ’n inspuiting saam diasepam gekombineer word nie, aangesien presipitasie voorkom wanneer die produkte vermeng word.**
- **Lorasepam inspuiting moet nie gebruik word vir hersamestelling van ZYPREXA IM nie, aangesien hierdie kombinasie lei tot vertraagde rekonstitusie tyd.**
- **ZYPREXA IM moet nie in ’n inspuiting saam haloperidol gegee word nie, want die olansapien word oor tyd gedegradeer deur die lae pH.**

NEWE-EFFEKTE EN SPESIALE VOORSORGMAATREëLS:

Newe-effekte:

Die volgende tabel is ‘n opsomming van die kern newe-effekte wat voorgekom het met ZYPREXA behandeling tydens orale en intramuskulêre kliniese studies en/of uit post bemarking ondervinding:

Liggaamsisteem/Newe Effek Terme	**Frekwensie**				
Gevalle	≥ 10 %	< 10 % en ≥ 1 %	< 1 % en ≥ 0,1 %	< 0,1 % en ≥ 0,01 %	< 0,01 %
	Baie algemeen	Algemeen	Selde	Raar	Baie raar
Liggaam as 'n Geheel					
Allergiese reaksie					X
Astenie		X			
Diskontinuasie reaksie					X
Fotosensitiwiteitsreaksie			X		
Gewigstoename	X				
Kardiovaskulêre Stelsel					
Bradikardie			X		
Ortostatiese hipotensie		X			
Veneuse trombo embolisme					X
Spysvertering Stelsel					
Hardlywigheid		X			
Droë mond		X			
Hepatitis					X
Verhoogde aptyt		X			
Pankreatitis					X
Hematologiese Sisteem					
Leukopenia				X	
Trombositopenia					X
Metaboliese Stelsel					
Diabetiese koma					X
Diabetese ketoasidose					X
Hipercholestrolemia[1]					X
Hiperglisemie					X
Hipertrigliseridemie[1]					X
Perifere edeem		X			
Skeletspierstelsel					
Rabdomiolise					X
Senuwee Stelsel					
Akatisie		X			
Duiseligheid		X			
Stuipe				X	
Slaperigheid	X				
Urogenitale Stelsel					

Liggaamsisteem/Newe Effek Terme	**Frekwensie**				
Gevalle	≥ 10 %	< 10 % en ≥ 1 %	< 1 % en ≥ 0,1 %	< 0,1 % en ≥ 0,01 %	< 0,01 %
	Baie algemeen	Algemeen	Selde	Raar	Baie raar
Priapisme					X
Vel en aanhangsels					
Uitslag				X	
Laboratorium Analise					
Kliniese Chemie					
ALT/SGPT - Verhoog		X			
AST/SGOT - Verhoog		X			
Prolaktien - Verhoog	X				
Hematologie					
Eosinofilie		X			

[1] **Ewekansige cholesterol vlakke van ≥ 240 mg/dL en ewekansige trigliseried vlakke van ≥ 1000 mg/dL is baie raar aangemeld.**

Algemeen (< 10 % en ≥ 1 %) newe effekte spesifiek geassosieer met die gebruik van intramuskulêre olansapien in kliniese studies het hipotensie, tagikardie en bradikardie ingesluit.

Die volgende tabel is ‘n opsomming van die kern newe effekte wat geïdentifiseer is tydens intramuskulêre kliniese studies:

Liggaamsisteem/Newe Effek Terme	**Frekwensie**				
Gevalle	≥ 10 %	<10 % en ≥ 1 %	< 1 % en ≥ 0,1 %	< 0,1 % en ≥ 0,01 %	< 0,01 %
	Baie algemeen	Algemeen	Selde	Raar	Baie raar
Kardiovaskulêre Stelsel					
Hipotensie		X			
Tagikardie		X			
Bradikardie		X			

Die volgende tabel is ‘n opsomming van die kern newe effekte wat geïdentifiseer is tydens kliniese studies in pasiënte met demensie van die Alzheimer tipe:

Liggaamsisteem/Newe Effek Terme	**Frekwensie**				
Gevalle	≥ 10 %	< 10 % en ≥ 1 %	< 1 % en ≥ 0,1 %	< 0,1 % en ≥ 0,01 %	< 0,01 %
	Baie algemeen	Algemeen	Selde	Raar	Baie raar
Senuweestelsel					
Abnormale stap	X				
Val	X				
Urogenitale Stelsel					
Urinêre inkontinensie		X			
Respiratoriese Stelsel					
Pneumonie		X			

Die volgende tabel is ‘n opsomming van die kern newe effekte wat geïdentifiseer is tydens kliniese studies in middel geïnduseerde (dopamien agonis) psigose geassosieër met Parkinson se siekte:

Liggaamsisteem/Newe Effek Terme	**Frekwensie**				
Gevalle	≥ 10 %	< 10 % en ≥ 1 %	< 1 % en ≥ 0,1 %	< 0,1 % en ≥ 0,01 %	< 0,01 %
	Baie algemeen	Algemeen	Selde	Raar	Baie raar
Senuwee Stelsel					
Hallusinasies	X				
Parkinson simptomatologie	X				

Die volgende tabel is ‘n opsomming van die kern newe effekte wat geïdentifiseer is tydens kliniese studies in pasiënte wat olansapien in kombinasie met litium of valproaat ontvang:

Liggaamsisteem/Newe Effek Terme	**Frekwensie**				
Gevalle	≥ 10 %	< 10 % en ≥ 1%	< 1 % en ≥ 0,1 %	< 0,1 % en ≥ 0,01 %	< 0,01 %
	Baie algemeen	Algemeen	Selde	Raar	Baie raar
Liggaam as 'n Geheel					
Gewigstoename	X				
Spysvertering Stelsel					
Droë mond	X				
Verhoogde aptyt	X				
Senuweestelsel					
Spraak afwyking		X			
Bewing	X				

Spesiale voorsorgmaatreëls:

Tydens antipsigotiese behandeling kan verbetering van die pasiënte se kliniese toestand etlike dae tot weke neem. Pasiënte moet noukeurig gemoniteer word tydens hierdie periode.

Hipotensie en/of bradikardie is waargeneem tydens ZYPREXA IM toediening. Pasiënte moet bly lê as hulle slaperig of duiselig is na inspuiting, totdat 'n ondersoek aandui dat hulle nie hipotensie, posturale hipotensie en/of bradikardie ondervind nie. Weens die moontlikheid van bradikardie en/of hipotensie met IM olansapien, moet versigtigheid oorweeg word by pasiënte met ernstige kardiovaskulêre siekte waar die voorkoms van sinkopee, of hipotensie en/of bradikardie die pasiënt aan verhoogde mediese risiko kan blootstel.

Gelyktydige toediening van intramuskulêre olansapien en parenterale bensodiasepien is nog nie bestudeer nie, en vir hierdie rede nie aanbeveel nie. (Sien ook 'Interaksies'). As die pasiënt parenterale bensodiasepien benodig, moet dit nie gegee word tot 1 uur na die IM olansapien toediening gestaak is nie. As die pasiënt parenterale bensodiasepien ontvang het, moet IM olansapien nie oorweeg word sonder evaluasie van die kliniese status van die pasiënt nie, en die pasiënt moet streng gemonitor word vir oormatige sedasie en kardiorespiratoriese onderdrukking.

Gepaardgaande siektes: Kliniese ondervinding met ZYPREXA by pasiënte met gepaardgaande siekte is beperk. Aangesien ZYPREXA *in vitro* anticholinergiese aktiwiteit getoon het, moet dit met omsigtigheid vir pasiënte met simptomatiese prostaatvergroting, nouhoekgloukoom of paralitiese ileus en verwante toestande voorgeskryf word.

ZYPREXA is nie tot enige noemenswaardige mate geëvalueer of gebruik by pasïente met 'n onlangse geskiedenis van miokardiale infarksie of onstabiele hartsiekte nie. Pasïente met sulke diagnose is uitgesluit van voorbemarkings kliniese proewe. Weens die risiko van ortostatiese hipotensie met ZYPREXA, moet omsigtigheid by hartpasiënte aan die dag gelê word.

Daar is ’n verhoogde voorkoms van diabetes by pasiënte met skisofrenie. Soos met ander antipsigotiese middels is hiperglukemie of verergering van voorafbestaande diabetes selde gerapporteer tydens behandeling met ZYPREXA. In sommige gevalle is ‘n toename in liggaamsgewig vooraf gerapporteer, wat ’n predisponerende faktor kan wees. Toepaslike kliniese monitering is raadsaam by diabetiese pasiënte en by pasiënte met risikofaktore om diabetes mellitus te ontwikkel.

Nier- en lewerontoereikendheid: Sien ‘Farmakokinetiese eienskappe’.

Serebrovaskulêre newe effekte (CVAE), insluitend beroerte, in bejaarde pasiënte met demensie:
Serebrovaskulêre newe effekte (bv. beroerte, verbygaande ischemiese aanval), insluitend sterftes, was aangemeld in studies van ZYPREXA in bejaarde pasiënte met demensie-verwante psigose. In plasebo-gekontroleerde studies, was daar ’n hoër insidensie van CVAE in pasiënte op ZYPREXA behandeling as in pasiënte op plasebo (1,3 % vs 0,4 % onderskeidelik). Al die pasiënte wat ’n serebrovaskulêre aanval ondervind het, het bekende bestaande risiko faktore gehad wat geassosieër word met ’n verhoogde risiko vir CVAE (bv. geskiedenis van ’n vorige CVAE of verbygaande ischemiese aanval, hipertensie en sigaret rook) en het meegaande siektetoestande gehad en/of kombinasie medisyne gebruik wat ’n temporale verhouding toon met CVAE. ZYPREXA is nie goedgekeur vir die behandeling van pasiënte met demensie-verwante psigose nie.

Fenielalanien: ZYPREXA VELOTAB tablette bevat aspartaam, wat ’n bron van fenielalanien is.

Uitwerking op bestuursvermoë en op die gebruik van masjinerie: ZYPREXA kan slaperigheid veroorsaak. Pasiënte moet daarteen gewaarsku word om nie met gevaarlike masjinerie te werk of motorvoertuie te bestuur totdat hulle redelik seker is dat ZYPREXA-behandeling hulle nie nadelig beïnvloed nie.

Geriatriese gebruik: Tydens kliniese proewe was daar in die algemeen geen indikasie van enige verskille in die verdraagsaamheid van ZYPREXA by bejaardes en jonger volwassenes nie. Desnieteenstaande moet daar in die teenwoordigheid van faktore wat die farmakokinetiese opruiming verlaag, of die farmakodinamiese reaksie op ZYPREXA verhoog, 'n laer aanvangsdosis

oorweeg word. Omdat posturale hipotensie per geleentheid voorgekom het tydens kliniese studies op bejaarde pasiënte, word dit aanbeveel dat bloeddruk lesings periodies geneem word in pasiënte ouer as 65 jaar.

Ortostatiese hipotensie: ZYPREXA kan ortostatiese hipotensie veroorsaak wat met duiseligheid, hartkloppings en, by sommige pasïente, floute geassosieer word. Dit kom veral tydens aanvangsbehandeling voor.

Hiperprolaktinemie: Sien 'Waarskuwings'.

Verhoogde transaminases: Verbygaande verhoging in lewertransaminases (ALT, AST) is waargeneem. Omsigtigheid moet dus aan die dag gelê word by pasiënte met verhoogde ALT en/of AST, by pasiënte wat tekens en simptome van lewerontoereikendheid toon, by pasiënte met voorafbestaande toestande wat met beperkte lewerfunksie-reserwe geassosieer word en by pasiënte wat met potensieel hepatotoksiese middels behandel word. In die geval van verhoogde ALT en/of AST tydens behandeling, moet opvolging gereël gedoen word en dosisverlaging oorweeg word. In gevalle waar hepatitis gediagnoseer is, moet olansapienbehandeling gestaak word.

Hematologie: Omsigtigheid moet aan die dag gelê word wanneer olansapien by die volgende tipes pasiënte gebruik word:

- by pasiënte met lae witbloedsel- en/of neutrofieltellings te wyte aan enige oorsaak,
- by pasiënte met 'n geskiedenis van geneesmiddel-geïnduseerde beenmurgonderdrukking/ toksisiteit,
- by pasiënte met beenmurgonderdrukking veroorsaak deur 'n meegaande siekte, bestraling of chemoterapie en
- by pasiënte met hipereosinofiel-toestande of beenmurgproliferatiewe siekte.

Twee-en-dertig pasiënte met 'n geskiedenis van klosapienverwante neutropenie of agranulositose het olansapien ontvang sonder afnames in basislyn-neutrofieltellings.

Regulering van liggaamstemperatuur: Versteuring van die liggaam se vermoë om interne liggaamstemperatuur te verlaag, is toegeskryf aan antipsigotiese middels. Toepaslike sorg word aanbeveel indien ZYPREXA voorgeskryf word vir pasiënte wat toestande sal ondervind wat tot 'n verhoging van interne liggaamstemperatuur kan bydra.

Disfagie: Slukdermonbeweeglikheid en aspirasie is al met antipsigotiese geneesmiddels geassosieer. ZYPREXA moet met omsigtigheid gebruik word by pasiënte met 'n risiko vir aspirasie-longontsteking.

Selfmoord: Die moontlikheid van selfmoordpogings is inherent aan skisofrenie en noukeurige toesig van hoërisikopasiënte moet met ZYPREXA behandeling toegepas word.

Karsinogenese: Resultate van studies wat op muise en rotte gedoen is, het tot die gevolgtrekking gelei dat olansapien nie karsinogenies is nie. Prolaktienbemiddelde tumore: Sien 'Hiperprolaktinemie' onder 'Waarskuwings'.

Mutagenese: In 'n volle reeks standaard toetse, wat bakteriële mutasietoetse en *in vitro* en *in vivo* soogdiertoetse ingesluit het, was olansapien nie mutagenies of klastogenies nie.

Vrugbaarheidsbenadeling: By manlike rotte is paring, maar nie vrugbaarheid nie, benadeel. Staking van olansapien het die uitwerking op paringsgedrag omgekeer. By vroulike rotte is estrussiklusse en voortplantingsparameters beïnvloed met dosisse wat hoër as die maksimum mensedosis was.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:

Tekens en simptome: Baie algemene simptome wat met ZYPREXA-oordosering (≥ 10 % voorkoms) gerapporteer is, sluit in tagikardie, agitasie/aggressiwiteit, disartrie, verskeie ekstrapiramidale simptome en verlaagde bewussynsvlak wat wissel van kalmering tot koma.

Ander beduidende mediese gevolge van ZYPREXA-oordosering sluit in delirium, konvulsies, moontlike neuroleptiese maligne sindroom, asemhalingsonderdrukking, aspirasie, hipertensie of hipotensie, hartaritmieë (< 2 % van oordosisgevalle) en hart-long-stilstand. Noodlottige gevolge is gerapporteer vir akute oordosisse so laag as 450 mg, maar oorlewing is ook gerapporteer na akute oordosis van 1 500 mg.

Behandeling: Die moontlikheid van meervoudige geneesmiddelbetrokkenheid moet oorweeg word. In geval van akute oordosering, moet 'n lugweg bewerkstellig en instand gehou word en voldoende oksigenering en ventilasie verseker word. Maagspoeling (ná intubasie, indien die pasiënt bewusteloos is) en toediening van geaktiveerde houtskool saam met 'n lakseermiddel moet oorweeg word. Die moontlikheid van afstomping, stuipe of distoniese reaksies van die kop en nek wat op 'n oordosering volg, kan 'n risiko van aspirasie met geïnduseerde braking veroorsaak.

Kardiovaskulêre monitering moet onmiddellik begin word en moet volgehoue elektrokardiografiese monitering, om moontlike aritmieë te bespeur, insluit.

Daar is geen spesifieke teenmiddel vir ZYPREXA nie. Gevolglik moet toepaslike simptomatiese en ondersteunende behandeling toegepas word. Hipotensie en sirkulêre ineenstorting moet met toepaslike maatreëls, soos intraveneuse vloeistowwe en/of simpatomimetiese middels behandel word. Epinefrien, dopamien of ander simpatomimetiese middels met β-agonis-aktiwiteit moet nie gebruik word nie, aangesien β-stimulasie hipotensie kan vererger deur die daarstelling van 'n olansapien-geïnduseerde α-blokkade. Noukeurige mediese toesig en monitering moet aanhou totdat die pasiënt herstel het.

IDENTIFIKASIE:

ZYPREXA 2,5 (Tablette), TA 4112, is ronde, wit, filmbedekte tablette, waarop "LILLY" en "4112" in blou ink gedruk is.

ZYPREXA 5 (Tablette), TA 4115, is ronde, wit, filmbedekte tablette, waarop "LILLY" en "4115" in blou ink gedruk is.

ZYPREXA 10 (Tablette), TA 4117, is ronde, wit, filmbedekte tablette, waarop "LILLY" en "4117" in blou ink gedruk is.

ZYPREXA VELOTAB 5 (Tablette), TA4453, is geel, ronde, gevriesdroogde tablette.

ZYPREXA VELOTAB 10 (Tablette), TA4454, is geel, ronde, gevriesdroogde tablette.

ZYPREXA IM (Poeier vir Inspuiting) flessie, VL 7597, is ’n 5 ml Tipe I-flintglasflessie met ’n rubberproppie en geseël met ‘n aluminiumdoppie. Dit bevat ’n geel, steriele, geliofiliseerde poeierprop.

AANBIEDING:

ZYPREXA tablette word voorsien as stulpverpakkings met 28.

ZYPREXA VELOTAB tablette word voorsien in stulpverpakkings met 28. Die stulpverpakking bestaan uit aluminium-plastiek web film geseël met ’n aluminium foelie laag.

ZYPREXA IM (Poeier vir Inspuiting) flessies word voorsien as enkelverpakkings.

BERGINGSAANWYSINGS:

ZYPREXA tablette: Bewaar benede 30 ºC in stulpverpakkings. Beskerm teen lig en vogtigheid.

ZYPREXA VELOTAB tablette: Bewaar benede 30 ºC in stulpverpakkings. Beskerm teen lig en vogtigheid.

MOET NIE VERWYDER VAN DIE STULPVERPAKKING VOOR U NIE GEREED IS VIR ADMINISTRASIE NIE

Poeier vir inspuiting flessie and oplosmiddelspuit: Bewaar benede 25 ºC. Moenie vries nie. Beskerm teen lig en vogtigheid.

Na hersamestelling met steriele water vir inspuiting: Stabiel vir een uur wanneer onder 25 ºC bewaar word (sien 'Dosis en gebruiksaanwysings').

Hou buite bereik van kinders.

REGISTRASIENOMMERS:

32/2.6.5/0685 vir ZYPREXA 2,5 tablette
31/2.6.5/0058 vir ZYPREXA 5 tablette
31/2.6.5/0060 vir ZYPREXA 10 tablette
38/2.6.5/0030 vir ZYPREXA VELOTAB 5 tablette
38/2.6.5/0073 vir ZYPREXA VELOTAB 10 tablette
35/2.6.5/0307 vir ZYPREXA IM (Poeier vir Inspuiting)

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIE SERTIFIKAAT:

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