

PACKAGE INSERT TEMPLATE FOR OLANZAPINE POWDER FOR INTRAMUSCULAR INJECTION

Brand or Product Name

[Product name] Powder for IM Injection

Name and Strength of Active Substance(s)

Olanzapine 10mg/vial. After reconstitution the solution contains olanzapine 5mg/ml.

Product Description

*[Visual description of the appearance of the product (eg colour, odour etc) eg :
Yellow lyophilised powder. Upon reconstitution, olanzapine powder yields a yellowish solution]*

Pharmacodynamics

Olanzapine is an antipsychotic agent that demonstrates a broad pharmacologic profile across a number of receptor systems. Olanzapine exhibited a range of receptor affinities (K_i ; < 100 nM) for serotonin 5 HT_{2A/2C}, 5 HT₃, 5 HT₆; dopamine D₁, D₂, D₃, D₄, D₅; cholinergic muscarinic receptors m1-m5; α_1 adrenergic; and histamine H₁ receptors. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an “anxiolytic” test.

Olanzapine produced a higher 5 HT_{2A} than dopamine D₂ receptor occupancy. In addition, olanzapine-responsive patients had lower striatal D₂ occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients. Olanzapine was associated with statistically significantly greater improvements in negative as well as positive symptoms.

Olanzapine demonstrated statistically significant superiority over placebo on the primary endpoint of bipolar recurrence. Olanzapine also showed a statistically significant advantage over placebo in terms of preventing either recurrence into mania or recurrence into depression.

Pharmacokinetics

A dose of 5mg of Olanzapine Intramuscular produced a maximum plasma concentration (C_{max}) approximately 5 times higher than that seen with the same dose of olanzapine administered orally. The C_{max} occurs earlier after intramuscular compared to oral use (15 to 45 minutes versus 5 to 8 hours). As with oral use, C_{max} and area under the curve after intramuscular use are directly

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proportional to the dose administered. For the same dose of olanzapine administered intramuscularly and orally, the associated area under the curve, half-life, clearance and volume of distribution are similar. The metabolic profiles following intramuscular and oral use are similar.

In non-smoking versus smoking subjects (males and females) administered olanzapine intramuscularly the mean elimination half-life was prolonged (38.6 versus 30.4 hr) and the clearance was reduced (18.6 versus 27.7 l/hr).

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

Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hr) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia > 65 years of age, dosing from 5 to 20 mg/day was not associated with any distinguishing profile of adverse events.

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

Adolescents (ages 13 to 17 years)

The pharmacokinetics of olanzapine are similar between adolescents and adults. In clinical studies, the average olanzapine exposure was approximately 27% higher in adolescents. Demographic differences between the adolescents and adults include a lower average body weight and fewer adolescents were smokers. Such factors likely contribute to the higher average exposure observed in adolescents.

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

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The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/mL. Olanzapine is bound predominantly to albumin and α_1 -acid-glycoprotein.

Indication

Olanzapine IM is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or manic episode, when oral therapy is not appropriate. Treatment with Olanzapine IM should be discontinued and the use of oral olanzapine should be initiated as soon as clinically appropriate.

Recommended Dosage

For intramuscular use. Do not administer intravenously or subcutaneously. Olanzapine IM is intended for short term use only, for up to a maximum of three consecutive days.

The recommended initial dose for olanzapine injection is 10 mg, administered as a single intramuscular injection. A lower dose (5 mg or 7.5 mg) may be given, on the basis of individual clinical status. A second injection, 5-10 mg, may be administered 2 hours after the first injection on the basis of individual clinical status. The maximum daily dose of olanzapine (including oral olanzapine) is 20 mg, with not more than 3 injections in any 24 hour period. Olanzapine IM should be reconstituted in accordance with the recommendation in Section Instructions for Use.

For further information on continued treatment with oral olanzapine (5 to 20 mg daily), see the package insert for olanzapine tablets or olanzapine orodispersible tablets.

Children

Olanzapine has not been studied in subjects under 18 years of age. It should not be used in this population until relevant clinical data are available.

Elderly patients

The recommended starting dose in elderly patients (> 60 years) is 2.5 - 5 mg. Depending on the patient's clinical status, a second injection, 2.5 - 5 mg, may be administered 2 hours after the first injection. Not more than 3 injections should be given in any 24 hour period.

Patients with renal and/or hepatic impairment

A lower starting dose (5 mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5 mg and only increased with caution.

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Gender

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

Smokers

The dose and dose range need not be routinely altered for non-smokers relative to smoker.

When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the dose. Additional injections, when indicated, should be conservative in such patients.

Mode of Administration

Intramuscular injection

Contraindications

Hypersensitivity to olanzapine or any of the excipients. Patients with known risk for narrow-angle glaucoma

Warnings and Precautions

[Specific package insert requirement for olanzapine]

WARNINGS:

Hyperglycemia and Diabetes Mellitus

Hyperglycemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given this confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of

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treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

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

Unstable medical conditions

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

Concomitant use of benzodiazepines and other medicinal products

Special caution is necessary in patients who have received treatment with other medicinal products having haemodynamic properties similar to those of intramuscular olanzapine including other antipsychotics (oral and/or intramuscular) and benzodiazepines. Temporal association of treatment with IM olanzapine with hypotension, bradycardia, respiratory depression and death has been very rarely (< 0.01%) reported particularly in patients who have received benzodiazepines and/or other antipsychotics.

Simultaneous injection of intramuscular olanzapine and parenteral benzodiazepine is not recommended. If the patient is considered to need parenteral benzodiazepine treatment, this should not be given until at least one hour after IM olanzapine administration. If the patient has received parenteral benzodiazepine, 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.

Hypotension

It is extremely important that patients receiving intramuscular olanzapine should be closely observed for hypotension including postural hypotension, bradyarrhythmia and/or hypoventilation, particularly for the first 4 hours following injection and close observation should be continued after this period if clinically indicated. Blood pressure, pulse, respiratory rate and level of consciousness should be observed regularly and remedial treatment provided if required. Patients should remain recumbent if dizzy or drowsy after injection until examination

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indicates that they are not experiencing hypotension including postural hypotension, bradyarrhythmia and/or hypoventilation.

The safety and efficacy of IM olanzapine has not been evaluated in patients with alcohol or drug intoxication (either with prescribed or illicit drugs)

Dementia-related psychosis and/or behavioural disturbances

Olanzapine is not approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

Cerebrovascular adverse events (CVAE e.g., stroke, transient ischemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in patients treated with olanzapine compared to patients treated with placebo. All olanzapine- and placebo-treated patients who experienced a cerebrovascular event had pre-existing risk factors. Age > 75 years and vascular/mixed type dementia were identified as risk factors for CVAE in association with olanzapine treatment. The efficacy of olanzapine was not established in these trials.

Parkinson's disease

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

Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially life-threatening condition associated with antipsychotic medicinal product. Rare cases reported as NMS have also been received in association with olanzapine. 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

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dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.

Lipid alterations

Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials. Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic agents, including olanzapine, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines.

Anticholinergic activity

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

Hepatic function

Transient, asymptomatic elevations of hepatic transaminases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicines. 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 (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

Neutropenia

Caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly.

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Discontinuation of treatment

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

QT interval

In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] \geq 500 milliseconds [msec] at any time post baseline in patients with baseline QTcF < 500 msec) were uncommon (0.1% to 1%) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. However, as with other antipsychotics, caution should be exercised when olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Thromboembolism

Temporal association of olanzapine treatment and venous thromboembolism has very rarely (< 0.01%) been reported. A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

General CNS activity

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

Seizures

Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur rarely in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

Tardive Dyskinesia

Olanzapine was associated with a statistically significant lower incidence of treatment emergent dyskinesia. However the risk of tardive dyskinesia increases with long term exposure, and therefore if signs or symptoms of tardive dyskinesia appear in a patient on olanzapine, a dose

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reduction or discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Postural hypotension

Postural hypotension was infrequently observed in the elderly in olanzapine clinical trials. As with other antipsychotics, it is recommended that blood pressure is measured periodically in patients over 65 years.

Effects on ability to drive and use machines

Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating hazardous machinery, including motor vehicles.

Interactions with Other Medicaments

IM olanzapine has not been studied in patients with alcohol or drug intoxication.

Caution should be exercised in patients who receive medicinal products that can cause central nervous system depression.

Potential for Interaction, Following Intramuscular Injection

In a single dose intramuscular study of olanzapine 5 mg, administered 1 hour before lorazepam 2 mg (metabolised by glucuronidation), the pharmacokinetics of both drugs were unchanged. However, the combination added to the somnolence observed with either drug alone. Concomitant injection of olanzapine and parenteral benzodiazepine has not been studied and is therefore not recommended

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.

Induction of CYP1A2

The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary.

Inhibition of CYP1A2

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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 nonsmokers and 77 % 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.

Decreased bioavailability

Activated charcoal reduces the bioavailability of oral olanzapine by 50 to 60% and should be taken at least 2 hours before or after olanzapine. Fluoxetine (a CYP2D6 inhibitor), single doses of antacid (aluminium, magnesium) or cimetidine have not been found to significantly affect the pharmacokinetics of olanzapine.

Potential for olanzapine to affect other medicinal products

Olanzapine may antagonise the effects of direct and indirect dopamine agonists. Olanzapine does not inhibit the main CYP450 isoenzymes in vitro (e.g. 1A2, 2D6, 2C9, 2C19, 3A4). Thus no particular interaction is expected as verified through in vivo studies where no inhibition of metabolism of the following active substances was found: tricyclic antidepressant (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2) or diazepam (CYP3A4 and 2C19).

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

Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant olanzapine.

Statement on Usage During Pregnancy and Lactation

[Specific package insert requirement for antipsychotic]

Pregnancy and lactation

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation.

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Quetiapine tablet should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with olanzapine.

In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant exposure (mg/kg) at steady state was estimated to be 1.8% of the maternal olanzapine dose (mg/kg). Patients should be advised not to breast feed an infant if they are taking olanzapine.

Adverse Effects / Undesirable Effects

A common undesirable effect associated with the use of intramuscular olanzapine in clinical trials was somnolence.

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

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

<i>Cardiac disorders</i> Common: Bradycardia with or without hypotension or syncope, tachycardia Uncommon: Sinus pause
<i>Vascular disorders</i> Common: Postural hypotension, hypotension
<i>Respiratory disorders</i> Uncommon: Hypoventilation
<i>General disorders and administration site conditions</i> Common: Injection site discomfort

The undesirable effects listed below have been observed following administration of oral olanzapine, but may also occur following administration of olanzapine IM.

Adults

The most frequently reported adverse reactions associated with the use of olanzapine were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride

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levels, glucosuria, increased appetite, dizziness, akathisia, parkinsonism, dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic transaminases, rash, asthenia, fatigue and oedema.

The following table lists the adverse reactions and laboratory investigations observed from spontaneous reporting and in clinical trials.

Very common	Common	Uncommon	Not known
<i>Blood and the lymphatic system disorders</i>			
	Eosinophilia	Leukopenia Neutropenia	Thrombocytopenia
<i>Immune system disorders</i>			
			Allergic reaction
<i>Metabolism and nutrition disorders</i>			
Weight gain	Elevated cholesterol levels Elevated glucose levels Elevated triglyceride levels Glucosuria Increased appetite		Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases Hypothermia
<i>Nervous system disorders</i>			
Somnolence	Dizziness Akathisia Parkinsonism Dyskinesia		Seizures where in most cases a history of seizures or risk factors for seizures were reported Neuroleptic malignant syndrome Dystonia (including oculogyration) Tardive dyskinesia Discontinuation symptoms
<i>Cardiac disorders</i>			
		Bradycardia QTc prolongation	Ventricular tachycardia/fibrillation, sudden death
<i>Vascular disorders</i>			
	Orthostatic		Thromboembolism

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	hypotension		(including pulmonary embolism and deep vein thrombosis)
<i>Gastrointestinal disorders</i>			
	Mild, transient anticholinergic effects including constipation and dry mouth		Pancreatitis
<i>Hepato-biliary disorders</i>			
	Transient, asymptomatic elevations of hepatic transaminases (ALT, AST), especially in early treatment		Hepatitis (including hepatocellular, cholestatic or mixed liver injury)
<i>Skin and subcutaneous tissue disorders</i>			
	Rash	Photosensitivity reaction Alopecia	
<i>Musculoskeletal and connective tissue disorders</i>			
			Rhabdomyolysis
<i>Renal and urinary disorders</i>			
			Urinary hesitation
<i>Reproductive system and breast disorders</i>			
			Priapism
<i>General disorders and administration site conditions</i>			
	Asthenia Fatigue Oedema		
<i>Investigations</i>			
Elevated plasma prolactin levels		High creatine phosphokinase Increased total bilirubin	Increased alkaline phosphatase

Long-term exposure (at least 48 weeks)

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

Additional information on special populations

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

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

Overdose and Treatment

Signs and Symptoms

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

Management of Overdose

There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60%.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring

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is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

Incompatibilities

Reconstitute Olanzapine IM only with water for injections. Olanzapine Powder for IM Injection must not be combined in the syringe with any commercially available medicinal product. Examples of incompatibilities are as below:

Olanzapine for injection 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 olanzapine for injection as this combination results in a delayed reconstitution time.

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

Instructions for Use

Reconstitute Olanzapine IM only with Water for Injections using standard aseptic techniques for reconstitution of parenteral products. No other solutions should be used for reconstitution.

1. Withdraw 2.1 ml of Water for Injection into a sterile syringe. Inject into a vial of Olanzapine IM.
2. Rotate the vial until the contents have completely dissolved, giving a yellow coloured solution. The vial contains 11.0 mg olanzapine as a solution of 5 mg/ml (1 mg olanzapine is retained in the vial and syringe, thus allowing delivery of 10 mg olanzapine).
3. The following table provides injection volumes for delivering various doses of olanzapine:

Dose (mg)	Volume of injection (ml)
10.0	2.0
7.5	1.5
5.0	1.0
2.5	0.5

4. Administer the solution intramuscularly. Do not administer intravenously or subcutaneously.
5. Discard the syringe and any unused solution in accordance with appropriate clinical procedures.
6. Use the solution immediately within 1 hour of reconstitution. Do not store above 25° C. Do not freeze.

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Parenteral drug products should be inspected visually for particulate matter prior to administration whenever solution and container permit.

Storage Conditions

Finished product - Store below ...°C

Reconstituted product (if applicable) - Store below ...°C for hours.

* If not, please include this statement - For single use only. Discard any unused portion after opening

Dosage Forms and Packaging Available

[Packaging type & pack size eg 10 ml type I clear glass vial, capped with a butyl rubber stopper/box]

Name and Address of Manufacturer

[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder

[Name & full address of marketing authorization holder]

Date of Revision of Package Insert

[day/month/year]