1. NAME OF THE MEDICINAL PRODUCT

ZYPADHERA 300 mg powder and solvent for prolonged release suspension for injection
ZYPADHERA 405 mg powder and solvent for prolonged release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZYPADHERA 300 mg powder and solvent for prolonged release suspension for injection
Each vial contains olanzapine pamoate monohydrate equivalent to 300 mg olanzapine. After reconstitution each ml of suspension contains 150 mg olanzapine.

ZYPADHERA 405 mg powder and solvent for prolonged release suspension for injection
Each vial contains olanzapine pamoate monohydrate equivalent to 405 mg olanzapine. After reconstitution each ml of suspension contains 150 mg olanzapine.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged release suspension for injection

Powder: yellow solid
Solvent: clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ZYPADHERA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis

4.1 Therapeutic indications

ZYPADHERA is indicated for the treatment of schizophrenia.
The use of ZYPADHERA is limited to patients who have been diagnosed as non-compliant regarding taking prescribed medicines and as a consequence are prone to outbursts of psychotic episodes.
ZYPADHERA is NOT to be used in patients whose condition is adequately controlled with oral ZYPREXA.
ZYPADHERA is available only through a restricted program which will be conducted according to ZYPADHERA EU Risk Management Plan.
For a patient to receive treatment, the prescribers, injection administrators, pharmacists and patients must all be trained on the appropriate elements of the ZYPADHERA Risk Management Plan conducted by Lilly. The ZYPADHERA Risk Management Plan has been developed to enable the safe use of ZYPADHERA in patients, including the management of those patients who develop Post-Injection Delirium and Sedation Syndrome. In addition to mandating label language around this risk, this plan includes education and training activities by Lilly to the following target audience as

appropriate: prescribers, administrators of treatment, patients and pharmacists. All training will be fully documented.

4.2 Posology and method of administration

ZYPADHERA 300 mg and 405 mg powder and solvent for prolonged release suspension for injection must not be confused with olanzapine 10 mg powder for solution for injection.

Posology
Patients should be treated initially with oral olanzapine before administering ZYPADHERA, to establish tolerability and response.

In order to identify the first ZYPADHERA dose for all patients the scheme in Table 1 should be considered.

Table 1 Recommended dose scheme between oral olanzapine and ZYPADHERA

Target oral olanzapine dose	Recommended starting dose of ZYPADHERA	Maintenance dose after 2 months of ZYPADHERA treatment
10 mg/day	210 mg/2 weeks or 405 mg/4 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300 mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks	300 mg/2 weeks

Dose adjustment
Patients should be monitored carefully for signs of relapse during the first one to two months of treatment. 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. During treatment dose may subsequently be adjusted on the basis of individual clinical status. After clinical reassessment dose may be adjusted within the range 150 mg to 300 mg every 2 weeks or 300 to 405 mg every 4 weeks. (Table 1)

Supplementation
Supplementation with oral olanzapine was not authorised in double-blind clinical studies. If oral olanzapine supplementation is clinically indicated, then the combined total dose of olanzapine from both formulations should not exceed the corresponding maximum oral olanzapine dose of 20 mg/day.

Switching to other antipsychotic medicinal products
There are no systematically collected data to specifically address switching patients from ZYPADHERA to other antipsychotic medicinal products. Due to the slow dissolution of the olanzapine pamoate salt which provides a slow continuous release of olanzapine that is complete approximately six to eight months after the last injection, supervision by a clinician, especially during the first 2 months after discontinuation of ZYPADHERA, is needed when switching to another antipsychotic product and is considered medically appropriate.

Special populations

Elderly
ZYPADHERA has not been systematically studied in elderly patients (> 65 years). ZYPADHERA is not recommended for treatment in the elderly population unless a well-tolerated and effective dose regimen using oral olanzapine has been established. A lower starting dose (150 mg/4 weeks) is not routinely indicated, but should be considered for those 65 and over when clinical factors warrant. ZYPADHERA is not recommended to be started in patients >75 years (see section 4.4).

Renal and/or hepatic impairment
Unless a well-tolerated and effective dose regimen using oral olanzapine has been established in such patients, ZYPADHERA should not be used. A lower starting dose (150 mg every 4 weeks) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 150 mg every 4 weeks and only increased with caution.

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. The metabolism of olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.5).

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. When indicated, dose escalation should be performed with caution in these patients.

Paediatric population
The safety and efficacy of ZYPADHERA in children and adolescents below 18 years has not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

Method of administration

FOR INTRAMUSCULAR USE ONLY. DO NOT ADMINISTER INTRAVENOUSLY OR SUBCUTANEOUSLY (See section 4.4)

ZYPADHERA should only be administered by deep intramuscular gluteal injection by a healthcare professional trained in the appropriate injection technique and in locations where post-injection observation and access to appropriate medical care in the case of overdose can be assured. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

After each injection, patients should be observed in a health care facility by appropriately qualified personnel for at least 3 hours for signs and symptoms consistent with olanzapine overdose. Immediately prior to leaving the health care facility, it should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose. If an overdose is suspected, close medical supervision and monitoring should continue until examination indicates that signs and symptoms have resolved (see section 4.4.). The 3-hour observation period should be extended as clinically appropriate for patients who exhibit any signs or symptoms consistent with olanzapine overdose.

For instructions for use, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk of narrow-angle glaucoma.

4.4 Special warnings and precautions for use

Special care must be taken to apply appropriate injection technique to avoid inadvertent intravascular or subcutaneous injection (see section 6.6).

Use in patients who are in an acutely agitated or severely psychotic state
ZYPADHERA should not be used to treat patients with schizophrenia who are in an acutely agitated or severely psychotic state such that immediate symptom control is warranted.

Post-injection syndrome
During pre-marketing clinical studies, reactions that presented with signs and symptoms consistent with olanzapine overdose were reported in patients following an injection of ZYPADHERA. These reactions occurred in <0.1% of injections and approximately 2% of patients. Most of these patients have developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsion. In most cases, initial signs and symptoms related to this reaction have appeared within 1 hour following injection, and in all cases full recovery was reported to have occurred within 24 – 72 hours after injection. Reactions occurred rarely (<1 in 1,000 injections) between 1 and 3 hours, and very rarely (<1 in 10,000 injections) after 3 hours. Patients should be advised about this potential risk and the need to be observed for 3 hours in a healthcare facility each time ZYPADHERA is administered. Post-marketing reports of post-injection syndrome since the marketing authorization of ZYPADHERA are generally consistent with the experience seen in clinical studies.

After each injection, patients should be observed and monitored in a healthcare facility by appropriately qualified personnel for at least 3 hours for signs and symptoms consistent with olanzapine overdose. The medical staff at each facility will maintain records of time of injection, patient response and time of the patient leaving the center.

Immediately prior to leaving the health care facility, it should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose. If an overdose is suspected, close medical supervision and monitoring should continue until examination indicates that signs and symptoms have resolved. The 3-hour observation period should be extended as clinically appropriate for patients who exhibit any signs or symptoms consistent with olanzapine overdose.

For the remainder of the day after injection, patients should be advised to be vigilant for signs and symptoms of overdose secondary to post injection adverse reactions, be able to obtain assistance if needed and should not drive or operate machinery (see section 4.7).

If parenteral benzodiazepines are essential for management of post injection adverse reactions, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended (see section 4.5).

Injection site related adverse events
The most commonly reported injection site related adverse reaction was pain. The majority of these reactions was reported to be of "mild" to "moderate" severity. In the event of an injection site related adverse reaction occuring, appropriate measures to manage these events should be taken (see section 4.8).

Dementia-related psychosis and/or behavioural disturbances
Olanzapine is not approved for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in oral olanzapine-treated patients compared to patients treated with placebo (3.5% vs. 1.5%, respectively). 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 oral olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse reactions (CVAEvents e.g., stroke, transient ischemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in patients

treated with oral olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All oral 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 (see section 4.8), and oral 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. Oral 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 products. Rare cases reported as NMS have also been received in association with oral 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 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.

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported uncommonly, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines, e.g. measuring of blood glucose at baseline, 12 weeks after starting olanzapine treatment and annually thereafter. Patients treated with any antipsychotic medicines, including ZYPADHERA, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly, e.g. at baseline, 4, 8 and 12 weeks after starting olanzapine treatment and quarterly thereafter.

Lipid alterations
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). 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 medicines, including ZYPADHERA, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines, e.g. at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter.

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 aminotransferases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised and follow-up organised 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 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 (see section 4.8).

Discontinuation of treatment
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported rarely (≥0.01% and <0.1%) when oral olanzapine is stopped abruptly.

QT interval
In clinical trials with oral olanzapine, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥ 500 milliseconds [msec] at any time post baseline in patients with baseline QTcF<500 msec) were uncommon (0.1% to 1%) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. In clinical trials with olanzapine powder for solution for injection or ZYPADHERA, olanzapine was not associated with a persistent increase in absolute QT or in QTc intervals. However, 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 been reported uncommonly (≥ 0.1% and < 1%). A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors 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 uncommonly in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

Tardive dyskinesia
In comparator studies of one year or less duration, 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 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. It is recommended that blood pressure is measured periodically in patients over 65 years.

Sudden cardiac death
In postmarketing reports with olanzapine, the event of sudden cardiac death has been reported in patients with olanzapine. In a retrospective observational cohort study, the risk of presumed sudden cardiac death in patients treated with olanzapine was approximately twice the risk in patients not using antipsychotics. In the study, the risk of olanzapine was comparable to the risk of atypical antipsychotics included in a pooled analysis.

Paediatric population
Olanzapine is not indicated for use in the treatment of children and adolescents. Studies in patients aged 13-17 years showed various adverse reactions, including weight gain, changes in metabolic parameters and increases in prolactin levels (see sections 4.8 and 5.1).

Use in elderly (>75 years)
No information on the use of ZYPADHERA in patients >75 years is available. Due to biochemical and physiological modification and reduction of muscular mass, this formulation is not recommended to be started in this sub-group of patients.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Caution should be exercised in patients who receive medicinal products that can induce hypotension or sedation.

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 (see section 4.2).

Inhibition of CYP1A2
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. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.

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.

General CNS activity
Caution should be exercised in patients who consume alcohol or receive medicinal products that can cause central nervous system depression.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
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. Nevertheless, because human experience is limited, olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

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

Breast feeding
In a study of oral olanzapine in breast feeding, 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.

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. As olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

Patients should be advised not to drive or operate machinery for the remainder of the day after each injection due to the possibility of a post-injection syndrome event leading to symptoms consistent with olanzapine overdose (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions seen with olanzapine pamoate
Post-injection syndrome reactions have occurred with ZYPADHERA leading to symptoms consistent with olanzapine overdose (see sections 4.2 and 4.4). Clinical signs and symptoms included symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety and other cognitive impairment). Other symptoms noted include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsion.

Other adverse reactions observed in patients treated with ZYPADHERA were similar to those seen with oral olanzapine. In clinical trials with ZYPADHERA, the only adverse reaction reported at a statistically significantly higher rate in the ZYPADHERA group than in the placebo group was sedation (ZYPADHERA 8.2%, placebo 2.0%). Among all ZYPADHERA treated patients, sedation was reported by 4.7% of patients.

In clinical trials with ZYPADHERA the incidence of injection site related adverse reactions was approximately 8%. The most commonly reported injection site related adverse reaction was pain (5%); some other injection site adverse reactions reported were (in decreasing frequency): nodule type reactions, erythema type reactions, non-specific injection site reactions, irritation, oedema type reactions, bruising, haemorrhage, and anaesthesia. These events occurred in about 0.1 to 1.1% of patients.

In a review of safety data from clinical trials and spontaneous postmarketing reports, injection site abscess was rarely (≥ 1/10,000 to < 1/1,000) reported.

Adverse reactions seen with olanzapine
The undesirable effects listed below have been observed following administration of olanzapine.

Adults
The most frequently (seen in ≥ 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases (see section 4.4), rash, asthenia, fatigue, pyrexia, arthralgia, increased alkaline phosphatase, high gamma glutamyltransferase, high uric acid, high creatine phosphokinase and oedema.

Tabulated list of adverse reactions

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

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

	Akathisia[6] Parkinsonism[6] Dyskinesia[6]	cases a history of seizures or risk factors for seizures were reported[11] Dystonia (including oculogyration)[11] Tardive dyskinesia[11] Amnesia [9] Dysarthria Restless Legs Syndrome	syndrome (see section 4.4)[12] Discontinuation symptoms[7,12]	
Cardiac disorder				
		Bradycardia QT_c prolongation (see section 4.4)	Ventricular tachycardia/fibrillation, sudden death (see section 4.4) [11]	
Vascular disorder				
Orthostatic hypotension[10]		Thromboembolism (including pulmonary embolism and deep vein thrombosis) (see section 4.4)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9]	Pancreatitis[11]	
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury)[11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	
Renal and urinary disorders				
		Urinary incontinence Urinary retention		

		Urinary hesitation[11]		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders				
	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhea in females Gynaecomastia/breast enlargement in males	Priapism[12]	
General disorders and administration site conditions				
	Asthenia Fatigue Oedema Pyrexia[10] Injection site pain		Injection site abscess	
Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase [10] High uric acid [10]	Increased total bilirubin		

[1] Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Following short term treatment (median duration 47 days), weight gain ≥ 7% of baseline body weight was very common (22.2 %), ≥ 15 % was common (4.2 %) and ≥ 25 % was uncommon (0.8 %). Patients gaining ≥ 7 %, ≥ 15 % and ≥ 25% of their baseline body weight with long-term exposure (at least 48 weeks) were very common (64.4 %, 31.7 % and 12.3 %, respectively).

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

[3] Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol/l) to high (≥ 6.2 mmol/l) were very common.

[4] Observed for fasting normal levels at baseline (< 5.56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 5.56 - < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5] Observed for fasting normal levels at baseline (< 1.69 mmol/l) which increased to high (≥ 2.26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥ 1.69 mmol/l - < 2.26 mmol/l) to high (≥ 2.26 mmol/l) were very common.

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

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

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

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

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

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

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

Long-term exposure (at least 48 weeks)
The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

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

In clinical trials in patients with 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.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1%; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥10%) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥7% from baseline body weight in 39.9% of patients.

Paediatric population
Olanzapine is not indicated for the treatment of children and adolescent patients below 18 years. Although no clinical studies designed to compare adolescents to adults have been conducted, data from the adolescent trials were compared to those of the adult trials.

The following table summarises the adverse reactions reported with a greater frequency in adolescent patients (aged 13-17 years) than in adult patients or adverse reactions only identified during short-term clinical trials in adolescent patients. Clinically significant weight gain (≥ 7%) appears to occur more frequently in the adolescent population compared to adults with comparable exposures. The magnitude of weight gain and the proportion of adolescent patients who had clinically significant weight gain were greater with long-term exposure (at least 24 weeks) than with short-term exposure.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10).

Metabolism and nutrition disorders *Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite. *Common:* Elevated cholesterol levels[15]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders

Common: Dry mouth
Hepato-biliary disorders *Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16].

[13] Following short term treatment (median duration 22 days), weight gain ≥ 7% of baseline body weight (kg) was very common (40.6 %), ≥ 15% of baseline body weight was common (7.1 %) and ≥ 25 % was common (2.5 %). With long-term exposure (at least 24 weeks), 89.4 % gained ≥ 7 %, 55.3 % gained ≥ 15 % and 29.1 % gained ≥ 25% of their baseline body weight.

[14] Observed for fasting normal levels at baseline (< 1.016 mmol/l) which increased to high (≥ 1.467 mmol/l) and changes in fasting triglycerides from borderline at baseline (≥ 1.016 mmol/l - < 1.467 mmol/l) to high (≥ 1.467 mmol/l).

[15] Changes in total fasting cholesterol levels from normal at baseline (< 4.39 mmol/l) to high (≥ 5.17 mmol/l) were observed commonly. Changes in total fasting cholesterol levels from borderline at baseline (≥ 4.39 - < 5.17 mmol/l) to high (≥ 5.17 mmol/l) were very common.

[16] Elevated plasma prolactin levels were reported in 47.4% of adolescent patients.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

If signs and symptoms of overdose consistent with post injection syndrome are observed, appropriate supportive measures should be taken (see section 4.4).

While overdose is less likely with parenteral than oral medicinal products, reference information for oral olanzapine overdose is presented below:

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 oral overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

Management
There is no specific antidote for olanzapine. 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 is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines thiazepines and oxepines, ATC code N05A_H03.

Pharmacodynamic effects
Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

In preclinical studies, olanzapine exhibited a range of receptor affinities (K_i; < 100 nM) for serotonin 5-$HT_{2A/2C}$, 5-HT_3, 5-HT_6; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors M_1-M_5; α-1 adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin 5-HT_2 than dopamine D_2 receptors and greater 5-HT_2 than D_2 activity *in viv*o, models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an "anxiolytic" test.

In a Positron Emission Tomography (PET) study in patients treated with ZYPADHERA (300 mg/4 weeks), mean D_2 receptor occupancy was 60% or higher at the end of a 6 month period, a level consistent with that found during treatment with oral olanzapine.

Clinical efficacy
The effectiveness of ZYPADHERA in the treatment and maintenance treatment of schizophrenia is consistent with the established effectiveness of the oral formulation of olanzapine.

A total of 1469 patients with schizophrenia were included in 2 pivotal trials:
The first, an 8-week, placebo controlled trial conducted in adult patients (n=404) who were experiencing acute psychotic symptoms. Patients were randomized to receive injections of ZYPADHERA 405 mg every 4 weeks, 300 mg every 2 weeks, 210 mg every 2 weeks, or placebo every 2 weeks. No oral antipsychotic supplementation was allowed. Total Positive and Negative Symptom Scores (PANSS) showed significant improvement from baseline (baseline mean Total PANSS Score 101) to endpoint (mean changes -22.57, -26.32, -22.49, respectively) with each dose of ZYPADHERA (405 mg every 4 weeks, 300 mg every 2 weeks, and 210 mg every 2 weeks) as compared to placebo (mean change -8.51). Visitwise mean change from baseline to endpoint in PANSS Total score indicated that by Day 3, patients in the 300 mg/2 weeks and 405 mg/4 weeks treatment groups had statistically significantly greater reductions in PANSS Total score compared to placebo (-8.6, -8.2, and -5.2, respectively). All 3 ZYPADHERA treatment groups showed statistically significantly greater improvement than placebo beginning by end of Week 1. These results support efficacy for ZYPADHERA over 8 weeks of treatment and a drug effect that was observed as early as 1 week after starting treatment with ZYPADHERA.

The second, a long term study in clinically stable patients (n=1065) (baseline mean Total PANSS Score 54.33 to 57.75) who were initially treated with oral olanzapine for 4 to 8 weeks and then switched to continue on oral olanzapine or to ZYPADHERA for 24 weeks. No oral antipsychotic supplementation was allowed. ZYPADHERA treatment groups of 150 mg and 300 mg given every 2 weeks (doses pooled for analysis) and 405 mg given every 4 weeks were non inferior to the combined doses of 10, 15 and 20 mg of oral olanzapine (doses pooled for analysis) as measured by rates of exacerbation of symptoms of schizophrenia (respective exacerbation rates, 10%, 10% 7%). Exacerbation was measured by worsening of items on the PANSS derived BPRS Positive scale and hospitalization due to worsening of positive psychotic symptoms. The combined 150 mg and

300 mg/2 week treatment group was non inferior to the 405 mg/4 week treatment group (exacerbation rates 10% for each group) at 24 weeks after randomisation.

Paediatric population
ZYPADHERA has not been studied in the paediatric population. Controlled efficacy data in adolescents (ages 13 to 17 years) are limited to short term oral olanzapine studies in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Oral olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with oral olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin (see sections 4.4 and 4.8) were greater in adolescents than in adults. There are no controlled data on maintenance of effect or long term safety (see sections 4.4 and 4.8). Information on long term safety is primarily limited to open-label, uncontrolled data.

5.2 Pharmacokinetic properties

Absorption
Olanzapine is metabolised in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide. 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 a single IM injection with ZYPADHERA the slow dissolution of the olanzapine pamoate salt in muscle tissue begins immediately and provides a slow continuous release of olanzapine for more than four weeks. The release becomes diminishingly smaller within eight to twelve weeks. Antipsychotic supplementation is not required at the initiation of ZYPADHERA treatment (see section 4.2).

The combination of the release profile and the dosage regimen (IM injection every two or four weeks) result in sustained olanzapine plasma concentrations. Plasma concentrations remain measurable for several months after each ZYPADHERA injection. The half-life of olanzapine after ZYPADHERA is 30 days compared to 30 hours following oral administration. The absorption and elimination are complete approximately six to eight months after the last injection.

Distribution
Oral olanzapine is rapidly distributed. The plasma protein binding of olanzapine is about 93% over the concentration range of 7 to about 1000 ng/mL. In plasma, olanzapine is bound to albumin and α1-acid glycoprotein.

After repeated IM injections with 150 to 300 mg ZYPADHERA every two weeks, the 10^{th} to 90^{th} percentile of steady-state plasma concentrations of olanzapine were between 4.2 and 73.2 ng/ml. The plasma concentrations of olanzapine observed across the dose range of 150 mg every 4 weeks to 300 mg every 2 weeks illustrate increased systemic olanzapine exposure with increased ZYPADHERA doses. During the initial three months of treatment with ZYPADHERA, accumulation of olanzapine was observed but there was no additional accumulation during long-term use (12 months) in patients who were injected with up to 300 mg every two weeks.

Elimination
Olanzapine plasma clearance after oral olanzapine is lower in females (18.9 l/hr) versus males (27.3 l/hr), and in non-smokers (18.6 l/hr) versus smokers (27.7 l/hr). Similar pharmacokinetic differences between males and females and smokers and nonsmokers were observed in ZYPADHERA clinical trials. However, the magnitude of the impact of gender, or smoking on olanzapine clearance is small in comparison to the overall variability between individuals.

Elderly

No specific investigations have been conducted in the elderly with ZYPADHERA. ZYPADHERA is not recommended for treatment in the elderly population (65 years and over) unless a well-tolerated and effective dosage regimen using oral olanzapine has been established. In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hours) 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.

Renal impairment
In renally impaired patients (creatinine clearance < 10 ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hours) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57% of radiolabelled olanzapine appeared in urine, principally as metabolites. Although patients with renal impairment were not studied with ZYPADHERA, it is recommended that a well-tolerated and effective dosage regimen using oral olanzapine is established in patients with renal impairment before treatment with ZYPADHERA is initiated (see section 4.2).

Smokers
In smoking subjects with mild hepatic dysfunction, mean elimination half-life (39.3 hours) of orally administered olanzapine was prolonged and clearance (18.0 l/hr) was reduced analogous to non-smoking healthy subjects (48.8 hours and 14.1 l/hr, respectively). Although patients with hepatic impairment were not studied with ZYPADHERA, it is recommended that a well-tolerated and effective dosage regimen using oral olanzapine is established in patients with hepatic impairment before treatment with ZYPADHERA is initiated (see section 4.2).

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

5.3 Preclinical safety data

Preclinical safety studies were performed using olanzapine pamoate monohydrate. The main findings found in repeat-dose toxicity studies (rat, dog), in a 2-year rat carcinogenicity study, and in toxicity to reproduction studies (rat, rabbit) were limited to injection site reactions for which no NOAEL could be determined. No new toxic effect resulting from systemic exposure to olanzapine could be identified. However, systemic concentrations in these studies were generally less than that seen at effect levels in the oral studies; thus the information on oral olanzapine is provided below for reference.

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

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

Haematologic toxicity: Effects on haematology parameters were found in each species, including dose-related reductions in circulating leukocytes in mice and non-specific reductions of circulating leukocytes in rats; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia, or anaemia developed in a few dogs treated with 8 or 10 mg/kg/day

(total olanzapine exposure [AUC] is 12- to 15-fold greater than that of a man given a 12 mg dose). In cytopenic dogs, there were no undesirable effects on progenitor and proliferating cells in the bone marrow.

Reproductive toxicity
Olanzapine had no teratogenic effects. Sedation affected mating performance of male rats. Oestrous cycles were affected at doses of 1.1 mg/kg (3 times the maximum human dose) and reproduction parameters were influenced in rats given 3 mg/kg (9 times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
None

Solvent
Carmellose sodium
Mannitol
Polysorbate 80
Water for injections
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

Chemical and physical stability of the suspension in the vials has been demonstrated for 24 hours at 20°C-25°C. From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Do not refrigerate or freeze. Before reconstitution do not store above 30°C.

6.5 Nature and contents of container

300 mg powder: Type I glass vial. Bromobutyl stopper with olive colour seal.
405 mg powder: Type I glass vial. Bromobutyl stopper with steel blue colour seal.

3 ml solvent: Type I glass vial. Butyl stopper with purple seal.

One carton contains one vial of powder and one vial of solvent, one Hypodermic 3 ml syringe with pre-attached 19-gauge, 38 mm safety needle, one 19-gauge, 38 mm Hypodermic safety needle and two 19-gauge, 50 mm Hypodermic safety needles.

6.6 Special precautions for disposal and other handling

FOR DEEP INTRAMUSCULAR GLUTEAL INJECTION ONLY. DO NOT ADMINISTER INTRAVENOUSLY OR SUBCUTANEOUSLY.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Description:
The Jelco Hypodermic Needle-Pro® device is a sterile, single use device. It includes a needle and needle safety sheath. The Needle-Pro® device can be used with Luer slip or Luer lock syringe.

Indications for use:
This device is intended for injection or aspiration of fluids. The needle protection device covers the needle after use to help prevent needle sticks.

Contraindications:
None known.

Warnings:
A needle stick with a contaminated needle may cause infectious diseases.
Intentional disengagement of the Needle-Pro® device may result in a needle stick with a contaminated needle.
Bent or damaged needles can result in breakage or damage to the tissue or accidental needle puncture. If the needle is bent or damaged, no attempt should be made to straighten the needle or engage the Needle-Pro® device. The Needle-Pro® device may not properly contain a bent needle and/or the needle could puncture the needle protection device which may result in the needle stick with a contaminated needle.
Mishandling of the needle protection device may cause needles, especially short or small gauge needles, to bend whereby they protrude from the needle protector sheath which may result in a contaminated needle stick.
Do not use with Paraldehyde.

Caution:
Do Not Reuse: Medical devices require specific material characteristics to perform as intended. These characteristics have been verified for single use only. Any attempt to re-process the device for subsequent re-use may adversely affect the integrity of the device or lead to deterioration in performance.
Not made with natural rubber latex. Do not use if package is damaged.
Sterilized using ethylene oxide. Non-pyrogenic fluid path.

Needle-Pro and the color orange applied to the needle protection device, Jelco design mark and Smiths Medical design mark are trademarks of Smiths Medical. The symbol ® indicated the trademark is registered in the U.S. Patent and Trademark Office and certain other countries.

Reconstitution
STEP 1: Preparing materials
It is recommended that gloves are used as ZYPADHERA may irritate the skin.

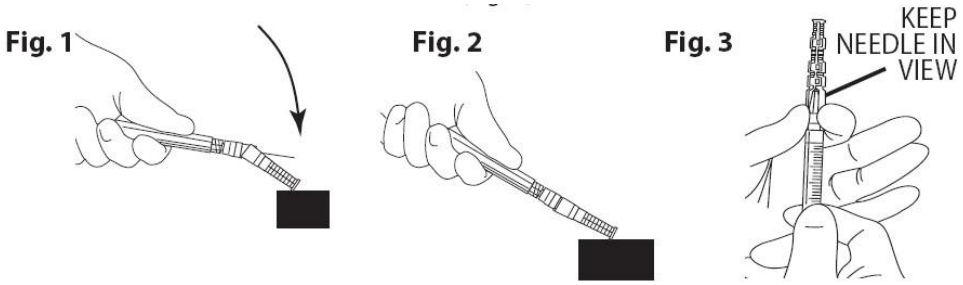
Reconstitute ZYPADHERA powder for prolonged release suspension for injection only with the solvent provided in the pack using standard aseptic techniques for reconstitution of parenteral products.

STEP 2: Determining solvent volume for reconstitution
This table provides the amount of solvent required to reconstitute ZYPADHERA powder for prolonged release suspension for injection.

ZYPADHERA vial strength (mg)	Volume of solvent to add (ml)
300	1.8
405	2.3

It is important to note that there is more solvent in the vial than is needed to reconstitute.

STEP 3: Reconstituting ZYPADHERA
1. Loosen the powder by lightly tapping the vial.
2. Open the pre-packaged Hypodermic syringe and needle with needle protection device. Peel blister pouch and remove device. Attach a syringe (if not already attached) to the Luer connection of the device with an easy twisting motion. Seat the needle firmly on the device with a push and a clockwise twist, then pull the needle cap straight away from the needle. Failure to follow these instructions may result in a needlestick injury.
3. Withdraw the pre-determined solvent volume (Step 2) into the syringe.
4. Inject the solvent volume into the powder vial.
5. Withdraw air to equalize the pressure in the vial.
6. Remove the needle, holding the vial upright to prevent any loss of solvent.
7. Engage the needle safety device. Press the needle into the sheath using a one-handed technique. Perform a one-handed technique by GENTLY pressing the sheath against a flat surface. AS THE SHEATH IS PRESSED (Fig. 1), THE NEEDLE IS FIRMLY ENGAGED INTO THE SHEATH (Fig. 2).
8. Visually confirm that the needle is fully engaged into the needle protection sheath. Only remove the device with the engaged needle from the syringe when required by a specific medical procedure. Remove by grasping the Luer hub of the needle protection device with thumb and forefinger, keeping the free fingers clear of the end of the device containing the needle point (Fig. 3). After use, place sharps in a suitable sharps container. Dispose the contaminated product in a safe manner according to local regulations.



9. Tap the vial firmly and repeatedly on a hard surface until no powder is visible. Protect the surface to cushion impact (See Figure A).


Figure A: Tap firmly to mix

10. Visually check the vial for clumps. Unsuspended powder appears as yellow, dry clumps clinging to the vial. Additional tapping may be required if clumps remain (See Figure B).


Unsuspended: visible clumps Suspended: no clumps
Figure B: Check for unsuspended powder and repeat tapping if needed.

11. Shake the vial vigorously until the suspension appears smooth and is consistent in color and texture. The suspended product will be yellow and opaque (See Figure C).

Figure C: Vigorously shake vial

If foam forms, let vial stand to allow foam to dissipate. If the product is not used immediately, it should be shaken vigorously to re-suspend. Reconstituted ZYPADHERA remains stable for up to 24 hours in the vial.

Administration

STEP 1: Injecting ZYPADHERA

This table confirms the final ZYPADHERA suspension volume to inject. Suspension concentration is 150 mg/ml olanzapine.

Dose (mg)	Final volume to inject (ml)
150	1.0
210	1.4
300	2.0
405	2.7

1. Determine which needle will be used to administer the injection to the patient. For obese patients, the 50 mm needle is recommended for injection:
   - If the 50 mm needle is to be used for injection, attach the 38 mm safety needle to the syringe to withdraw the required suspension volume.
   - If the 38 mm needle is to be used for the injection, attach the 50 mm safety needle to withdraw the required suspension volume.
2. Slowly withdraw the desired amount. Some excess product will remain in the vial.
3. Engage the needle safety device and remove needle from syringe.
4. Attach the selected 50 mm or 38 mm safety needle to the syringe prior to injection. Once the suspension has been removed from the vial, it should be injected immediately.
5. Select and prepare a site for injection in the gluteal area. DO NOT INJECT INTRAVENOUSLY OR SUBCUTANEOUSLY.
6. After insertion of the needle, aspirate for several seconds to ensure no blood appears. If any blood is drawn into the syringe, discard the syringe and the dose and begin reconstitution and administration procedure again. The injection should be performed with steady, continuous pressure.

DO NOT MASSAGE THE INJECTION SITE.

7. Engage the needle safety device (Fig. 1 and 2).

8. Discard the vials, syringe, used needles, extra needle and any unused solvent in accordance with appropriate clinical procedures. The vial is for single use only.

7. Manufacturer

Lilly S.A., Alcobendas, Madrid, Spain

8. License holder

Eli Lilly Israel Ltd., POB 2160 Herzliya Pituach 46120 Israel

The format of this leaflet has been defined by the MoH, its contents has been checked and approved on June 2017.

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