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28 September 2004

IMPORTANT SAFETY INFORMATION
REPORTED SERIOUS ADVERSE EVENTS FOLLOWING USE OF ZYPREXA INTRAMUSCULAR

Dear Healthcare Professional,

This communication is being provided by Eli Lilly and Company Limited with the support of the European Agency for the Evaluation of Medicinal Products (EMEA) in order to remind you of the recommended use of Zyprexa Intramuscular in view of reported serious adverse events.

- A total of 49 adverse events, of which 8 were fatal, have been spontaneously reported as of the 31st August 2004. The proportion of fatal adverse events reported for Zyprexa Intramuscular appears similar to that reported for other parenterally administered antipsychotic drugs.
- Worldwide, almost 100,000 patients have received injections of Zyprexa Intramuscular to date.
- Cardiorespiratory depression, hypotension and bradycardia have been reported amongst these cases.
- Comorbidities, co-administration of other medications and/or the risk of death associated with acute agitation make it difficult to attribute any of the reported fatalities to Zyprexa Intramuscular. However, this possibility cannot be excluded.
- A review of the reported fatalities indicates use of Zyprexa Intramuscular in a manner that is inconsistent with the Summary of Product Characteristics (SPC) including excessive dosing and/or inappropriate use of concomitant benzodiazepines and/or other antipsychotics.

Lilly therefore respectfully encourage prescribers to adhere to the recommendations of the SPC, the most important of which are:

- Zyprexa Intramuscular should be used to rapidly control agitation and disturbed behaviours in patients with schizophrenia or manic episode when oral therapy is not appropriate.
- The maximum combined intramuscular and oral daily dose of Zyprexa is 20 mg.
- The initial dose of Zyprexa Intramuscular is 10 mg as a single injection (use lower doses in elderly patients and those with renal or hepatic impairment).
- A maximum of 3 injections of Zyprexa Intramuscular may be administered in 24 hours. A minimum of 2 hours should elapse between the 1st and 2nd injections.
- Zyprexa Intramuscular is intended for short term use only, for up to a maximum of three consecutive days.

ZYPREXA (OLANZAPINE) TABLETS ABBREVIATED PRESCRIBING

INFORMATION ZYPREXA VELOTABS ZYPREXA ▼ INTRAMUSCULAR INJECTION

Presentations: Tablets, 2.5mg, 5mg, 7.5mg, 10mg, or 15mg of olanzapine. Also contain lactose. Velotab* 5mg, 10mg, or 15mg orodispersible tablets. Also contain gelatin, aspartame, mannitol, and parahydroxybenzoates. Powder for Solution for Injection, containing 10mg olanzapine. **Uses:** Tablets and Velotabs: Schizophrenia, both as initial therapy and for maintenance. Moderate to severe manic episode and prevention of recurrence in bipolar disorder. Injection: Rapid control of agitation and disturbed behaviours in patients with schizophrenia or manic episode, when oral therapy is not appropriate. **Dosage and Administration:** Tablets and Velotabs: Schizophrenia: 10mg/day orally. Manic episode: 15mg/day in monotherapy; 10mg/day in combination therapy. Preventing recurrence in bipolar disorder: 10mg/day or for patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. May subsequently be adjusted to 5-20mg daily. Injection: Intramuscular use only for up to a maximum of three consecutive days. Initial dose is 10mg. A second injection, 5-10 mg, may be administered 2 hours after. Maximum daily dose is 20mg, with not more than 3 injections in any 24-hour period. Treatment with Zyprexa Intramuscular Injection should be discontinued, and the use of oral Zyprexa should be initiated, as soon as clinically appropriate. Do not administer intravenously or subcutaneously. Children: Not recommended (under 18 years). Elderly patients: Oral therapy - a lower starting dose (5mg/day) is not routinely indicated but should be considered when clinical factors warrant. Injection - recommended starting dose is 2.5-5mg. Renal and/or hepatic impairment: 5mg starting dose in moderate hepatic insufficiency. When more than one factor which might cause slower metabolism (female gender, elderly age, non-smoking status), consider a decreased starting dose. **Contra-indications:** Known hypersensitivity to any ingredient. Known risk of narrow-angle glaucoma. **Warnings and Special Precautions:** Olanzapine is not approved for the treatment of dementia related psychosis and/or behavioural disturbances, and it is not recommended for use in this particular group of patients because of an increase in mortality and the risk of cerebrovascular accident. Injection: Efficacy not established in patients with agitation and disturbed behaviours related to conditions other than schizophrenia or manic episode. Should not be administered to patients with unstable medical conditions (see Summary of Product Characteristics [SPC]). Safety and efficacy have not been evaluated in patients with alcohol or drug intoxication. Patients should be closely observed for hypotension, including postural hypotension, bradyarrhythmia, and/or hypoventilation (see SPC). Simultaneous injection with parenteral benzodiazepine is not recommended. Special caution in patients who receive other medicinal products having haemodynamic properties similar to those of Zyprexa Intramuscular Injection (see SPC). Clinical monitoring advisable in diabetic patients and those with risk factors for diabetes. Caution with prostatic hypertrophy, or paralytic ileus and related conditions. With oral Zyprexa, improvement in clinical condition may take several days to some weeks. Phenylalanine: Velotabs contain aspartame - a source of phenylalanine. Sodium methyl parahydroxybenzoate and sodium propyl parahydroxybenzoate: Velotabs contain these preservatives, known to cause urticaria, contact dermatitis, and, rarely, immediate reactions with bronchospasm. Caution in patients with elevated ALT and/or AST, hepatic impairment, limited hepatic functional reserve, and in patients being treated with hepatotoxic drugs. Where hepatitis has been diagnosed, discontinue Zyprexa. Caution in patients with low leucocyte and/or neutrophil counts, bone marrow depression, in patients receiving medicines known to cause neutropenia, and in patients with hypereosinophilic conditions or with myeloproliferative disease. Discontinue if signs and symptoms indicative of NMS, or unexplained high fever. Caution in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. If tardive dyskinesia appears, consider dose reduction or discontinuation. Caution when taken with other centrally acting drugs and alcohol. May antagonise effects of dopamine agonists. Blood pressure should be measured periodically in patients over 65 years. As with other antipsychotics, caution when prescribed with drugs known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia, or hypomagnesaemia. In clinical trials, Zyprexa was not associated with a persistent increase in absolute QT intervals. Gradual dose reduction should be considered when discontinuing olanzapine. Use of olanzapine to treat drug-induced psychosis in patients with Parkinson's disease is not recommended. **Interactions:** Metabolism may be affected by substances that can specifically induce (eg, concomitant smoking or carbamazepine) or inhibit (eg, fluvoxamine) the isoenzyme P450-CYP1A2 which metabolises olanzapine. Activated charcoal reduces the bioavailability of oral olanzapine. Olanzapine may antagonise the effects of direct and indirect dopamine agonists. Olanzapine showed no interaction when co-administered with lithium or biperiden. Zyprexa Intramuscular Injection 5mg, administered 1 hour before lorazepam 2mg, added to the somnolence observed with either drug alone. **Pregnancy and Lactation:** There are very rare reports of tremor, hypertonia, lethargy, and sleepiness in infants born to mothers who used olanzapine during the 3rd trimester. Should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Patients should be advised not to breast-feed an infant if they are taking Zyprexa. **Driving, etc:** May cause somnolence or dizziness. Patients should be cautioned about operating hazardous machinery, including motor vehicles. **Undesirable Effects:** Clinical trial adverse event reporting and investigations with oral Zyprexa: In placebo-controlled clinical trials of elderly patients with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in mortality in olanzapine-treated patients compared to placebo (3.5% vs 1.5%, respectively). In the same clinical trials, there was a 3-fold increase in cerebrovascular adverse events (CVAE, eg, stroke, transient ischaemic attack) in patients treated with olanzapine compared to placebo (1.3% vs 0.4%, respectively). Very common (>10%) undesirable effects in this patient group were abnormal gait and falls. Pneumonia and urinary incontinence were observed commonly (1-10%). Blood and lymphatics. Common (1-10%): Eosinophilia. Neutropenia was seen in a valproate combination therapy trial in bipolar mania patients; a potential contributing factor could be high plasma valproate levels. Metabolism and nutritional. Very common (>10%): Weight gain. Common (1-10%): Increased appetite, elevated glucose levels (incidence 1.0% for Zyprexa versus 0.9% for placebo for non-fasting levels ≥11mmol/l), elevated triglyceride levels. Nervous. Very common (>10%): Somnolence, abnormal gait in Alzheimer's disease patients. Worsening of Parkinsonian symptomatology and hallucinations were reported in patients with Parkinson's disease. Common (1-10%): Dizziness, akathisia, parkinsonism, dyskinesia. (Zyprexa-treated patients had a lower incidence of parkinsonism, akathisia, and dystonia compared with titrated doses of haloperidol.) Cardiac. Uncommon (0.1-1%): Bradycardia, with or without hypotension or syncope. Vascular. Common (1-10%): Orthostatic hypotension. Gastro-intestinal. Common (1-10%): Mild, transient, anticholinergic effects, including constipation and dry mouth. Hepato-biliary. Common (1-10%): Transient, asymptomatic elevations of ALT, AST. Skin and subcutaneous tissue. Uncommon (0.1-1%): Photosensitivity reaction. General. Common (1-10%): Asthenia, oedema. Investigations. Very common (>10%): Elevated plasma prolactin levels, but associated clinical manifestations (eg, gynaecomastia, galactorrhoea, breast enlargement) were rare. Uncommon (0.1-1%): High creatine phosphokinase. Post-marketing spontaneous reporting with oral Zyprexa: Blood and lymphatics. Rare (0.01-0.1%): Leucopenia. Very rare (<0.01%): Thrombocytopenia, neutropenia. Immune system disorder. Very rare (<0.01%): Allergic reaction. Metabolism and nutritional. Very rare (<0.01%): Hyperglycaemia and/or development or exacerbation of diabetes, occasionally associated with ketoacidosis or coma, including some fatal cases. Hypertriglyceridaemia. Nervous. Rare (0.01-0.1%): Seizures, mostly when there was a history of seizures or risk factors. Very rare (<0.01%): Cases reported as NMS. Parkinsonism, dystonia, and tardive dyskinesia. Discontinuation reactions have been reported; gradual tapering of the dose should be considered. Gastro-intestinal. Very rare (<0.01%): Pancreatitis. Hepato-biliary. Very rare (<0.01%): Hepatitis. Skin and subcutaneous tissue. Rare (0.01-0.1%): Rash. Reproductive. Very rare (<0.01%): Priapism. Renal and urinary disorders. Very rare (<0.01%): Urinary hesitation. Additional clinical trial adverse event reporting and investigations with Zyprexa Intramuscular Injection: Cardiac. Common (1-10%): Bradycardia, with or without hypotension or syncope, tachycardia. Uncommon (0.1-1%): Sinus pause. Vascular. Common (1-10%): Postural hypotension, hypotension. Respiratory. Uncommon (0.1-1%): Hypoventilation. General. Common (1-10%): Injection site discomfort. For further information see SPCs. **Legal Category:** POM. **Marketing Authorisation Numbers:** EU/1/96/022/002, EU/1/96/022/004, EU/1/96/022/006, EU/1/96/022/009, EU/1/96/022/010, EU/1/96/022/012, EU/1/99/125/001, EU/1/99/125/002, EU/1/99/125/003, EU/1/96/022/016, **Basic NHS Cost:** £33.29 per pack of 28 2.5mg tablets. £48.78 per pack of 28 5mg tablets. £146.34 per pack of 56 7.5mg tablets. £97.56 per pack of 28 10mg tablets. £195.11 per pack of 56 10mg tablets. £146.34 per pack of 28 15mg tablets. £56.10 per pack of 28 5mg Velotabs. £112.19 per pack of 28 10mg Velotabs. £168.29 per pack of 28 15mg Velotabs. £3.48 per pack of 1 10mg Powder for Solution for Injection. **Date of Preparation or Last Review:** March 2004 **Full Prescribing Information is Available From:** Eli Lilly and Company Limited, Lilly House, Priestley Road, Basingstoke, Hampshire, RG24 9NL. Telephone: Basingstoke (01256) 315999 *ZYPREXA (olanzapine) and VELOTAB are trademarks of Eli Lilly and Company. 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The SPC further advises that

- Zyprexa Intramuscular should not be administered to patients with unstable medical conditions.
- Patients treated with Zyprexa Intramuscular should have their heart and respiratory rates, blood pressure and level of consciousness carefully observed for 2-4 hours following administration.
- Simultaneous injection of Zyprexa Intramuscular and parenteral benzodiazepines is not recommended.
- If parenteral benzodiazepines are essential, administration should be a minimum of 1 hour after administration of Zyprexa Intramuscular.
- Zyprexa Intramuscular should only be administered to patients who have received parenteral benzodiazepines after careful clinical evaluation. Such patients should be carefully observed for excessive sedation and cardiorespiratory depression.

You can assist in monitoring the safety of Zyprexa Intramuscular by reporting adverse events to Eli Lilly and Company Limited (01256 315999), or complete a Committee on Safety of Medicines (CSM) Yellow Card (http://www.yellowcard.gov.uk).

The safety of patients is Lilly's highest priority and we greatly value your collaboration with us in this regard. Please contact our Medical Information Department on 01256 315999 if you have any questions or if you wish to receive further information.

Yours sincerely,

Dr Joanna Nakielny DRCOG, MRCPsych, MSc, FFPM
Medical Director UK & RoI

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