Labeling Comparison for Canada IM Negotiations
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Health Canada Revisions	CDS Text	EU SPC Text	USPI Text	CDS Compliance Comments
Precautions – Hypotension and Syncope Infrequently hypotension and/or syncope associated with bradycardia have been observed with ZYPREXA IM. The incidence of this adverse event appeared to be higher with single IM doses greater (i.e., 12.5 mg IM) than those recommended. Patients receiving intramuscular olanzapine should be closely observed for hypotension including postural hypotension, bradyarrhythmia and/or hypoventilation, particularly for the first 2 to 4 hours following injection. Patients should remain recumbent if dizzy or drowsy after injection until examination indicates they are not experiencing hypotension including postural hypotension, bradyarrhythmia and/or hypoventilation.	**Precautions** Hypotension and/or bradycardia have been observed during intramuscular administration of olanzapine for injection. Patients should remain recumbent if drowsy or dizzy after injection, until examination has indicated that they are not experiencing hypotension, postural hypotension and/or bradycardia. In view of the possibility of bradycardia and/or hypotension with intramuscular olanzapine for injection, caution should be considered in patients with serious cardiovascular disease where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.	**4.4 Special warnings and special precautions for use** Patients receiving intramuscular olanzapine should be closely observed for hypotension including postural hypotension, bradyarrhythmia and/or hypoventilation, particularly for the first 2 to 4 hours following injection. Blood pressure, pulse, respiratory rate and level of consciousness should be recorded if clinically indicated and remedial treatment provided if required. Patients should remain recumbent if dizzy or drowsy after injection until examination indicates that they are not experiencing hypotension including postural hypotension, bradyarrhythmia and/or hypoventilation. Special caution is necessary in patients who receive treatment with other medicinal products having haemodynamic properties similar to those of intramuscular olanzapine (see also Section 4.5. Interaction with other medicinal products and other forms of interaction).	**Precautions - General** Hemodynamic Effects—Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonistic properties. Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in non-agitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥30 mmHg) (*see* DOSAGE AND ADMINISTRATION). Syncope was reported in 0.6% (15/2500)	In my opinion, changes proposed by TPD are compliant with CDS. Text provided by TPD provides more detail than that included in the CDS (mentions hypoventilation).

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			of olanzapine-treated patients in phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the events occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD (*see* DOSAGE AND ADMINISTRATION). A more gradual titration to the target dose should be considered	

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			if hypotension occurs. For intramuscular olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension and/or bradycardia. Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.	

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Precautions - Drug Interactions Caution should be exercised in patients who receive medicinal products than can induce hypotension, bradycardia, or respiratory depression.	**C.5 Interactions with Other Medicaments and Other Forms of Interaction** Caution should be exercised in patients who receive treatment with medicinal products that can lower blood pressure by mechanisms other than alpha-1 adrenergic antagonism.	**4.5. Interaction with other medicinal products and other forms of interaction** Caution should be exercised in patients who receive medicinal products that can induce hypotension, bradycardia, respiratory or central nervous system depression (see also Section 4.4 Special warnings and special precautions for use).	**Precautions – Drug Interactions** Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents.	In my opinion, changes proposed by TPD are compliant with CDS. Proposed text reflects what is approved in the EU with minor modifications.
Precautions – Lorazepam Simultaneous injection of intramuscular olanzapine and parenteral benzodiazepine has not been studied and therefore not recommended. In a clinical pharmacokinetic/pharmacodynamic study however, administration of intramuscular lorazepam (2 mg) two hours following intramuscular olanzapine (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. Administration of intramuscular lorazepam 2 hours after injection of intramuscular olanzapine however, added to the somnolence observed with either drug alone.	**C.5 Interactions with Other Medicaments and Other Forms of Interaction** Concomitant administration of intramuscular lorazepam and intramuscular olanzapine did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, coadministration of intramuscular lorazepam and intramuscular olanzapine added to the somnolence observed with either drug alone.	**4.5. Interaction with other medicinal products and other forms of interaction** 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 medicines were unchanged. However, the combination added to the somnolence observed with either medicines alone. Concomitant injection of olanzapine and parenteral benzodiazepine has not been studied and is therefore not recommended (see Section 4.4 Special warnings and special precautions for use).	**Precautions - Drug Interactions** Lorazepam—Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone.	Text provided by TPD provides more detail than that included in the CDS. CDS does not mention simultaneous injection of olanzapine and lorazepam. Newly added statement reflects text that is approved in the EU.

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Precautions – Use in Patients with other Concomitant Illness Due to the more rapid and higher peak plasma concentrations following intramuscular compared to oral administration (see PHARMACOLOGY), particular caution is advised with the use of ZYPREXA IM. ZYPREXA IM should not be administered to patients with unstable medical conditions, such as acute or unstable cardiovascular conditions such as myocardial infarction, unstable angina pectoris, severe hypotension and/or bradycardia, or sick sinus syndrome. If the patient's medical history with regard to unstable medical conditions cannot be determined, the risk and benefits of IM olanzapine should be considered in relation to other alternative treatments.	**Precautions** In view of the possibility of bradycardia and/or hypotension with intramuscular olanzapine for injection, caution should be considered in patients with serious cardiovascular disease where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk. **C.5 Interactions with Other Medicaments and Other Forms of Interaction** Caution should be exercised in patients who receive treatment with medicinal products that can lower blood pressure by mechanisms other than alpha-1 adrenergic antagonism.	**4.4. Special warnings and special precautions for use** 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. The safety and efficacy of IM olanzapine has not been evaluated in patients with alcohol or drug intoxication (see also Section 4.5 Interaction with other medicinal products and other forms of interaction).	**Precautions – Use in Patients with Concomitants Illness** Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients (*see* Hemodynamic Effects). **Precautions - General** Hemodynamic Effects—Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonistic properties. Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in	Text proposed by TPD is more stringent than that provided in the CDS and is aligned with the EU SPC text. Proposed text reflects that which is approved in the EU.

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			non-agitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥30 mmHg) (*see* DOSAGE AND ADMINISTRATION). Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the events occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and	

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			sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD (*see* DOSAGE AND ADMINISTRATION). A more gradual titration to the target dose should be considered if hypotension occurs. For intramuscular olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension and/or bradycardia. Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to	

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			hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.	
Precautions – Use in Patients with Other Concomitant Illness Hyperglycemia, diabetes, or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma associated with the use of ZYPREXA has been reported rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.	**C.8 Undesirable Effects** Random plasma glucose levels ≥200mg/dL (suggestive of potential diabetes) as well as random levels ≥160mg/dL but <200mg/dL (suggestive of potential hyperglycemia) in patients with baseline random glucose levels ≤140mg/dL have been seen occasionally in clinical trials. The following glucose related terms are documented with their appropriate frequencies in the AE tables: • Diabetic coma • Diabetic ketoacidosis • Hyperglycemia • Random glucose levels ≥200mg/dL (suggestive of	**4.4 Special warnings and special precautions for use** Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.	**Adverse Reactions – Other Adverse Observed During the Clinical Trial Evaluation of Olanzapine** Endocrine System – Infrequent: diabetes mellitus; Rare: diabetic acidosis Metabolic and Nutritional Disorders – Infrequent: hyperglycemia, hypoglycemia; Rare: ketosis Postintroduction Reports – diabetic coma	Text proposed by TPD is more stringent than that provided in the CDS and is aligned with the EU SPC text. CDS does not recommend monitoring. Must have team approval for inclusion. We have challenged such text in multiple affiliates.

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	potential diabetes) • Random glucose levels ≥160mg/dL but <200mg/dL (suggestive of potential hyperglycemia)			
Dosage and Administration - ZYPREXA IM Usual Dose for Agitated Patients with Schizophrenia: In clinical trials, individual doses of 5 mg, 7.5 mg and 10 mg of intramuscular olanzapine for injection have been shown to be effective in controlling agitation in patients with schizophrenia (see CLINICAL PHARMACOLOGY). Lower doses (eg 2.5 mg) should be considered when clinical factors warrant (eg in the elderly or debilitated). In clinical trials over a 24 hour period, a minority of patients required a second dose, and only a few percent of patients required a third dose of ZYPREXA IM is limited. Nevertheless, if it is judged that the clinical situation warrants, a second dose should be given no more frequently than 2 hours after the first dose. A third dose, if required, should be given no sooner than four hours after the	**C.2 Posology/Dosing and Method of Administration** Do not administer intravenously or subcutaneously. The recommended dose for olanzapine for injection is 10 mg, administered as a single intramuscular injection. On the basis of individual clinical status, a second injection, up to 10 mg, may be administered as early as 2 hours after the first injection and a third injection, up to 10 mg, may be administered as early as 4 hours after the second injection. The safety of total daily doses greater than 30 mg has not been evaluated in clinical trials. If ongoing olanzapine therapy is clinically	**4.2. Posology and method of administration** For intramuscular use. Do not administer intravenously or subcutaneously. Zyprexa Powder for Solution for Injection 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. ZYPREXA powder for solution for injection should be reconstituted in accordance	**Dosage and Administration** *Agitation Associated with Schizophrenia, Bipolar I Mania, and Dementia* Usual Dose for Agitated Patients with Schizophrenia or Bipolar Mania—The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant (*see* CLINICAL PHARMACOLOGY). If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical	Total daily dose of not greater than 20 mg is not in line with the CDS, but reflects what was approved in the EU. In my opinion, the newly proposed TPD text does not clearly indicate the recommended starting dose.

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second dose. The recommended maximum daily dose of olanzapine (oral and IM) is 20 mg, with no more than three injections in a 24 hour period.	therapy is clinically indicated, treatment with intramuscular olanzapine for injection should be discontinued and oral olanzapine treatment, in a range of 5-20 mg/day, should be initiated as soon as clinically appropriate. *General Considerations for Intramuscular Dosing in Special Populations:* A dose of 5 mg per injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg per injection is suggested for geriatric patients with dementia, as this dose has been shown to be efficacious. Olanzapine has not been studied in subjects under 18 years of age.	with the recommendation in Section 6.6, Instructions for use, handling and disposal. For further information on continued treatment with oral olanzapine (5 to 20 mg daily), see the Summary of Product Characteristics for ZYPREXA coated tablets or ZYPREXA VELOTAB orodispersible tablets. Elderly patients: The recommended starting dose in elderly patients (> 60 years) is 2.5 - 5 mg. Depending on the patient's clinical status (see Section 4.4 Special warnings and special precautions for use), 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.	trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., three doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension (*see* PRECAUTIONS, Hemodynamic Effects). Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended. If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as	

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		Children and adolescents: ZYPREXA 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 (see Section 4.4 Special warnings and special precautions for use), 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.	clinically appropriate (*see* Schizophrenia or Bipolar Mania *under* DOSAGE AND ADMINISTRATION). <u>Intramuscular Dosing in Special Populations</u>—A dose of 5 mg per injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg per injection should be considered for patients with dementia or who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine (*see* CLINICAL PHARMACOLOGY; also *see* Use in Patients with Concomitant Illness and Drug Interactions *under* PRECAUTIONS).	