GLUCOSE RELATED STATEMENTS IN OLANZAPINE LABELING

CDS	USPI	EU SmPC	Japan
			CONTRAINDICATIONS
			Patients with diabetes mellitus and those who have a history of diabetes mellitus.
		4.4 Special warnings and special precautions for use	**WARNINGS**
		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.	1. From marked increase in blood glucose, serious adverse reactions such as diabetic ketoacidosis, diabetic coma, etc. may appear leading potentially to death. Observe sufficiently with such as measurement of blood glucose during the olanzapine administration. 2. Upon administration, explain sufficiently in advance to the patient and family members possible occurrence of above adverse reactions. Provide guidance to them to pay attention to such abnormalities as thirst, polydipsia, polyurea, frequent urination, etc., and to see a physician suspending administration immediately, if such symptoms appear. (See the section on "Important Precautions")

CDS	USPI	EU SmPC	Japan
			PRECAUTIONS
			1. Careful Administration 6. Patients with risk factors for diabetes mellitus such as family history of diabetes mellitus, hyperglycemia, obesity, etc. (See the section on "Important Precautions"). **2. Important Precautions** 1. By administration of this drug, marked increase in blood glucose may appear leading to fatal clinical course such as diabetic ketoacidosis, diabetic coma, etc. Observe sufficiently with such as measurement of blood glucose (appearance of) thirst, polydipsia, polyurea, and frequent urination during the olanzapine administration. In particular, patients with risk factors for diabetes mellitus such as hyperglycemia, obesity, etc., blood glucose may increase, leading to acute worsening of metabolic state. 2. Upon administration, explain sufficiently in advance to patients and family members possible occurrence of above adverse reactions. Provide guidance to them to pay attention to such abnormalities as thirst, polydipsia, polyurea, frequent urination, etc., and to see a physician suspending administration immediately, if such symptoms appear.

CDS	USPI	EU SmPC	Japan
Section C.8 Undesirable Effects	**Adverse Reactions**	**4.8 Undesirable effects**	**4. Adverse Reactions**
Random plasma glucose levels ≥200mg/dL (suggestive of potential diabetes){ **XE "37141" }** as well as random levels ≥160mg/dL but <200mg/dL (suggestive of potential hyperglycemia){ **XE "37142" }** 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 adverse event tables: • Diabetic coma • Diabetic ketoacidosis • Hyperglycemia • Random glucose ≥160 mg/dL <200 mg/dL (suggestive of potential hyperglycemia) • Random glucose ≥200 mg/dL (suggestive of potential diabetes)	Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Endocrine System--***Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis **Metabolic and Nutritional Disorders--***Infrequent*: hyperglycemia, hypoglycemia; *Rare:* ketosis *Postintroduction Reports--* Adverse events reported since market introduction which were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: diabetic coma	The following table of undesirable effects is based on adverse event reporting and laboratory investigations from clinical trials. **Metabolism and nutrition disorders** *Common (1-10%):* Elevated glucose levels (see note 1 below). *[1]In clinical trials with olanzapine in over 5000 patients with baseline non-fasting glucose levels ≤ 7.8 mmol/l, the incidence of non-fasting plasma glucose levels ≥ 11 mmol/l (suggestive of diabetes) was 1.0%, compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels ≥ 8.9 mmol/l but < 11 mmol/l (suggestive of hyperglycaemia) was 2.0%, compared to 1.6% with placebo. Hyperglycaemia is also reported as a Very Rare (<0.01%) spontaneous event.* The following table of undesirable effects is based on post-marketing spontaneous reports. **Metabolism and nutrition disorders** *Very rare (<0.01%):* Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been spontaneously reported very rarely, including some fatal cases (see also	**(1) Clinically significant adverse reactions** 1. Hyperglycemia, Diabetic ketoacidosis, Diabetic coma: Hyperglycemia may develop leading to fatal clinical course, such as diabetic ketoacidosis and diabetic coma leading to death. Thus, make a close observation, with such as blood glucose measurement, (appearance of) thirst, polydipsia, polyurea, and frequent urination. If any abnormalities are noted, discontinue administration and take an appropriate measure(s) including administration of insulin. The following terms are identified in a table titled, "Japanese clinical studies and postmarketing reports:" • Sugar urinary • Diabetes The following terms are identified in a table titled, "Foreign clinical studies and postmarketing spontaneous reports:" • Hyperglycemia (Casual blood glucose: Not less than 160 mg/dL) • Coma diabetic • Diabetic ketoacidosis

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		Note 1 above and Section 4.4, Special warnings and special precautions for use).	

S. Africa MCC Response to Labeling Supplement

Original Proposed Text:	MCC Comments:	Lisa's Comments:
In clinical trials, abnormal gait was reported in patients with dementia of the Alzheimer's type. NOTE: text added on to Nervous System side effect list.	Did not approve proposed text, countered with the following: "and abnormal gait especially in Alzheimer's patients." NOTE: text added on to Nervous System side effect list.	MCC proposal still in line with CDS.
Random plasma glucose levels > 200 mg/dL (suggestive of potential diabetes) as well as random levels ≥ 160 mg/dL but < 200 mg/dL (suggestive of potential hyperglycaemia) in patients with baseline random glucose levels ≤ 140 mg/dL have been seen occasionally in clinical trials. NOTE: proposed location - clinical chemistry list in Side Effects list.	Did not approve proposed paragraph. Instead, proposed the following paragraph under special precautions, concomitant illnesses: Hyperglycemia or exacerbation of pre-existing diabetes has been reported in rare cases during Zyprexa treatment. In some cases a prior increase in body weight has been reported which may be a pre-disposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for developing diabetes mellitus.	Rejection of original glucose paragraph is acceptable for CDS compliance efforts, it will be noted as "submitted and rejected." **NEED APPROVAL FROM PRODUCT TEAM AND PHV FOR NEWLY PROPOSED PARAGRAPH.**
In overdose section: Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of 1,500 mg.	MCC rejected sentence.	Rejection of statement is acceptable for CDS compliance efforts, it will be noted as "submitted and rejected."

To: CN=Patrizia Cavazzoni/OU=AM/O=LLY@Lilly; CN=James A Edwards/OU=AM/O=LLY@Lilly
CC: CN=Bonnie A Meloche/OU=AM/O=LLY@Lilly
Date: 09/23/2002 09:06:31 AM
From: CN=Lisa A Vierhile/OU=AM/O=LLY
Subject: Canadian IM Labeling Negotiations
Attachments: Canada IM Negot Comparison 21SEP02.doc

Patrizia and Jamie,

I reviewed the Canadian IM labeling proposal this weekend and created a table which compares the TPD text with that of the CDS, EU SPC, and negotiated USPI. I have also added some of my comments regarding where I think we stand from a CDS compliance perspective.

Bonnie created a similar table and we were hoping to compare notes this weekend, but because I had problems trying to RAS in and a water pipe breaking in my house, I did not get to make such a comparison.

Overall my thoughts are as follows:

From a CDS perspective, most of the changes are in compliance although more stringent than what we document in the CDS. Therefore, we must have medical and pharmacovigilance alignment for approval of the changes. The changes to the overdose section are completely in line with the CDS and therefore I did not bother to include them in the table.

The most important discrepancies noted relate to the glucose statements which are in line with the SPC, but clearly more than what is contained within the CDS. Also of note is the mentioning of hypoventilation in the proposed precautionary text regarding hypotension and syncope. Again, it looks as though this is being driven by what is in the EU SPC.

I hope this information helps. I will be calling into the 9:00 mtg, but will only be here a half day since I must meet with a plumber today!!! Thanks.

Canada IM Negot Comparison 21SEP02.doc

Best regards,
Lisa
3-0861