World Wide Labeling

Country	Section	Wording
US	Adverse Events Laboratory Changes **FDA rejected** this label change 10/11/00 This descriptive date expressed a certain level of impled safety with respect to treatment emergent hyperglycemia. This reassuring language is not appropriate…	In the olanzapine clinical trial database, as of September 30, 1999, 4577 loanzapine-treated patients (representing approximately 2255 patiente-years of exposure) and 445 placebo-treated patients who had no history of diabetes mellitus and whose baseline random plasma glucose levels were 140mg/dL or lower were identified. Persistent random glucose levels ≥200mg/dL (suggestive of possible diabetes) were observed in 0.8% of olanzapine-treated patients (placebo 0.7%). Transient (i.e., resolved while the patients remained on treatment) random glucose levels ≥200mg/dL were found in 0.3% of olanzapine-treated patients (placebo 0.2%). Persistent random glucose levels ≥ 160mg/dL but <200mg/dL (possibly hyperglycemia, not necessarily diabetes) were observed in 1.0% of olanzapine-treated patients (placebo 1.1%). Transient random glucose levels ≥160mg/dL but <200mg/dL were found in 1.0% of olanzapine-treated patients (placebo o.4%).
US	Adverse Reactions	**Body System:** **Endocrine System**--*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis and goiter. **Hemic and Lymphatic System**--*Frequent:* leukopenia; *Infrequent:* anemia, cyanosis, leukocytosis, lymphadenopathy, thrombocythemia, and thrombocytopenia; *Rare:* normocytic anemia. **Metabolic and Nutritional Disorders**--*Infrequent*: acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema, and water intoxication; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, and ketosis. *Postintroduction Reports*--Adverse events reported since market introduction which were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, pancreatitis, and priapism.

Australia	Precautions	***There is an increased prevalence of diabetes in patients with schizophrenia. As with some other antipsychotics, exacerbation of pre-existing diabetes has been reported very rarely. Hyperglycaemia, diabetic coma and diabetic ketoacidosis have been reported in very rare cases, sometimes in patients with no reported history of hyperglycaemia (see ADVERSE REACTIONS). Appropriate clinical monitoring is advisable in diabetic patients.***
Australia		***<u>Adverse events identified from clinical trials</u>*** ***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 11mmol/L (suggestive of diabetes) was 1.0%, compared to 0.9% with placebo. The incidence of non-fasting plasma glucose levels 8.9mmol/L but <11mmol/L (suggestive of hyperglycaemia) was 2.0%, compared to 1.6% with placebo;***
EU- SmPC	Section 4.4 Special warnings and special precautions for use	Hyperglycaemia or exacerbation or 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.
EU-SmPC	Section 4.8 Undesirable Effects	Rare(<1%) Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also Section 4.4, Special warnings and special precautions for use). Common (1-10%) Non-fasting plasma glucose levels ≥11mmol/l (suggestive of diabetes) as well as non-fasting levels ≥8.9mmol/l but<11 mmol/l (suggestive of hyperglycemia in patients with baseline non-fasting glucose levels ≤7.8mmol/l have been seen occasionally in clinical trials. Hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or come has been spontaneously reported very rarely, includingsome fatal cases (see also Section 4.4, Special warings and special precautions for use) **Common (1-10%):** 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. For further information, see Section "Very Rare (<0.01%)"

		below. **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 Section 4.4, Special warnings and special precautions for use).
EU-SmPC		*Information put into two tables as below:* 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 Note 1 above and Section 4.4, Special warnings and special precautions for use).
Japan	Contraindication	
New Zealand		
Clozapine-US	Precautions	Severe hyperglycemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL® (clozapine) treatmene in patients with no prior history of hyperglycemia. While a clausal relationship to CLOZARIL® (clozapine) use has not been definitively established, glucose levels normalized in most patients after discontinuation of CLOZARIL® (clozapine), and a rechallenge in one patient produced a recurrence of hyperglycemia. The effect of CLOZARIL® (clozapine) on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving

		CLOZARIL® (clozapine) who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergenbt hyperglycemia, the discontinuation of CLOZARIL® (clozapine) should be considered.