DM
Dyslipidemia

# Standby Statement

## Sweden Medical Products Agency
## Adverse Reactions News

## (September 2001)

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# 1. Purpose

The Swedish Medical Products Agency stated in recent adverse drug reaction newsletter specific adverse event associations with olanzapine that Eli Lilly and Co. (Lilly) finds inaccurate. This standby statement is being provided by Lilly to clarify these suggested associations with olanzapine.

# 2. Article 1

"Leponex (clozapine) may cause metabolic syndrome including insulin resistance and hyperlipidemia - olanzapine and risperidone are suspected to give similar effects" by Karin Hedenmalm.[1]

## 2.1. Response

### *2.1.1. Type II Diabetes Mellitus*

An association between antipsychotics hyperglycemia and/or diabetes has been reported since the 1950s.[2] Recently, case reports have suggested that some atypical antipsychotics, including Zyprexa® and Risperdal®, may significantly alter glycemic control, or blood glucose levels, which can lead to hyperglycemia and/or diabetes.[3-18] However, the prevalence of Type 2 Diabetes Mellitus has been reported in some instances to be two to four times greater among patients with schizophrenia and bipolar patients than in the general population.[19-22] Studies in populations with schizophrenia have shown a prevalence of elevated blood glucose levels ranging from 2.5 to 24.5%.[20-23]

A retrospective analysis conducted by Lilly of clinical trial data of more than 3,000 schizophrenia patients was performed to investigate glycemic changes during treatment with olanzapine relative to haloperidol, risperidone and clozapine. The analysis found that the likelihood of elevation of random glucose levels above the critical thresholds that may suggest the possibility of an individual experiencing a diabetic event during treatment with olanzapine was not statistically significantly different compared to haloperidol or risperidone treated patient groups and was significantly less compared to the patient group treated with clozapine.

In addition, Lilly has conducted a retrospective study of a large patient database to assess the risk of patients developing diabetes while being treated with antipsychotics. The PCS database which contains information on nearly 6 million prescription claims in the United States that is managed by an independent commercial company. This study found that there was a comparable increase in the risk of diabetes in patients treated with either typical or atypical antipsychotics compared to reference populations. These results suggest that the decisions regarding the choice of antipsychotic for treating major psychiatric illness should be based on the best treatment option rather than solely on the relatively modest differences in diabetes rates observed during treatment with these agents.

Adverse events reported during open clinical use of a medication are relatively uninformative when attempting to compare the frequency of a particular event during treatment with one drug with another. Nevertheless, spontaneously reported adverse events are tracked because they can provide signals of safety issues after market approval. In a review of olanzapine's spontaneous safety database between September 27, 1996 through April 30, 2000, the reporting rate frequency of events potentially related to

glucose dysregulation (including cases of diabetes mellitus, ketoacidosis, and hyperosmolar coma) in the olanzapine spontaneous safety database was found to be "very rare", defined as a frequency of <0.01% according to guidelines published by the Council for International Organizations of Medical Sciences (CIOMS). Most reports of glucose dysregulation during olanzapine treatment were in patients with one or more risk factors for diabetes, such as family/personal history of diabetes, pancreatic disorders or alcoholism, obesity, weight gain during treatment, or treatment with drugs that have been temporally associated with hyperglycemia.

Further work is needed to clarify this important issue and Lilly is rigorously pursuing studies to further determine the relationship between Zyprexa® and diabetes. Suggestions of a class effect for antipsychotics remain unclear possibly due to the diverse chemical, therapeutic, anatomical, and mechanistic properties of the compounds included in this class. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

### *2.1.2. Hyperlipidemia*

Single and combined random triglyceride data from two randomised, double-blind, olanzapine trials were analyzed and compared to haloperidol over an 8 week period of observation, in patients with no metabolic abnormalities at baseline. Lilly has conducted an analysis of the incidence of ***random*** triglyceride values above 1*, 2* and 3* ULN laboratory thresholds for ***fasting*** triglyceride measurements. In these two small clinical trials, in patients (n=107) with random triglyceride below the upper limits of normal for fasting triglyceride at baseline, 1.9% showed a random triglyceride level greater than 2-fold the upper-limit of normal for fasting triglyceride at any point during up to 8 weeks of treatment with olanzapine. Given the large intrasubject variability of random triglyceride levels and the small clinical sample size, the clinical significance of these findings is not known.

Lilly has studies in progress or planned to investigate metabolic parameters in patients treated with Zyprexa®.

### *2.1.3. Conclusion*

While case reports are a valid form of identifying possible safety issues with a compound regulatory decisions should not be based on spontaneous data reports. Case reports of adverse events temporally associated with treatment with a particular agent cannot establish whether the rates of events on that agent differ from either the base rate in the study population or from the incidence rate associated with other treatment. Such comparative data can only be obtained from large head-to-head trials, such as those used in the olanzapine clinical trial analyses, or from large-scale epidemiological studies. The decision of which antipsychotic medication to prescribe should be based on well-established efficacy and a variety of safety factors such as extrapyramidal symptoms,

tardive dyskinesia, hyperprolactinemia or QTc prolongation, in addition to glucose regulation and lipid metabolism.

# 3. Article 2

"Adolescents treated with Zyprexa® developed striae" by Kerstin Blomgren, Erik Eliasson, Birgitta Wode Helgodt, and Ann-Marie Ling.[24]

## 3.1. Response

According to the current US package information sheet (PV 3394AMP):

*Pediatric Use*--Safety and effectiveness in pediatric patients have not been established.

Therefore, Eli Lilly and Co., while concerned with all patients using olanzapine is unable to support or contradict any data on the development of striae in adolescents.

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