

# 1 Statement

Eli Lilly treats very seriously any report of an adverse event occurring in association with a Lilly drug. The occurrence of an adverse event does not necessarily indicate that it was caused by the patient's drug treatment, but requires urgent and thorough investigation. All reports are carefully reviewed by Lilly and analysed in detail in the light of each patient's clinical history. The patient's doctors and other health care providers work with Lilly to determine whether the patient's drug therapy contributed to the adverse event. The results of these investigations are regularly reported to Irish and international drug regulatory authorities.

Eli Lilly developed Zyprexa (olanzapine) for the treatment of serious mental illness, and it has been available on medical prescription for three years.

Hyperglycaemia (raised blood sugar) or worsening of pre-existing diabetes has been reported in very rare cases during Zyprexa (olanzapine) treatment. Around the world, there have been some 200 reports of raised blood sugar, of an estimated 3.25 million patients who have been treated with Zyprexa (olanzapine).

In the UK, there have been nine cases reported of raised blood sugar in the three years that Zyprexa has been available, of a total estimated patient exposure of over 100,000 patients.

In some cases, a prior increase in body weight has been reported, which may be a predisposing factor as this is known to significantly increase the risk of one type of diabetes (Type II).

Diabetes itself is a common disorder, affecting at least 3-5% of the general population. There is also evidence that diabetes is two to four times more common in patients with serious mental illness.

Where a patient on Zyprexa has diabetes or risk factors for diabetes, Lilly recommends appropriate clinical monitoring.

ZY 1971 1601

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ZY 1971 1602

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ZY 1971 1604

# 1 Statement

~~Eli Lilly and Company carefully monitors all adverse event reports for its marketed and investigational pharmaceutical products. The occurrence of these events does not imply that olanzapine is an etiologic contributor to the events. Eli Lilly treats very seriously any report of an adverse event occurring in association with a Lilly drug. The occurrence of an adverse event does not necessarily indicate that it was caused by the patient's drug treatment. All reports are carefully reviewed by Lilly and analysed in detail in the light of each patient's clinical history. The results of these investigations are regularly reported to Irish and international drug regulatory authorities.~~

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~~The adverse event reporting database, Clintrace, was searched on July 16, 1999 for all spontaneous olanzapine adverse event reports entered into Clintrace from September 29, 1996 through September 30, 1998 that contain one or more of the following COSTART (the Coding Symbol and Thesaurus for Adverse Reaction Terms) terms: ACIDOSIS, DIABETES MELLITUS, DIABETIC ACIDOSIS, DIABETIC COMA, GLUCOSE TOLERANCE DECREASED, GLYCOSURIA, HYPERGLYCEMIA, KETOSIS, and/or LACTIC ACIDOSIS. A total of 197 reports were identified utilizing this search. Based upon this search and over 3 million patients exposed to olanzapine worldwide, hHyperglycaemia (raised blood sugar) or worsening of pre-existing diabetes has been very rarely reported (< 0.01%). A majority of cases are confounded by a frank history of diabetes and/or risk factors for diabetes, in very rare cases during Zyprexa (olanzapine) treatment. Around the world, there have been some 200 reports of raised blood sugar or related adverse events, of an estimated 3.25 million patients who have been treated with Zyprexa (olanzapine).~~

~~In the UK, there have been nine cases reported of raised blood sugar in the three years that Zyprexa has been available, of a total estimated patient exposure of over 100,000 patients.~~

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Diabetes itself is a common disorder, affecting at least 3-5% of the general population. There is also evidence that diabetes is two to four times more common in patients with serious mental illness. [References?]

ZY 1971 1605

Kimberly Spencer

08/04/99 04:11 PM

To: Charles M Beasley Jr/AM/LLY@Lilly, Julie M Bennett/AM/LLY@Lilly, Jamie Dananberg/AM/LLY@Lilly, John A Krueger/AM/LLY@Lilly, Kimberly Spencer/AM/LLY@Lilly, Anna Thornton/AM/LLY@Lilly

cc:

Subject: Minutes from the 8/2/99 Glucose Control Study meeting

Attached please find the minutes from the meeting. Please forgive (and send me a correction) any therapeutic stupidity.

I will wait until conversation takes place between Jamie and Alain before I schedule another meeting.

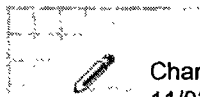
thanks,

Kim



Glucose Control Protocol HGIM Mee

ZY 1971 1660



Charles M Beasley Jr  
11/03/99 02:11 PM

To: Lori M Vance/AM/LLY@Lilly  
cc: Kenneth C Kwong/AM/LLY@Lilly, Anna Thornton/AM/LLY@Lilly  
Subject: Re: HCAM manuscript

Interest in a temporal association between olanzapine administration and alterations in glucose homeostasis, as well as such a relationship between antipsychotic agent in general and alterations in glucose homeostasis was precipitated by ongoing review of spontaneous adverse event reports for marketed olanzapine as well as academic literature discussing these subjects.

With regard to marketed olanzapine spontaneous adverse event reports, the following summarize our experience:

- 1) In first 2 years of marketing, an estimated 1.581 million persons were treated with marketed olanzapine.
- 2) During this interval, Lilly received 197 spontaneous adverse event reports for marketed olanzapine which may have involved a hyperglycemic event, based on COSTART terms used to code events.
- 3) The degree of hyperglycemia varied considerably as did the clinical presentations described in these reports.
- 4) Where adequate information was available to characterize the presentation (n = 143), 23 presented with glucose <300 mg/dl, 47 presented with glucose  $\geq$ 300 mg/dl and <600 mg/dl, and 73 (>50% of total characterized) presented with glucose  $\geq$  600 mg/dl or DKA or hyperosmolar coma. Among the latter group, many patients experienced glucose >1000 mg/dl, and the highest reported glucose was 1825 mg/dl (survived).
- 5) Among the patients with presenting glucose <600 mg/dl, 84% had a history of diabetes or hyperglycemia. A majority of the patients, whether with a diabetic history or not, had risk factors for diabetes.
- 6) Among the 3rd group of patients, where data were available, 70% **did not** have a history of diabetes. Where known, a majority of these patients did have risk factors for diabetes.
- 7) Among the 3rd group of patients, where data were available, and **including patients with both a history and no history of diabetes**, 25% presented within 26 days of initiation of olanzapine.
- 8) Available demographic data did not reveal a pattern suggestive of at risk patients.

With regard to medical literature:

- 1) Multiple case series/reports have been published (total cases may now exceed those reported for clozapine).
- 2) One reported case was of resolution on dechallenge and recurrence on rechallenge.

Charles

ZY 1971 1661