

## 1. Introduction

### 1.1. Purpose

In response to the May 1, 2000 letter from the United States Food and Drug Administration (FDA) regarding the effect of olanzapine on glucose metabolism, a review of published literature, a historical review of preclinical data and previously submitted Phase I, II and III studies, an analysis of the current, complete clinical trial database, a review of spontaneous postmarketing reports with an estimate of patient exposure, and copies of correspondence with foreign regulatory agencies are provided.

An analysis of 78 controlled trials in the clinical trial database comparing the incidence and rates of treatment-emergent potential impaired glucose tolerance (IGT) and potential diabetes mellitus (DM) temporally associated with antipsychotic agents and placebo was undertaken. The duration of drug exposure and risk factors for hyperglycemia (gender, age, ethnicity, baseline obesity [body mass index (BMI)], increase in obesity, and weight gain) were examined in this analysis. This analysis was the basis for the labeling change submitted to FDA on May 9, 2000. An extension and refinement of this May 9, 2000 submission is contained in this present submission.

A review of all spontaneous reports relating to hyperglycemia for patients treated with olanzapine was also undertaken. This analysis took into account the following: the result of dechallenge and rechallenge with olanzapine; dosage; potential risk factors including age, gender, ethnicity, obesity/BMI, weight gain, personal and family history of diabetes mellitus (DM), alcohol abuse/pancreatitis, other medications; and duration of treatment.

The data cut-off for the clinical trials analyses was September 30, 1999 and the data cut-off for spontaneous report analyses was April 30, 2000.

### 1.2. Executive summary

Olanzapine (LY170053) is a dopaminergic, serotonergic, cholinergic, histaminergic, adrenergic receptor antagonist (Moore et al. 1992) that has been shown to be an effective antipsychotic agent with an "atypical" profile. It is now marketed in an oral dosage form as Zyprexa® in the United States and other countries. Olanzapine has a well-established safety record. During the 3 years and 7 months of marketing as of April 30, 2000, approximately 4.5 million persons were treated with commercially prescribed olanzapine, primarily for the treatment of schizophrenia.

An association between schizophrenia and diabetes was described as early as the mid-1920's (Kasanin, 1926). This association is also reflected in current literature. The prevalence of type II diabetes mellitus in patients with schizophrenia is approximately 2 to 4 times greater than in the general population as demonstrated by the prevalence of elevated glucose levels in up to 24.5% in the population with schizophrenia (Keskiner et al. 1973, McKee et al. 1986, Mukherjee 1995, Mukherjee et al. 1996). By comparison,

the estimated prevalence of DM in the general U.S. population (adults  $\geq 20$  years of age) is 7.8% (Harris et al. 1998).

The incidence of diabetes in the general population has been shown to increase with age, and to be higher in women and individuals of African American, Hispanic, and Native American descent. Additional risk factors in the general population include weight gain, obesity, and a family history of DM.

Possible explanations for the increased prevalence of diabetes mellitus in the schizophrenic population include poor diet and lack of exercise associated with institutionalization, brain changes associated with schizophrenia that could influence neuroendocrine homeostasis, or a common underlying and linked pathology of schizophrenia and type II DM.

Antipsychotics have been reported to be associated with hyperglycemia since the mid-1950's following the introduction of chlorpromazine (Charactan et al. 1955). Typical antipsychotic medications were reported to inhibit glucose-mediated insulin release (Erle et al. 1977) or to have no effect (Hagen et al. 1979). In 1968, Korenyi and Lowenstein reported an association between typical antipsychotic therapy and the development of Type II diabetes mellitus. Later, the temporal association of diabetes to treatment with the atypical antipsychotic clozapine was reported (Kamran et al. 1994, Pierides 1997, Popli et al. 1997, Wirshing et al. 1998). Such reports have led to speculation that, as a class, the atypical antipsychotics might alter glucose tolerance more than the typical antipsychotics. However, this speculation fails to consider the substantial body of older literature describing similar findings with older antipsychotics used less commonly today (Charatan & Bartlett 1955, Jori & Bianchetti 1966, Korenyi & Lowenstein 1968, Thonnard-Neumann 1968, Erle et al. 1975, 1977, Bugajski & Lech 1979, Tollefson & Lesar 1983, Vukicevic & Zjadic-Rotkvic 1994, Goncalves & Gruneberg 1997, Abuzzahab & Zimmerman 1998).

Several published case reports and case studies have temporally associated olanzapine with hyperglycemia. These include a report of resolution of hyperglycemia on withdrawal of olanzapine followed by recurrence on rechallenge with the medication (Fertig et al. 1998). In a report of 7 patients who developed hyperglycemia while on olanzapine, 2 of these patients were also reported to have acidosis. Although the authors interpret this information as indicative of diabetic ketoacidosis, the data presented cannot differentiate between true, diabetic ketoacidosis and the syndrome frequently seen in hyperosmolar coma: ketosis plus lactic acidosis (Goldstein et al. 1999).

### 1.3. Possible Mechanisms of Antipsychotic-Induced Hyperglycemia

The mechanism by which antipsychotics alter carbohydrate metabolism, if indeed they do, is not presently understood. Studies in animals and healthy volunteers suggest that insulin output may be reduced by antipsychotics (Erle et al. 1977, Bugajski et al. 1979)

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Additional postulated mechanisms to account for antipsychotic-induced hyperglycemia include: weight gain and/or obesity leading to decreased insulin receptor sensitivity, a direct influence impairing insulin receptor sensitivity, a direct effect on glucose homeostasis, an indirect effect related to prolactin, or the effects of drug interactions with combination therapy.

### **1.3.1. Weight Gain and/or Obesity – Insulin Receptor Sensitivity**

A strong positive association has been demonstrated between weight gain as well as obesity and the risk of type II DM (Chan et al. 1994, Carlson et al. 1998). In general, the risk of type II DM increases by approximately 4.5% for every kilogram increase in weight. In men, the rate of weight gain is also strongly and significantly related to the incidence of type II DM, while weight fluctuation does not appear to be associated with an increased incidence of type II DM in either gender (Hanson et al. 1995). Even small increases in weight may worsen glycemic control in some patients with diabetes, and to lead to overt diabetes in patients with impaired glucose tolerance or abnormally elevated fasting glucose (Colditz et al. 1990, Chan et al. 1994, Ford et al. 1997). Thus, some authors have suggested that the increased incidence of hyperglycemia and/or type II DM in schizophrenia may be secondary to weight gain and/or obesity induced by antipsychotic agents, which leads to insulin insensitivity, glucose intolerance, and diabetes (Wirshing et al. 1998).

Average weight gain during treatment with atypical antipsychotic agents varies, possibly due to their differing affinity for different receptors, particularly 5HT<sub>2A/C</sub> and H<sub>1</sub>. Of the atypical antipsychotics, clozapine appears to have the greatest potential to induce weight gain and ziprasidone the least (Allison et al. 1999). However, in several case reports of hyperglycemia, no weight gain from baseline was noted. Therefore, if antipsychotics do induce hyperglycemia, weight gain alone can not be the only mechanism for this phenomenon. Insulin receptor sensitivity might be adversely affected by antipsychotics independent of weight gain.

The clinical presentation of new-onset hyperglycemia, in temporal association with olanzapine, is variable. In addition to cases of relatively moderate increases in blood glucose, a very small number of cases involving the onset of life-threatening acidosis, as well as hyperglycemia-induced hyperosmolar coma also exist. Hyperosmolar coma has never been reported in the diabetes literature to be due exclusively to weight gain leading to decreased insulin receptor sensitivity.

Additional data support the proposition that weight gain and changes in insulin sensitivity independent of other factors are unlikely explanations of severe hyperglycemia. Patients with the most severe forms of insulin resistance, that of mutations of the insulin receptor, do not universally develop frank diabetes, or even impaired glucose tolerance. In those who do, gross abnormalities of glucose concentrations do not usually become evident until a later stage of the natural course of these syndromes (Tritos and Mantzoros 1998).

### **1.3.2. Glucose Homeostasis Systems**

Glucose homeostasis is regulated by a number of classic hormones and neurohumoral molecules, including insulin, glucagon, glucocorticoids, catecholamines, insulin-like growth factor-1 and -2, and several incretion hormones (e.g. glucagon-like peptide-1). These hormones regulate hepatic, muscle, and adipose uptake and release of glucose, and hepatic synthesis of glucose or glycogen. Secretion of the various molecules that regulate glucose concentrations are themselves under complex regulation. There is evidence that the uptake of glucose by muscle and adipose, the two tissues responsible for a significant portion of whole-body glucose utilization, is affected by hormonal, neural, nutritional, and vascular factors (Reaven 1995). Changes in these factors can lead to significant changes in the responsivity of muscle and adipose to glucose regulatory hormones, leading to hyperglycemia. Olanzapine and other antipsychotics might be associated with hyperglycemia through an influence on these complex homeostatic mechanisms that are partly under neural control.

### **1.3.3. Impaired Pancreatic Insulin Release – Severe Hyperglycemia**

Hyperosmolar coma is a relatively rare syndrome in the general population. There are no population-based studies of hyperosmolar coma. Hospitalization discharge data in the US over the 3-year period from 1989 to 1991, by ICD9-CM code, showed 10,800 discharges for this condition (0.37% of diabetic hospitalizations and 0.03% of all hospitalizations), compared to 100,200 for diabetic ketoacidosis, and nearly 3 million discharges for any diabetes diagnosis (Fishbein and Palumbo 1995). The mean age at presentation with hyperosmolar coma is 60 years old and more females than males are affected. In 30% to 60% of cases of hyperosmolar coma, the hyperosmolar coma is the first presentation for diabetes mellitus. Hyperosmolar coma carries a high mortality rate, ranging from 10% to 50% (Fishbein and Palumbo 1995).

Several physiologic conditions appear to be necessary for glucose-induced hyperosmolality to occur. By its nature, the hyperosmolar state depends on the renal handling of glucose and water. Because of the renal threshold for glucose, modest increases in blood glucose cause compensatory increases in urinary glucose losses, restraining large increases in blood glucose concentrations. However, as urinary glucose losses increase, osmotic diuresis occurs, leading inevitably to loss of free water and significant dehydration. When access to free water is limited or when water requirements are increased (eg, in febrile illness), the level of dehydration can be great. This level of dehydration has two effects: further increases in glucose concentration and a reduction in the glomerular filtration rate (GFR). To the extent that urinary glucose loss is GFR-dependent, reductions in GFR result in the loss of an important mechanism by which glucose elevation is restrained. By some estimates, GFR must be diminished by greater than 50% to achieve a blood glucose concentration >500 mg/dl. To achieve a glucose concentration >1000 mg/dl, the GFR must be decreased by 75%. Eventually, the

incremental rise in blood glucose concentration leads to additional water loss, worsening dehydration, escalating glucose, and ultimately to hyperosmolar coma (Siperstein 1992, Fishbein and Palumbo 1995, Lorber 1995, Genuth 1997).

However, this model does not explain the initial insult that leads to an increase in blood glucose. Therefore, a hypothesis has emerged for diabetic hyperosmolar coma, in which there are baseline pathological factors that put patients at risk. These baseline risk factors may include mild renal insufficiency, immobility or cognitive deficits that limit normal water consumption, glucose intolerance or mild diabetes, and insulin resistance. Superimposed on this pathological baseline state, an initiating event occurs that markedly alters the *insulin secretory capacity:insulin requirement* ratio. Most commonly, this initiating event is thought to be an infectious challenge (eg, bacterial pneumonia), but other stresses could also precipitate this state.

Although weight changes may cause a worsening of insulin resistance and result in modest to moderate increases in blood glucose, it is widely accepted that some impairment in insulin secretory capacity must play a role in cases in which glucose concentrations rise to levels exceeding 600 mg/dl to 800 mg/dl. Thus, the inhibition of insulin secretion becomes a primary hypothesis for the mechanism by which olanzapine (and antipsychotics in general), might contribute to severe hyperglycemia and hyperosmolar coma (Siperstein 1992, Fishbein and Palumbo 1995, Lorber 1995, Genuth 1997).

#### **1.3.4. Prolactin and Drug Interactions**

Other potential mechanisms by which antipsychotics might contribute to hyperglycemia include an insulin-resistant state induced by prolactin (Foss et al. 1995). However, most atypical antipsychotics, in contrast to typical antipsychotics, have not been associated with significant hyperprolactinemia. Risperidone is the one atypical antipsychotic associated with sustained prolactin elevations above the upper limit of normal (Chung and Eun 1998).

Finally, hyperglycemia could be the result of additive effects previously described or of drug interactions with concurrently administered medications (Goldstein et al. 1999).

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**Section 2**