

Policy Committee Meeting

April 12, 2002

Zyprexa® Safety Overview

MIKE,

FYI - you may want to

EXEMPT SOME OF THIS

MATERIAL FOR J.L. DISCUSSION.

Introduction

A key to the success of Zyprexa is its unparalleled efficacy and paucity of dose-dependent side effects including extrapyramidal symptoms, prolactin elevation, blood dyscrasias, cardiac conduction abnormalities (QTc prolongation), drug interactions, and excessive sedation. This profile has led to the preferential use of Zyprexa in more severely ill patients who tend to require higher doses. A side effect that is associated with Zyprexa is weight gain and the sequelae of weight gain. Following is an overview of Zyprexa's metabolic profile, as well as a brief update on agranulocytosis.

I. Clinical Data

A. Weight gain

- Five atypical antipsychotic agents are associated with more weight gain than most traditional neuroleptic agents in the following order (most to least):

Clozaril>Zyprexa >Seroquel>Risperdal

- Zyprexa weight gain is roughly twice that of Risperdal. (average 7kg versus 3.5kg)
- Pfizer's Geodon and BMS's aripiprazole appear to have less metabolic issues than other atypicals

B. Diabetes (DM)

- Worldwide, DM is a significant and growing health concern. The prevalence of DM in the US is ~8% and is the 6th leading cause of death. The prevalence of DM among patients with schizophrenia is 2 to 4 times the general population.
- A recent Zyprexa clinical trial analysis indicates patients with baseline DM risk factors (obesity, family history, non-Caucasian, advanced age) have higher occurrences of DM during Zyprexa treatment and treatment with other antipsychotic drugs.
- Results of two Lilly epidemiological studies (analysis of AdvancePCS and GPRD databases) indicate that the risk of DM is increased in patients treated with antipsychotics, including Zyprexa. AdvancePCS found no differences among antipsychotic drugs but did not control for psychiatric diagnoses. The GPRD study and other independent reports suggest that risk of DM is greater with atypical antipsychotics than conventional neuroleptics in schizophrenic patients.
- FDA FOI Database of reports of DM cases: Clozaril: 542; Zyprexa: 434; Risperdal: 244; Seroquel: 57

Possible explanations for differences among these drugs are differences in weight gain, illness severity in target populations, and reporting bias. Seroquel's low rate may be secondary to its very low dosing trends.

C. Diabetic Ketoacidosis (DKA)

- DKA is a very rarely reported serious event that is a known complication of DM. It may result in death and is therefore closely monitored by regulatory agencies. In reports of DKA during antipsychotic drug use, DKA is frequently but not always associated with weight gain or risk factors for DM.
- FDA FOI Database cases of DKA (cases/total exposures):
Clozaril: 103/not available; Zyprexa: 132/3.7 million, Risperdal: 36/6.6 million, Seroquel: 14/0.75 million
- Lilly sponsored hyperglycemia clamp study in healthy volunteers (gold standard for assessment of potential toxic effect on pancreatic insulin secretion) found no evidence of a direct effect of Zyprexa or Risperdal on insulin release which argues against one possible cause of DKA

II. Regulatory Environment

- Our philosophy with regulatory agencies on these issues is to be proactive and support our positions with strong science.
- We are currently engaged with several regulatory authorities regarding queries on metabolic issues (e.g., Japan - Current label change request: patients with DM or risk factors for DM; EU - Precautionary statement regarding use in patients with DM or risk factors for DM (implemented); Canada - Requested data from all sponsors of antipsychotic drugs on cerebrovascular events, hypotension, hyperglycemia and weight gain. Linked to RAIM approval process.)

III. Competitive Environment

- Fierce counter-detailing and intense (singular) focus by all of our major competitors including the use of symposia, CMEs, citing foreign labels, etc.

IV. Action Steps

- Multidisciplinary Safety Team 100% dedicated to these issues
- Publications – Weight gain characterization - published; PCS - in press (Q3 publication); Clamp study - in press (Q2 publication); GPRD – submitted; Risk factors for DM manuscript - completed; Nizatidine manuscript - completed; Behavioral interventions (IITs) – published.
- Implemented (ongoing): slide sets, medical letters, speaker training programs, opinion leader (psychiatry and endocrine) involvement, sales force education, CMEs, DTP, peer-to-peer; ADA; advocacy groups; and Neuroendocrine Consultant Summit, North America Diabetes Advisory Board.
- Clinical Studies - Pharmacological Intervention Studies: nizatidine and amantadine (completed); Behavioral Intervention Studies: IITs in US (ongoing or completed); Epidemiological Studies: AdvancePCS and UK GPRD (completed); Analysis of Integrated Clinical Trial Database (completed), Hyperglycemic Clamp Study (completed); Euglycemic Clamp Study (insulin resistance) (enrollment completed); Analysis of Post-marketing Spontaneous Glucose-related adverse events (ongoing); DKA Prevalence study in US Veteran Affairs Centers (under development); Lipids/Metabolic Syndrome Cross-sectional Study (nearly complete); Genetic Markers of Weight Gain and Hyperglycemia (ongoing).

V. Summary of Metabolic Issues

The prevalence of obesity and DM in the general population is increasingly high worldwide, and even more so in the US. Obesity is a well-recognized risk factor for DM. In addition, we know that patients with severe mental illness are at greater risk of obesity and DM, and that some of the atypical antipsychotics, including Zyprexa, may lead to significant weight gain in a proportion of patients. Thus, increasing psychiatrists' awareness and clinical management acumen of obesity and DM will contribute to the overall public health of chronic mentally ill patients. Finally, current competitors and new entrants into the market are expected to continue to apply pressure on this front. Therefore, we can expect metabolic issues to present ongoing challenges, and continue to require the proactive, intensive and focused management that has contributed to the ongoing growth of Zyprexa.

VI. Agranulocytosis

- Post-Marketing Database of Spontaneous Adverse Events

Very rare: only 19 cases of confirmed agranulocytosis / 8+ million exposures. The vast majority of cases were confounded. The frequency of agranulocytosis reports is same as background rate in general populations. There is no conclusive evidence of a causal relationship.

- CPMP requested to include the term “agranulocytosis” as a “very rare” post-marketing event.
- Action: We have been engaged with the CPMP on this issue for over 1 year and Drs. Breier and Cavazzoni, along with a world’s expert in this field, will meet with the Rapporteur next week in Helsinki in a final attempt to avoid a change in EU labeling.