Zyprexa Presentation Overview - GPLC Meeting
May 15, 2002

Introduction:

As a result of the Zyprexa label change in Japan, the question posed by GPLC is as follows: Is a change to the olanzapine Core Data Sheet warranted?

To date, extensive data has been generated by Lilly on olanzapine and glucose dysregulation, including data from spontaneous post-marketing adverse events, clinical trials, epidemiological analyses of two large prescription/health care provider databases, and a hyperglycemic clamp study investigating insulin secretion in healthy volunteers administered olanzapine or risperidone. Based upon the data that has been generated to date on olanzapine and glucose dysregulation (described below in this document), the Zyprexa Product Team and the Pharmacovigilance Department do not agree with the changes recently made to the Zyprexa Japan label and do not recommend a change to the olanzapine Core Data Sheet.

The purpose of the remainder of this document is to provide an overview of the analyses that have been completed and that are in process to examine the issues involving olanzapine and glucose dysregulation. In addition, a brief overview is provided of Regulatory reports that have been recently prepared for submission as requested. Documents providing additional information, including several in-press manuscripts that describe completed analyses, are provided as attachments in the accompanying email.

Analyses and documents that have been completed (May 2002):

1. Spontaneous Post-Marketing Adverse Event Reports
    - **Hyperglycemia, Weight Gain, and Olanzapine** (Submitted to the FDA and CPMP, summer 2000)
        - A large, 3-volume document prepared in response to requests from the FDA and CPMP in the spring of 2000 (due to length not attached)
        - Included analyses of spontaneous post-marketing adverse event reports thru April 2000
        - Also included extensive analyses of clinical trial data

2. Clinical Trial Data
    - **Analyses of Random Blood Glucose Concentrations in Patients with Schizophrenia Treated with Typical and Atypical Antipsychotic Agents** (Initially submitted to Canadian HPB, April 2002)
        - A series of analyses conducted using the olanzapine integrated clinical trial database of direct-comparator trials for schizophrenia-spectrum patients (report section "clinical trial analysis – April 2002" attached)

3. Epidemiological Studies
    - **Pharmacoepidemiological Study of Diabetes Mellitus and Antipsychotic Treatment in the United States Using the AdvancePCS Prescription Claim Database**
        - Prescription claims for diabetes medications used to identify subjects with diabetes. (manuscript attached)

    Diabetes Mellitus and Antipsychotic Treatment in the United Kingdom
        - Patients with recorded diagnosis of diabetes or prescribed any antidiabetic medication were considered to have diabetes. (manuscript attached)

4. Clinical Pharmacology Study
    - **Hyperglycemic Clamp Assessment of Insulin Secretory Responses in Normal Subjects Treated with Olanzapine, Risperidone, or Placebo**
        - Changes (baseline to endpoint) in insulin levels were studied using a hyperglycemic clamp in healthy subjects treated with olanzapine, risperidone, or placebo. (manuscript attached)

5. Educational Tools/Documents Created for Customer Health Care Professionals
    - Global Response Documents (from Global Medical Information)
        - **Blood Glucose Changes and Olanzapine** (attached)
        - **Acute Complications or Presentations of Diabetes – DKA & HHNS** (attached)
    - US Medical Letter: **Natural History, Diagnosis and Management of Diabetes** (from US Medical Information; intended for a Psychiatrist audience - attached)

Ongoing analyses and documents in ongoing development:

1. Spontaneous Post-Marketing Adverse Event Reports
   - **Glucose Dysregulation Adverse Events (Spontaneous) and Commercially Marketed Olanzapine**. This document will contain: Analyses of all post-marketing reports of glucose dysregulation thru 30 Sep 2001, including detailed narratives for selected serious cases.

2. Clinical Trial Analysis
   - **Treatment-Emergent Diabetes Clinical Trial Analysis:** A large non-diabetic cohort receiving olanzapine, risperidone, haloperidol, clozapine, or placebo (n=5013) was retrospectively identified from 24 clinical trials and examined for evidence of treatment-emergent diabetes. The relationship between pre-existing risk factors for diabetes (entry glucose levels, age, BMI, ethnicity, hypertension, or evidence of impaired glucose tolerance), treatment-emergent weight gain, and therapy assignment on the risk of TED are assessed. (See the attached abstract)

3. Clinical Pharmacology Study
   - **S013 Study Report**: F1D-MC-S013 seeks to determine the effect of antipsychotic therapy on insulin receptor sensitivity in healthy lean and obese subjects. The primary objective of this study is to assess whether olanzapine 10 mg/day and risperidone 4 mg/day for 2 weeks, compared to placebo, have adverse effects on glucose metabolic parameters in healthy, lean and obese, non-diabetic subjects as measured by changes in the glucose infusion rate during a euglycemic, hyperinsulinemic clamp. This study is completed and analysis is ongoing. The final study report is targeted for completion in Q3 2002.

Documents recently prepared for global affiliates for the basis of their responses to local regulatory authorities (provided on an as needed basis):

1. **Glucose Regulatory Response Document** (Sent to several affiliates for submission to local regulatory agencies)
   - The purpose of this document is to address issues raised by global regulatory authorities regarding the recent label change in Japan.
   - The document is an executive summary of completed and ongoing analyses individualized (sections included or excluded) according to the nature of the regulatory request.

2. **Glucose Dysregulation Adverse Event Reports (Spontaneous) and Commercially Marketed Olanzapine in Japan** (Submitted to the FDA 25 Apr 2002)
   - This report provides narrative summaries for the 13 Japanese adverse event reports that were the basis of the label change in Japan.

3. **Glucose Dysregulation Adverse Event Reports (Spontaneous) with Outcome of Death and Commercially Marketed Olanzapine** (Prepared in case needed for a regulatory response)
   - This document provides narrative summaries of the 36 adverse event reports with an outcome of death for reports received thru 30 Sep 2001. Also includes a summary data from the 36 spontaneous reports.
   - This is a subset of the spontaneous post-marketing document that is in preparation.