

## 4. Phase I Historical Data

### 4.1. Introduction

This is a response to request for analysis of incidence of hyperglycemia and/or weight gain during olanzapine Phase I studies. Data from the Clinical Pharmacology studies (in healthy volunteers) listed below were reviewed, and changes from baseline in weight and blood glucose several multiple doses of olanzapine were assessed.

### 4.2. Methods

The criteria for selecting data to be included were as follows:

- The study was to have been conducted in the US
- Multiple doses of olanzapine for at least 7 days were to have been administered
- Data only from olanzapine (single agent) or olanzapine-placebo combination dosing
- Data only from locked databases as of April 30, 2000
- Pre-dose observations: weight and blood glucose measurements taken within 24 hours prior to the first olanzapine dose
- Post-dose observations: weight and blood glucose measurements taken within 24 hours after the last olanzapine dose

The studies included in this analysis are shown in Table 4.1. Each subject's predose weight was subtracted from postdose weight, and the differences were summarized as arithmetic means, standard deviations, minimum and maximum. The pre- and postdose blood glucose values were similarly summarized. The majority of the blood glucose measurements were made under fasting conditions. The complete observed data are tabulated in the Appendix 10.1.

**Table 4.1. Clinical Pharmacology studies included in olanzapine hyperglycemia assessment.**

Study	Objective	Number of subjects represented	Dosing Regimen
F1D-LC-HGAC	Multiple Dose Tolerance	3	12 mg OLZ for 14 days
F1D-LC-HGAN	Ethanol Interaction	13	Increasing doses from 2.5 to 10 mg OLZ for 11 days
F1D-LC-HGCB	Theophylline Interaction	12	10 mg OLZ for 7 days
F1D-LC-HGDC	Fluvoxamine Interaction	17	Increasing doses from 2.5 to 7.5 mg for 8 days
F1D-LC-HGEA	Breast Milk Study	6	5 mg OLZ for 8 days

### 4.3. Results

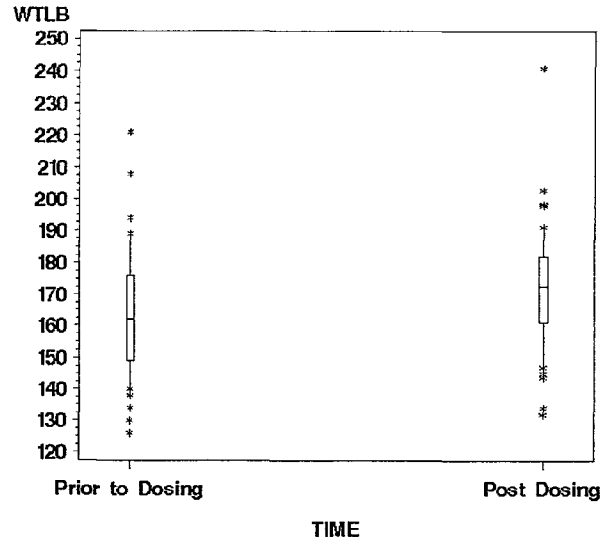
Results of this assessment are shown in Table 4.2, and graphically in Figures 4.1 and 4.2.

The average weight gain observed in the clinical pharmacology studies was  $8.9 \pm 7.1$  pounds (mean  $\pm$  standard deviation). A paired t-test for the difference in body weight indicated that this difference is significant ( $p < .001$ ). The maximum observed weight gain in these studies was 27.4 pounds from subject #0860 in study HGAN following multiple dosing up to a maximum dose of 10 mg olanzapine. The clinical meaning of the weight gain is difficult to assess, since in the experience of the investigator over 20 years, patients generally tend to gain weight while enrolled in studies at the Lilly Clinic. The reasons for weight gain may be attributed to lack of exercise and liberal access to high fat meals. Further, there are usually no restrictions on weight gain in these studies.

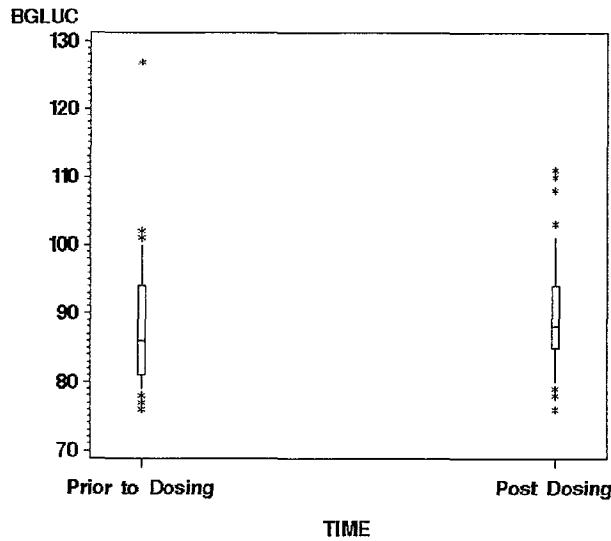
Blood glucose values increased by an average of  $1.5 \pm 10.6$  mg/dl following multiple dosing with olanzapine. The maximum increase in blood glucose was 30 mg/dl, and was observed in a non-fasting subject, #1006 from study HGEA, in which the dose amount was 5 mg. None of the blood glucose values observed following multiple dosing with olanzapine exceeded 140 mg/dl, and only two values exceeded 110 mg/dl, one of which was a pre-olanzapine observation.

**Table 4.2. Summary Statistics of Clinical Pharmacology Studies for Hyperglycemia and Weight Gain**

	N	Mean	Standard Deviation	Minimum	Maximum
Difference in Body Weight (pounds)	51	8.9	7.1	-6	27.4
Difference in Blood Glucose (mg/dl)	51	1.5	10.6	-38	30



**Figure 4.1.** Box plot of weight in pounds. The bottoms and tops of the boxes represent the 25th and 75th percentiles, respectively, and the central line denotes the median. The lengths of the whiskers extend to the 10th and 90th percentiles, and stars denote extreme values.



**Figure 4.2.** Box plot of observed blood glucose values in mg/dl. The bottoms and tops of the boxes represent the 25th and 75th percentiles, respectively, and the central line denotes the median. The lengths of the whiskers extend to the 10th and 90th percentiles, and stars denote extreme values.

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