

Office of Clinical Pharmacology Review

NDA/Supplement/Serial #:	21,520/S039/0091
Brand Name:	SymByax
Generic Name:	Olanzapine/Fluoxetine Combination (OFC)
Dosage Form:	Capsule
Strengths:	3/25, 6/25, 12/25, 6/50 or 12/50 mg
Sponsor:	Eli Lilly
Indication:	Bipolar Depression
Submission Date:	9/28/2012, 4/4/2013
Review Type:	Pediatric sNDA
Review Team:	Huixia Zhang, Ph.D., Hao Zhu, Ph.D.

This document serves as an addendum to the OCP review checked in DARRTS on 7/1/2013. The analysis in that review showed the average steady-state olanzapine, fluoxetine, and norfluoxetine concentrations were 42%, 55%, and 27% higher, respectively, in pediatric patients with low body weight (less than 50 kg) than patients with high body weight (greater than or equal to 50 kg) based on observations in Study H6P-MC-HDAX. During the labeling negotiation, the sponsor performed their own calculation and their numbers were different. It was found that the difference came from different subsets of data that were employed to perform the calculation. The subset of data the reviewer used was described below:

1. Only concentrations from last visit (Visit 11) was used in the analysis;
2. Patients were categorized into low body weight group (<50kg) and high body weight group (≥ 50 kg), using baseline (Visit 1) body weight values.

The method the sponsor utilized can be found in the Appendix. The two methods are both acceptable and conclusions are consistent. Using the sponsor's analysis approach, the reviewer confirmed the sponsor's results and decided they are acceptable. Hence the values are included in the current label.

SIGNATURES

Huixia Zhang, Ph.D.
Reviewer, Psychiatry Drug Team, DCP1
Office of Clinical Pharmacology

RD/FT, Initialized by Hao Zhu, Ph.D.
Team leader, Psychiatry Drug Team, DCP1
Office of Clinical Pharmacology
Cc: NDA 21,520 (Mehta, Upoor, Zhu, Zhang)

Appendix: an email attachment from Ashraff A Rampersaud (Lilly) to Keith Kiedrow sent on Thursday, July 25, 2013 3:37 PM

Lilly has utilized the following method to summarize the concentration results.

- Datasets: HDAX_NONMEM_PK_FINAL2_28JUN2012.xls to obtain baseline body weight (visit 2) and hdax_descriptive_dataset.csv to obtain steady state concentration data. Both these files were provided at submission
- Concentration data from Sites 210 and 215 (per HDAX CSR) were excluded (reasons provided in HDAX CSR)
- Patients were categorized into lower body weights (<50kg) and higher body weights (≥50kg)
- Visits 10 and 11 concentration data were utilized.
- Dose normalized concentrations were utilized for comparison between the 2 body weight groups. Norfluoxetine concentrations were dose-normalized using fluoxetine dose.
- Assuming data is log normally distribution, the confidence intervals were calculated between the 2 body weight categories.

Lilly proposes to use both Visit 10 and visit 11 data. The steady state concentrations of olanzapine are expected to be achieved within a week (olanzapine USPI) and that of fluoxetine and norfluoxetine are expected to achieve within 3 to 4 weeks (fluoxetine USPI). Review of the data showed that most of the patients did not change their doses between visit 10 and visit 11. Inclusion of data from visits 10 and 11 provides more data for summarization rather than one concentration per patient. This approach maximizes the available information with nearly twice the number of concentrations available for analyses as compared to analyses using last visit only.

Provided below are the summary statistics of the steady state concentrations for Visit 10 & 11 and for Visit 11 only.

Summary of Visits 10 and 11

GeoMean	Geomean Ratio	5th CI	95th CI	%increase	FDA		# Patients	# Concentrations
OLZ	1.31	1.03	1.67	31%	42%	OLZ (<50kg)	34	61
FLX	1.76	1.41	2.20	76%	55%	OLZ (≥50kg)	75	145
NOR	1.38	1.17	1.62	38%	27%	FLX (<50kg)	33	62
						FLX (≥50kg)	75	144
						NOR (<50kg)	34	63
						NOR (≥50kg)	76	147

Summary of Visits 11

GeoMean	Geomean Ratio	5th CI	95th CI	%increase	FDA		# Patients	# Concentrations
OLZ	1.66	1.19	2.32	66%	42%	OLZ (<50kg)	27	27
FLX	1.78	1.23	2.58	78%	55%	OLZ (≥50kg)	71	71
NOR	1.48	1.15	1.90	48%	27%	FLX (<50kg)	29	29
						FLX (≥50kg)	72	72
						NOR (<50kg)	29	29
						NOR (≥50kg)	74	74

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/s/

HUIXIA ZHANG
07/26/2013

HAO ZHU
07/26/2013