CLINICAL PHARAMACOLGY REVIEW

NDA Number:	21427
Submission Type; Code:	Efficacy Supplement, S-041
Applicant Name:	Eli Lilly
Submission Dates:	04/19/2012
Brand Name:	Cymbalta®
Generic Name	Duloxetine
Dosage Form/ Strength:	Capsule/ 20 and 30 mg
Proposed Indication:	Major Depressive Disorder
OCP Review Team	Islam R.Younis, Ph.D., Hao Zhu, Ph.D.

1. EXECUTIVE SUMMARY

Duloxetine is a potent dual inhibitor of serotonin and norepinephrine reuptake and is currently approved in the United States for the treatment of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, and fibromyalgia. It is mainly eliminated through hepatic metabolism (into inactive metabolites), predominantly by CYP1A2 and to a lesser extent by CYP2D6.

The current submission is a pediatric supplement in response to FDA amended WR dated November 2, 2009. It contains one open-label efficacy, safety, and pharmacokinetic study in pediatrics 7-17 years of age and two randomized, double-blind, placebo and fluoxetine controlled efficacy and safety trials in pediatrics 7 – 17 years of age. One of on these studies used flexible dosing (30 to 120 mg) and the other used fixed dosing (30 and 60 mg). Both of the efficacy trials failed to differentiate treatment effect between placebo, duloxetine, and fluoxetine arms although the tested doses are similar to the doses approved in adults. A population pharmacokinetic analysis was performed using sparse PK samples from the three studies.

Duloxetine steady state plasma concentration was comparable in pediatrics and adults (Figure 1). The PK of duloxetine were well characterized by a 1 compartment model. Duloxetine clearance estimated to be 79.7 L/h (%SE = 4%), and volume of distribution as 1200 L (%SE= 9%). Unexplained interpatient variability was 68% for CL/F and 87% V/F. Dose, body surface area, and race had a statistically significant effect on duloxetine PK parameters. The effect of dose and race were consistent to those observed in adults and did not appear to have a clinically meaningful effect on duloxetine exposure. The concentrations in the pediatric population were encompassed within the range in adults and did not exceed the concentration range in adults, although duloxetine CL/F and V/F were higher in the pediatric population compared to the adult population which in turn leads to slightly lower duloxetine steady-state concentrations the pediatric population relative to adults.

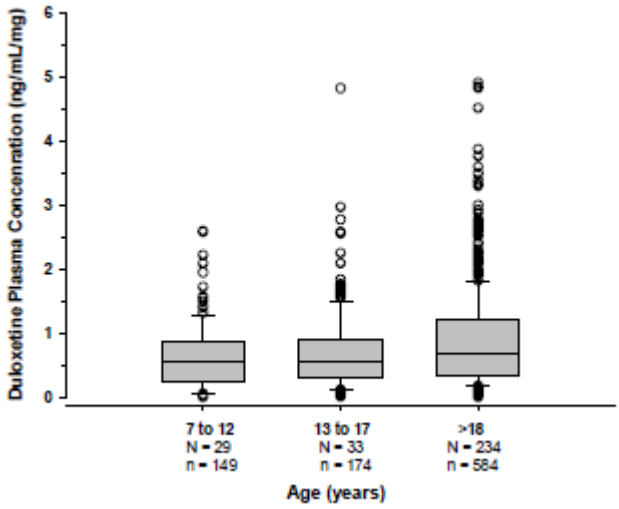

Figure 1. Dose normalized duloxetine plasma concentration in pediatrics and adults. N= number of patients and n = number of samples. (Adapted from study F1J-MC-HMFN report)

The sponsor has met the clinical pharmacology requirements of the written request (Appendix I). While the sample size was not prospectively determined and sparse sampling has been used in the dedicated PK study, sufficient power was attained to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution. This power was further increased among adding PK obtained from sparse sampling in the efficacy trials.

1.1 Recommendations

The Office of Clinical Pharmacology recommends no approval of duloxetine for the treatment of MDD in pediatric population due to the failure of the efficacy trials to differentiate treatment effect between placebo, duloxetine, and fluoxetine arms.

1.2 Labeling Recommendations

The following sentence should be added to section 8.4 of the label: “Duloxetine steady state plasma concentration was comparable in children (7 - 12 years), adolescents (13 - 17 years) and adults.”

Appendix I. Individual Studies Review

CLINICAL PHARMACOLOGY STUDY REVIEW

Pediatric Pharmacokinetic Study

Report #: F1J-MC-HMFN	**Study Period:** 08/31/2007 – 07/31/2008
Title	An open-label study of tolerability, safety, and pharmacokinetics of duloxetine in the treatment of children and adolescents with major depressive disorder (MDD)

Study Design

- **Overall design:** A 32-week, outpatient, phase II, multi-center, open-label, single arm study. The study consisted of five periods:
  1. Period I: Two weeks washout phase.
  2. Period II: Ten weeks dose titration with pharmacokinetic sampling.
  3. Period III: Eight weeks safety and tolerability phase.
  4. Period IV: Twelve weeks extended safety and tolerability phase.
  5. Period V: Two weeks taper phase.
- **Population:** Children and adolescents (aged 7 to 17 years, inclusive) who met the criteria for MDD.
- **Dose and dose titration:** Initial duloxetine dose was 20 mg QD in patients in the weight group (20 to 40 kg) and 30 mg QD in patients in the body-weight group (>40 kg). Patients remained on the initial dose for approximately a 2-week period. Subsequent dose increases occurred at 1- to 2-week intervals, based on investigator's assessment of safety and tolerability and treatment response (CGI-Severity score) in 30 mg QD increments up to a maximum dose of 120 mg QD. Doses were escalated if the patient tolerated the dose and the CGI-Severity score was ε3 for 2 consecutive visits.
- **Assessment Visits:** Every week in period II and at weeks 12, 14, 18, 22, 26, 30, and 32.
- **Formulation:** Commercially available 20 and 30 mg duloxetine capsules were used.
- **Efficacy Measure:** Children Depression Rating Scale-Revised (CDRS-R), CGI-Severity, and CGI-Improvement.
- **PK Sampling:** Sparse sampling on weeks 2, 4, 6, 8, 10, 14, and 18. Total number of samples is 5 at the end of period II.
- **PK Analysis:** Population PK.

Analytical Method

Method Type	LC/MS-MS	Matrix	Plasma
Analytes	Duloxteine		

Validation	▪ Method validated prior to use	☑ Yes ☐ No
	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Results

Study Population

Randomized	72
Treated	72
Completed (Period II/Period III/Period IV)	58/48/41
Discontinued Due to AE	3/0/1

Age Category (Years)	N	Male/Female
7 - 9	26	6/10
10 - 12	15	10/5
13 – 14	12	6/6
15 – 17	12	4/8

Efficacy Results

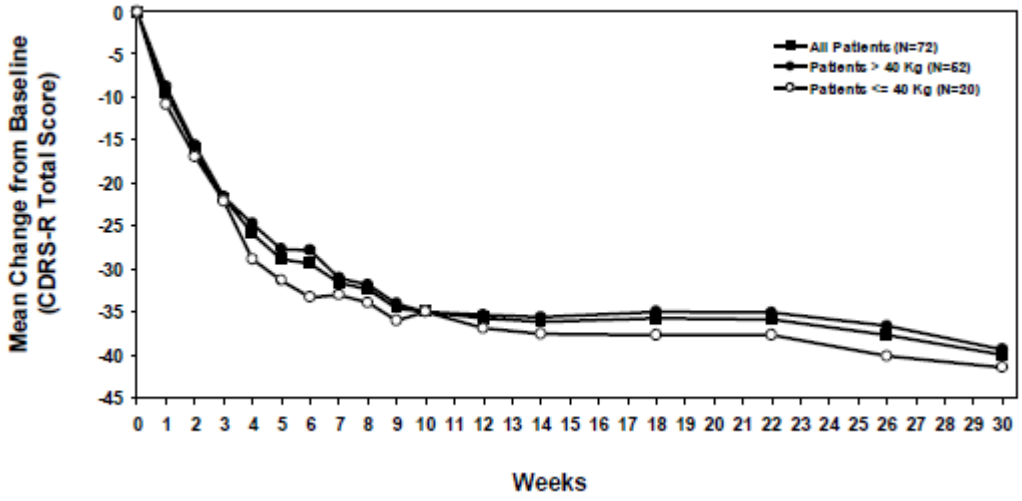

Figure 1. CDRS total score change form baseline by week.

Pharmacokinetics

A total of 413 plasma samples were obtained from the patients for the measurement of duloxetine concentrations, of which 90 samples (22%) were BQL. Samples were available form 51 out of 58 of the patients who completed Period II and in 42 out of the 55 of the patients in Period III. Duloxetine plasma concentrations are summarized in the table below.

Table. Summary of Observed Duloxetine Plasma Concentration

Dose (mg)	20 (N = 14) (n = 16)	30 (N = 53) (n = 89)	60 (N = 41) (n = 97)	90 (N = 33) (n = 75)	120 (N = 19) (n = 42)
Concentration (ng/mL)	15.2 ± 12.0 (3.9 - 51.6)	20.8 ± 21.2 (0.5 - 144.5)	41.1 ± 34.7 (0.7 - 177.9)	57.6 ± 43.2 (1.7 - 249.6)	77.6± 54.6 (1.2 - 210.7)
Age (years)	9.8 ± 1.3 (7.9 - 12.1)	12.3 ± 2.7 (7.8 - 17.3)	12.0 ± 2.9 (7.9 - 17.6)	14.2 ± 2.5 (7.9 - 17.6)	13.3 ± 2.4 (9.1 - 17.3)
Body Weight (kg)	31.5 ± 3.6 (23.6 - 36.9)	53.7 ± 21.8 (25.7 - 111.1)	53.1 ± 23.4 (23.6 – 110.0)	63.0 ± 18.4 (23.2 - 107)	61.6 ± 21.3 (23.6 - 107)

Abbreviations: N = number of patients; n = number of duloxetine concentrations.
[a] Summary statistics reported as Mean ± Standard Deviation (Minimum – Maximum)

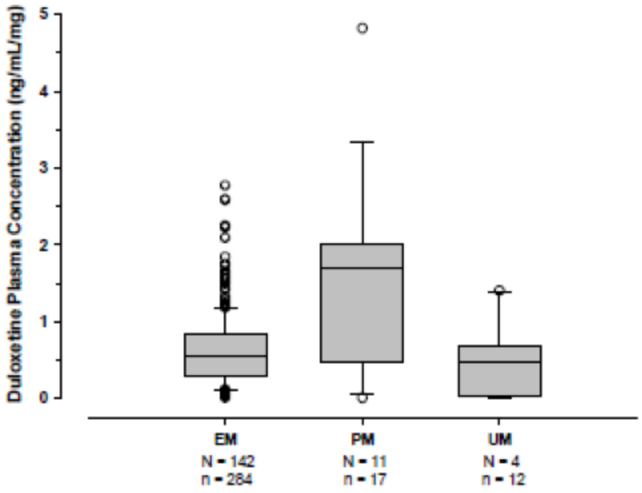

Figure 2. Dose-normalized duloxetine plasma concentration in CYP2D6 poor metabolizers (PM), extensive metabolizers (EM) and ultrametabolizers (EM). N= number of patients and n = number of samples.

Safety	
Was there any death or serious adverse events?	☐ Yes ☑ No ☐ NA

Conclusions

The median steady state duloxetine concentrations in pediatric patients are lower than in adults. Weight and age do not affect duloxetine plasma concentration in pediatrics and hence no need for differential dosing in pediatrics based on body weight or age.

CLINICAL PHARMACOLOGY STUDY REVIEW

Population Pharmacokinetic Report

Overview: A population pharmacokinetic model of duloxetine was developed using data from 3 studies, F1J-MC-HMFN (HMFN), F1J-MC-HMCK (HMCK) and F1J-MC-HMCL (HMCL) were used to

Studies Overview

FIJ-MC-HMFN:

Please refer to individual study review for details.

FIJ-MC-HMCK and FIJ-MC-HMCL

These were randomized, double-blind, placebo- and fluoxetine-controlled, 10 week, efficacy and safety clinical trials conducted in children and adolescents with MDD. These studies used stratified randomization by age children, aged 7 through 11 years, and adolescents, aged 12 through 17 years and incorporated a 6-month, double-blind (duloxetine or fluoxetine), flexible-dose long-term safety extension period. Study HMCK used flexible duloxetine dose range of 60 to 120 mg QD while study HMCL used fixed doses of 30 and 60 mg. The total number of randomly assigned patients was 336 in study HMCK was and 448 in study HMCL randomized (1:1:1) to duloxetine, fluoxetine, and placebo. PK sampling was scheduled to occur during the double-blind phase at weeks 4 and 10 (optional at weeks 2 and 7) and at weeks 14, 20, 28, 36 in the safety extension period. An additional sample was collected if a patient discontinued early from the studies.

Results

PK samples: A total of 2363 plasma samples were obtained from 520 patients for the measurement of duloxetine concentrations. A total of 757 samples were reported as BQL.

A total of 1581 quantifiable plasma concentrations from 428 patients were available for inclusion in the PK evaluation (Table 1). The data distribution of the available duloxetine concentration across the steady-state dosing interval was appropriate for the estimation of the population PK

Table 1. Summary of plasma samples included in the model development.

	Number of Patients	Number of PK samples
HMFN	62	319
HMCK	152	532
HMCL	214	730

Patients Characteristics:

Of the 428 patients that contributed quantifiable plasma concentrations, 34% were children (7 to 11 years old) and 66% were adolescents (12 to 18 years old). The number of males and females were approximately similar at 52% and 48%, respectively. The majority of the patients were nonsmokers (91%), extensive CYP2D6 metabolizers (88%), and Caucasian (69%). Sixty-seven percent of female patients had attained menarche.

Base Model: A 1-compartment model parameterized in terms of Ka, CL/F, and V/F was selected as an appropriate base structural model. During model development, the estimation of Ka resulted in flip-flop kinetics with high interpatient variability in V/F (130%). Since attempts to remove the flip-flop kinetics were unsuccessful, Ka was fixed to the adult value of 0.168 h^{-1}. The interpatient variability in CL/F and V/F was described using an exponential error model with covariance between CL/F and V/F, and the residual error was described with an additive/proportional model. Visual predictive checks showed that most of the observed concentrations are within the model-predicted concentration range (5th to 95th percentile Model evaluation using parameter sensitivity analysis showed that all parameters were estimated with adequate precision. Model parameters are displayed in Table 2.

Table 2. Base Model Pharmacokinetic Parameters

Parameter	Population Estimation	Inter-Patient Variability
CL/F	76.1 L/h	69%
V/F	1380 L	100%
Interaction Term (CL/F and V/F)		0.188
Residual Error Additive Proportional	 2.26 ng/mL 57%	

Final Model: Age, gender, Creatinine clearance, CYP2D6 status, and menarche status did not have a statistically significant effect on any of the duloxetine PK parameters. On the other hand, body surface area (BSA) and dose had an effect on CL/F and race had an effect on V/F. The inclusion of these covariates in the model reduced the interpatient variability in duloxetine CL/F from 69% to 68%, and interpatient variability in V/F from 100% to 87%. Residual error remained constant at 57%. The following equation describes the final model:

$$CL/F = 79.7*(BSA/1.55)^{0.786} \cdot (Dose/60)^{-0.216}$$

$$V/F = 1200 * (RACE+1.31)$$

POP PK parameters in adults and pediatrics: In adults, PK data are available at 20 and 60 mg QD dosing regimen in patients. Table 3 displays duloxetine POP PK in pediatrics and adults

Table 3. Duloxetine POP PK parameters in pediatrics and adults

Parameters		Pediatrics (95% CI)	Adults (95% CI)
CL/F	Male	87.1 (80.8-93.4)	52.2 (47.0 – 57.5)
	Female		74.5 (62.6 – 86.3)
V/F	Male	1340 (1250-1440)	941 (878 – 1000)
	Female		1450 (1350 – 1560)
Interpatient variability on CL/F (%)		68	59
Interpatient variability on V/F (%)		87	97
Residual Error (%)		57	31

Comments

In general, the reviewer finds the sponsor modeling approach and the final model acceptable. Unexplained interpatient variability is high for CL/F (68%), V/F (87%), and the residual error (57%). This can be due the nature of the data and the presence of flip flop kinetics, which have forced the fixation of the absorption rate constant to the adult value in order to stabilize the model.

<table>
<tr><th colspan="3">NDA 21247-S041
Drug: Cymbalta® (duloxetine hydrochloride) Clinical Pharmacology Pediatric Exclusivity Assessment</th></tr>
<tr><th>Item</th><th>Sponsor Response</th><th>Reviewer Comment</th></tr>
<tr><td>Pediatric Pharmacokinetic Study
You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to preliminary efficacy trials or to other safety trials.
You must perform preliminary tolerability studies (in which kinetic data can be obtained) to fully explore the range of tolerated doses, before conducting the definitive pharmacokinetic study and before conducting the definitive efficacy and safety studies.</td><td>[Required element] Study HMFN was an open label safety and tolerability PK study, and Pop PK was collected in both Phase 3 studies. (Source: HMFN 9.2.2., Pop PK)
[Required element] Study HMFN was an open label safety and tolerability PK study that explored the dose range of 20-120 mg daily. Lilly conducted HMFN and submitted results prior to initiating the definitive efficacy and safety phase 3 studies HMCK and HMCL. (Source: HMFN 9.1.)</td><td>Agree
Dose range = 20-120 mg
Completed = 09/21/2008
Date of Report = 03/04/2009
Efficacy trial date
HMCK
1st patient = 03/26/2009
HMCL
1st patient = 03/16/2009</td></tr>
<tr><td>Age group and population in which study will be performed: All Studies
Both children (ages 7 to 11 years) and adolescents (ages 12 to 17 years) should be approximately evenly distributed over the age range
in the study (at least 40% in younger stratum), and the numbers of male and female patients should be approximately equal within these samples as well.</td><td>Age group and population in which study was performed:
[Not a required element] Both children (ages 7 to 11 years) and adolescents (ages 12 to 17 years) were approximately evenly distributed over the age range in the study (at least 40% in younger stratum). The numbers of male and female patients were approximately equal within these samples. (Source: Table HMCL 11.1, Table HMCK 11.1, Table HMFN 11.1)</td><td>Agree

Enrolled = 72
Completed Period II= 58
Completed Period III= 48
Completed Period IV= 41

By visit 16 (Week 18)
<table>
<tr><th>Age</th><th>Male</th><th>Female</th></tr>
<tr><td>7-9</td><td>6</td><td>10</td></tr>
<tr><td>10-12</td><td>10</td><td>5</td></tr>
<tr><td>13-14</td><td>6</td><td>6</td></tr>
<tr><td>15-17</td><td>4</td><td>8</td></tr>
<tr><td>Total</td><td>26</td><td>29</td></tr>
</table>
Younger (≤12) = 56%</td></tr>
</table>

Number of Patients to be Studied *Pediatric Pharmacokinetic Study* A sufficient number of patients to adequately characterize the appropriate dose range, tolerability, and pharmacokinetics of the study drug and its major active metabolite(s) in the relevant age group must be studied. The full spectrum of age strata in the 7 to 17 continuum must be represented (e.g., 7-9, 10-12, 13-14, 15-17) and should have at least 4 completers per stratum. A study should be designed with sufficient N to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution. If statistical power is not attained in this preliminary tolerability study, an additional intensive sampling pharmacokinetic study or population pharmacokinetic study (i.e., during the definitive efficacy and safety trials) can be conducted. Final power will be estimated from the combined N of the tolerability and pharmacokinetic studies.	[Required element] A sufficient number of patients to adequately characterize the appropriate dose range, tolerability, and pharmacokinetics of the study drug and its major active metabolite(s) in the relevant age group were studied. (Source: Table HMFN 10.1.) [Required element] The full spectrum of age strata in the 7 to 17 continuum were represented (e.g., 7-9, 10-12, 13-14, 15-17) and had at least 4 completers per stratum. (Source: Table HMFN 10.1.) [Not a required element] While sufficient power was attained on HMFN alone, final power calculations are based on the combined analyses with PopPK. CL : geometric mean = 79.7, 95%CI : 73.2 to 85.9 which is within the 60% to 140% of 79.7 (48 to 112) V : geometric mean = 1200, 95%CI : 1026 to 1400 which is within the 60% to 140% of 1200 (720 to 1680) (Source: HMFN, Pop PK Table 6.)	Sample size was not prospective; however, the numbers are enough to retain power
Pediatric Pharmacokinetic Study Data from the tolerability studies should be accumulated prior to the start of the definitive safety and efficacy trials.	Not a required element] Study HMFN was an open label safety and tolerability PK study that explored the dose range of 20-120 mg daily. Lilly conducted HMFN and submitted results prior to initiating HMCK and HMCL. (Source: HMFN)	Agree
Clinical endpoints: *Pediatric Pharmacokinetic Study*	Required element] Pharmacokinetic assessments were made with respect to the study drug and any metabolites that make	Agree

Pharmacokinetic assessments must be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite measured, the data collected should provide estimates of important pharmacokinetic parameters, e.g., AUC, half-life, Cmax , Tmax, and apparent oral clearance in pediatric subjects in the relevant age range.	substantial contributions to its efficacy and/or toxicity. (Source: HMFN, Pop PK) [Not a required element] For the parent and each metabolite measured, the collected data provided estimates of important pharmacokinetic parameters, e.g., AUC, half-life, Cmax, Tmax, and apparent oral clearance in pediatric subjects in the relevant age range. (Source: HMFN, Pop PK)	
Statistical Information: *Pediatric Pharmacokinetic Study* Descriptive analysis of the pharmacokinetic parameters.	[Required element] Descriptive analysis of the pharmacokinetic parameters was included. (Source: HMFN 11.5., Pop PK, HMCK 11.4.6., HMCL 11.4.6.)	Agree

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/s/

ISLAM R YOUNIS
10/02/2012

HAO ZHU
10/02/2012