Clinical Pharmacology Review

NDA:	021427
Generic Name:	Duloxetine
Trade Name:	CYMBALTA©
Strength and Dosage Form:	20 mg, 30 mg and 60 mg oral capsules (enteric coated)
Indication:	Generalized Anxiety Disorder (GAD)
Sponsor:	Eli Lilly
Submission Type:	sNDA, Pediatric efficacy supplement (S#43) and Geriatric efficacy supplement (S#44)
Priority Classification:	Standard
Submission Date:	Dec 2103
OCP Division:	DCP1
OND Division:	DPP
Reviewer:	Praveen Balimane, Ph.D.
Team Leader:	Hao Zhu, Ph.D.

Executive Summary

Eli Lilly and Company (Lilly) has submitted a supplemental New Drug Application (sNDA-021427, S #43) in fulfillment of the required pediatric study commitment (Pediatric Research Equity Act [PREA] requirement) issued by the Food and Drug Administration (FDA) as part of the 23 February 2007 sNDA approval for the use of Cymbalta for the treatment of generalized anxiety disorder (GAD). In addition, a separate sNDA, S#44 regarding a post-marketing study in elderly patients with GAD that was conducted to fulfill a European (Committee for Medicinal Products for Human Use [CHMP]) post-authorization commitment has also been submitted.

The Office of Clinical Pharmacology believes that the two sNDA's are acceptable from clinical pharmacology point-of-view. There are no additional PMR requirements or labeling change at this time.

Listed below are the main features of the two supplements:

1.) **Pediatric GAD indication**:

- Duloxetine efficacy in pediatric patients for GAD: The final medical review will provide a detailed analysis of efficacy and safety of duloxetine in this population. Pivotal study (F1J-MC-HMGI) was a10-week, *flexible-dose*, placebo-controlled trial in pediatric patients with GAD, 7 to 17 years of age. The starting dose was 30 mg once daily for 2 weeks before further dose increases in 30 mg increments up to 120 mg once daily.
- Historical pediatric PK data demonstrated similarity of PK between children, adolescents and adults: There was no new PK data collected in pediatric patients in the pivotal GAD study. However, a dedicated open label PK study of Duloxetine (F1J-MC-HMFN) had been performed in children and adolescents with MDD (flexible dosing 20 to 120 mg once daily) in the past. The results of PK study (F1J-MC-HMFN) had been reviewed by OCP and the review was placed in DARRTS on 10/02/2012 (NDA 021427, S-41). It had demonstrated that PK in children (7-12 yr) was comparable to PK in adolescents and adults. There was also considerable overlap in duloxetine plasma concentration range

observed in children (7-12 yr) vs. the concentrations observed in other age groups (adolescents and adults). Additionally, the range of concentrations observed in pediatric subjects (7-12 yr) was fully bracketed within the range observed in adults (>18 yr). There was no additional dose-response or population PK analysis performed or submitted with the current submission.

- Same formulation and strength of oral capsules were used in pediatric studies as in the past adult efficacy studies: Pediatric study used the same formulation and strength of duloxetine capsules used in the adult efficacy studies thus requiring no new bridging studies.

2.) **Geriatric GAD indication**:

- Duloxetine efficacy in geriatric patients for GAD: The final medical review will provide a detailed analysis of efficacy and safety of duloxetine in this population. Pivotal study (F1J-MC-HMGF) was a10-week, *flexible-dose*, placebo-controlled trial in geriatric patients with GAD, 65 years of age and older. The starting dose was 30 mg once daily for 2 weeks before further dose increases in 30 mg increments up to 120 mg once daily.
- Historical geriatric PK data demonstrated similarity of PK between elderly and young adults: Study F1J-LC-SAAY, investigated the PK of duloxetine in the elderly and was completed on 04 September 1998. In a comparison of the PK of duloxetine between middle aged (32 – 50 years) and geriatric (65 – 77 years) healthy women, the mean percent difference for the area under the plasma drug concentration time curve (AUC), apparent clearance (CL/F), and maximum time (Tmax) was about 25%, which was not statistically significant. The half-life (t1/2) was longer in the geriatric than in middle age subjects (14 hours versus 10 hour), but this difference was judged to be not clinically meaningful. The terminal elimination rate constant (λz) was lower (31%) in the elderly group compared to the middle age group. There was no additional dose-response or population PK analysis performed or submitted with the current submission.
- Same formulation and strength of oral capsules were used in geriatric studies as in the past adult efficacy studies: Geriatric study used the same formulation and strength of duloxetine capsules used in the adult efficacy studies thus requiring no new bridging studies.

Clinical Pharmacology Summary

- Cymbalta® (Duloxetine) is a serotonin and norepinephrine reuptake inhibitor (SNRI) by Eli Lilly. It is approved in ADULTS for several indications:
    - Major Depressive Disorder (MDD)
    - *Generalized Anxiety Disorder (GAD*)
    - Diabetic Peripheral Neuropathic Pain (DPNP)
    - Fibromyalgia (FM)
    - Chronic Musculoskeletal Pain

The clinical program for the **pediatric efficacy application** is supported by the following clinical study and historical PK data:

- F1J-MC-HMGI (HMGI): A Double-Blind, *Efficacy* and Safety Study of Duloxetine versus Placebo in the Treatment of Children and Adolescents with Generalized Anxiety Disorder (duloxetine flexible dosing range 30-120 mg QD) (7-17 yr)
    - The starting dose was 30 mg once daily for 2 weeks before further dose increases in 30 mg increments up to 120 mg once daily were allowed based on investigator judgment of clinical response and tolerability.
    - The mean dose for completers of the 10-week acute treatment phase was 57.6 mg/day.
    - Cymbalta (N=135) efficacy was compared against placebo (N= 137) as measured by greater improvement in the Pediatric Anxiety Rating Scale (PARS) for GAD severity score.
- Duloxetine steady-state plasma concentration was comparable in children (7 to12 years of age), adolescents (13 to 17 years of age) and adults (18+ yr).
    - F1J-MC-HMFN (HMFN): An Open-Label Study of Tolerability, Safety, and Pharmacokinetics of Duloxetine in the Treatment of Children and Adolescents with MDD (duloxetine flexible dosing: 20, 30, 60, 90, 120 mg once daily [QD]
    - The median duloxetine concentration-time profile was slightly lower in the pediatric population relative to adults.
    - However, there was considerable overlap in the concentration range, and the range of concentration in pediatric patients was within the range observed in adults

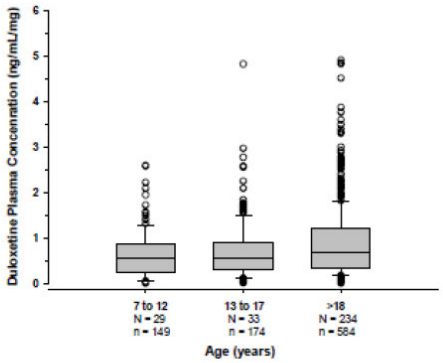

Figure 1. Dose normalized duloxetine plasma concentration in pediatrics and adults. N= number of patients and n = number of samples. (Adapted from study F1J-MC-HMFN report)

The clinical program for the **geriatric efficacy application** is supported by the following clinical study:

- F1J-MC-HMGF (HMGF): A Phase 4, parallel, double-blind, placebo-controlled study comparing the efficacy and safety of duloxetine 30-120 mg once daily (QD) with placebo for the acute treatment of generalized anxiety disorder in elderly patients (≥65 years old).
- Elderly patients who met criteria for GAD as defined by the DSM-IV-TR were eligible to participate in this study. A total of 291 patients (151 to duloxetine 30-120 mg QD and 140 to placebo) were randomly assigned to 10 weeks of double-blind treatment. The starting dose was 30 mg once daily for 2 weeks before further dose increases in 30 mg increments up to 120 mg once daily were allowed based on investigator judgment of clinical response and tolerability.

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/s/

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07/15/2014

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