CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21,427/Supplement 43
Priority or Standard	Standard
Submit Date(s)	12/16/2013
Received Date(s)	12/16/2013
PDUFA Goal Date	10/16/2014
Division / Office	DPP/ODE-I
Reviewer Name(s)	Tiffany R Farchione, MD
Review Completion Date	
Established Name	Duloxetine hydrochloride
(Proposed) Trade Name	Cymbalta
Therapeutic Class	Serotonin and Norepinephrine Reuptake Inhibitor
Applicant	Eli Lilly & Co.
Formulation(s)	Capsules
Dosing Regimen	20, 30, and 60mg
Indication(s)	Generalized Anxiety Disorder
Intended Population(s)	Children (7-11yo) and Adolescents (12-17yo)

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that this supplement be approved. In this reviewer's opinion, the sponsor has demonstrated the efficacy and reasonable safety of duloxetine for the treatment of Generalized Anxiety Disorder (GAD) in children and adolescents. This recommendation is based on the results of a single positive trial in patients aged 7-17 years, as well as partial extrapolation from adult clinical trials.

1.2 Risk Benefit Assessment

Cymbalta has been demonstrated to be reasonably safe and effective in the treatment of Generalized Anxiety Disorder in pediatric patients.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This review identified no new major risks that would merit a Risk Evaluation and Mitigation Strategy.

1.4 Recommendations for Postmarket Requirements and Commitments

According to the approval letter of duloxetine for the treatment of GAD, the sponsor agreed to conduct a post-marketing study of efficacy and safety of duloxetine as a treatment for GAD in pediatric patients ages 7 to 17. This commitment has been fulfilled with the current submission. No additional postmarketing studies have been identified as necessary based on this review.

2 Introduction and Regulatory Background

2.1 Product Information

Duloxetine hydrochloride (Cymbalta™) is a member of the serotonin and norepinephrine reuptake inhibitor (SNRI) class. It is currently approved in both the European Union (EU) and in the United States for the treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD), and diabetic peripheral neuropathic pain (DPNP). Cymbalta™ was first approved in the United States in August 2004 and in the EU in December 2004. Duloxetine also is approved for the treatment of fibromyalgia in the US (approved June 2008) and for the treatment of moderate to severe stress urinary incontinence in women in the EU (Yentreve™ approved in August 2004). Duloxetine is not indicated for use in children and adolescents.

2.2 Currently Available Treatments for Proposed Indications

There are no medications approved for the treatment of GAD in pediatric patients.

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient of Cymbalta (duloxetine hydrochloride) is readily available in the United States. Cymbalta is currently approved for the treatment of MDD, GAD, diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain. It is available in 20, 30, and 60mg capsules for oral administration.

2.4 Important Safety Issues with Consideration to Related Drugs

All antidepressant labels include boxed warning language describing an increased risk of suicidal ideation and behavior in patients aged 24 and younger. Other known safety issues associated with SNRIs include elevated blood pressure, increased risk of bleeding, serotonin syndrome, and discontinuation syndrome.

Duloxetine has also been associated with rare cases of hepatic failure and Stevens-Johnson syndrome (SJS).

No other important safety issues related to this drug were identified from this submission.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Cymbalta was approved for the treatment of GAD based on adult (≥18 yo) data on February 23, 2007. At the time of approval, FDA included a Post-Marketing Commitment (PMC) for deferred pediatric studies under the Pediatric Research Equity Act (PREA) as follows:

> *You are required to assess the safety and effectiveness of duloxetine hydrochloride as a treatment for Generalized Anxiety Disorder in pediatric patients ages 7 to 17 (children and adolescents). Both children (ages 7 to 11) and adolescents (ages 12 to 17) should be equally represented in the samples, and there should be a reasonable distribution of both sexes in these age strata.*
>
> *Final Report Submission: by February 28, 2011*
>
> *Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".*

On December 18, 2009, the sponsor requested a revised PMC submission date of August 31, 2013, which FDA granted. In addition, the sponsor requested feedback on

their planned sample age distribution, and their plan to allow inclusion of patients with certain comorbidities. The sponsor's specific questions and FDA's responses are below:

> 1. Lilly requests that the Division revise the PMC submission date to August 31, 2013.
>
> *Division response: Your proposal for an extension of the Final Report Submission date to August 31, 2013 is reasonable, and has been acknowledged.*
>
> *Please note that the original schedule serves as the basis for defining the status of a postmarketing commitment, even if a revised schedule has been provided. Your annual progress reports, required under 21 CFR 314.81(b)(2)(vii), should include both the original and revised schedules, and the reason for the revision.*
>
> 2. Does FDA agree with a patient population sampling distribution of (b)(4)% for adolescent (ages 13-17) and (b)(4)% for children (ages 7-12) for the GAD trials?
>
> *Division response: Although the diagnosis of generalized anxiety disorder may have a higher incidence and prevalence in the adolescent (12-17 y.o.) age group compared to the younger children (7-11 y.o.) age group, the disease is well described and recognized in both children and adolescents. Both child and adolescent age groups are considered potential candidates for medication treatment for GAD symptoms. Therefore, it is important that both children (ages 7 to 11 years) and adolescents (ages 12 to 17 years) be studied and that there be an approximately even distribution over the age ranges in the study. This would require that at least 40% of the patients to be in the younger stratum.*
>
> 3. Does FDA agree with the allowance of these secondary anxiety diagnoses, such as social and separation anxieties in the patient population?
>
> *Division response: Your proposal to exclude specific diagnoses and to allow co-morbid illnesses appears to be acceptable. Please include all rationales in your proposed protocol.*

On July 3, 2013, FDA granted a Deferral Extension to allow Lilly to include both the acute phase and extension phase of the study in a single submission, with a revised Final Report Submission date of January 31, 2014. A pre-sNDA meeting was held on July 18, 2013.

2.6 Other Relevant Background Information

In the EU, a full waiver for the need to undertake studies of duloxetine in a pediatric patient population was received after submitting a pediatric investigational plan (PIP) in 2009.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A sample of case report forms (CRFs) was reviewed to evaluate the consistency of adverse event information across the CRFs, corresponding narrative summary, and adverse event tabulation. Among the CRFs reviewed, the adverse event information was generally found to be consistent across the above documents. The sponsor submitted CRFs for all subjects listed as "permanently discontinued" in the adverse event (AE) database, as well as for all subjects who had a serious adverse event (SAE) in the course of the study.

The coding of adverse event investigator terms to preferred terms (PT) was audited. In study F1J-MC-HMGI (hereafter, HGMI), the sponsor used MedDRA coding. The adverse event tabulations for study HMGI were examined, comparing the variables' AE versus PT. In general, it appeared that most verbatim terms were appropriately coded to preferred terms.

3.2 Compliance with Good Clinical Practices

According to the HMGI study report, this study was conducted in accordance with the consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guideline [E6], and applicable laws and regulations.

Lilly certifies that none of the investigators have been debarred under section 306 of the Federal Food, Drug, and Cosmetic Act.

One site was excluded from HMGI by the sponsor for GCP violations. The sponsor confirmed scientific misconduct in the form of falsified records at Site 190 (Canton, OH) and, thus, decided to exclude the 9 subjects enrolled at that site from the Intent to Treat (ITT) population in efficacy analyses. Sensitivity analyses that included data from subjects enrolled at Site 190 performed on the primary efficacy endpoint (PARS) yielded results that were similar to those obtained in the ITT population.

The Office of Scientific Investigations (OSI) was consulted to inspect one of the clinical sites from study HMGI. Site #340 (Arifulia Khan, MD, of Bellvue, WA) was selected because it was one of the sites with the largest influence on the efficacy result. A Clinical Inspection Summary was completed by John Lee, M.D., Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, OSI on August 4, 2014.

The site was inspected for compliance with study protocols, Good Clinical Practice regulations, and standard operating procedures. A form FDA 483 was issued for deficiencies related to four protocol violations—three related to subject eligibility, and one to adequacy of treatment compliance. The investigator concluded that, with the exception of the noted discrepancies, the data are reliable in support of the application.

The inclusion of subjects in the study who have not met eligibility criteria could make interpretation of the resultant data very difficult. The statistical reviewer, Eiji Ishida, MS, followed up on this finding to determine the extent of this problem. Based on his analyses, 267 of the 272 subjects in the intent-to-treat population met inclusion criteria. Excluding the five subjects who did not meet entry criteria did not change the results of the primary efficacy analysis.

3.3 Financial Disclosures

The sponsor submitted the certification of financial disclosure of clinical investigators participating in study HMGI in compliance with 21 CFR Part 54. No clinical investigator reported participating in any financial arrangement with the sponsor whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study, or having proprietary interest in this product or significant equity interest in the sponsor.

Two investigators reported being the recipients of significant payments of other sorts. These arrangements do not appear to raise questions about the integrity of the data due to the study design (randomized, double-blind). In addition, the primary outcome is unchanged with vs. without these sites included in the analyses.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new information on the chemistry, manufacturing, and controls of duloxetine was submitted to this sNDA.

4.2 Clinical Microbiology

No new clinical microbiology information was submitted with this sNDA.

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology or toxicology information was submitted with this sNDA.

4.4 Clinical Pharmacology

No new clinical pharmacology information was submitted with this sNDA.

4.4.1 Mechanism of Action

No new information on mechanism of action was submitted with this sNDA. The current Cymbalta label states:

> Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.

4.4.2 Pharmacodynamics

No new pharmacodynamic information was submitted with this sNDA.

4.4.3 Pharmacokinetics

No new pharmacokinetic information was submitted with this sNDA. Pediatric pharmacokinetic data was previously reviewed under Supplement 041. The complete study report from Study HMFN, an open-label, Phase 2, pharmacokinetic study, was included with the s041 submission. The pharmacokinetics of oral duloxetine (20mg-120mg) in pediatric patients were found to be linear. Body weight and age did not have a statistically significant effect on duloxetine pharmacokinetic parameters.

5 Sources of Clinical Data

5.1 Studies/Clinical Trials

Study F1J-MC-HMGI (HGMI) is the study on which the proposed indication of treatment of GAD in child and adolescent patients is based, and is the primary focus of this review.

HMGI was a Phase 3b, multicenter, randomized, double-blind, clinical trial of duloxetine versus placebo in children (ages 7-11 years) and adolescents (ages 12-17 years) meeting DSM-IV-TR, criteria for GAD. The study was conducted at 33 sites in three countries, with most patients enrolled from the US (72.4%), followed by Mexico (19.1%), and South Africa (8.5%). This study was comprised of a 10-week double-blind acute treatment phase, and an 18-week open-label extension phase.

In total, 281 children and adolescents were enrolled; however, 9 patients (5 duloxetine, 4 placebo) were excluded from Site 190 due to quality issues at the site. Thus, the intent-to-treat (ITT) population included 272 patients. All patients in the ITT population

received at least one dose of study drug (135 duloxetine, 137 placebo) during the Acute Phase, 210 (104 duloxetine, 106 placebo) completed the Acute Phase and entered the Extension Phase, and 160 (79 DLX/DLX, 81 PLA/DLX) completed the Extension Phase.

5.2 Review Strategy

This review consisted of an examination of relevant background clinical information from the original application (NDA 21,427), efficacy and safety data from Study HMGI, and pooled safety data from duloxetine pediatric studies to date.

6 Review of Efficacy

Efficacy Summary

The efficacy of duloxetine for the treatment of GAD in children and adolescents was demonstrated in a single double-blind, placebo-controlled, randomized study (HMGI). This product is not currently labeled for use in children and adolescents.

Eiji Ishida, MS (statistical reviewer) confirmed the sponsor's efficacy results. Please see his review dated September 8, 2014.

6.1 Studies Pertinent to the Efficacy Claim

6.1.1 Rationale for Selection of Studies for Review

The sponsor submitted data from a single trial—Study F1J-MC-HMGI, a randomized, double-blind, placebo-controlled study of duloxetine versus placebo in children and adolescents (7-17 years of age) with GAD—in support of the proposed efficacy claim.

6.1.2 Study Summaries

F1J-MC-HMGI (HGMI)

Methods/Study Design/Analysis Plan
HMGI was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of duloxetine versus placebo in the treatment of children and adolescents (7-17 years of age) with Generalized Anxiety Disorder (DSM-IV-TR and MINI-KID). Safety and efficacy of duloxetine was assessed across a flexible dose range of 30 to 120 mg QD.

The study used stratified randomization by age: children (7 through 11 years) and adolescents (12 through 17 years).Enrollment was monitored to assure that at least 40% of the enrolled patients were children, aged 7 to 11 years old.

Objectives

Primary Objective: To assess whether duloxetine is superior to placebo in the acute treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) who met criteria for GAD as defined in the DSM-IV-TR. Superiority was defined as a statistically greater reduction in anxiety symptoms from baseline to endpoint (10 weeks) as measured by the Pediatric Anxiety Rating Scale (PARS) severity rating score evaluated for symptoms identified on the generalized anxiety subsection of the PARS symptom checklist.

Secondary Objectives:

- To evaluate the efficacy of treatment with duloxetine compared with placebo in the treatment of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with GAD, during a 10-week, double-blind, acute treatment period, as measured by the following:
    - change from baseline to endpoint on the Clinical Global Impression of Severity (CGI-S) scale
    - change from baseline to endpoint on the Children's Global Assessment Scale (CGAS)
    - change from baseline to endpoint on the PARS severity total score evaluated for all symptoms identified on the PARS symptom checklist
    - response rate at endpoint for GAD using PARS severity score for GAD
    - remission rate at endpoint for GAD using CGI-S scale
- To assess changes in anxiety symptoms of children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with GAD treated with duloxetine during a 4-month, open-label extension period as measured by the following:
    - change from baseline to endpoint on the PARS severity rating evaluated for symptoms identified on the generalized anxiety subsection of the PARS symptom checklist
    - change from baseline to endpoint on PARS severity total score evaluated for all symptoms identified on the PARS symptom checklist
    - change from baseline to endpoint on the CGI-S scale
    - change from baseline to endpoint on the CGAS

None of the above were identified as "key" secondary measures.

Key Inclusion Criteria

The study population for this trial included male and female patients aged 7 to 17 years diagnosed with GAD on clinical exam as defined by the DSM-IV-TR and supported by the MINI-KID. The GAD was of moderate or greater severity as determined by the following, assessed at Visits 1 and 2:

- presence of ≥4 symptoms identified on the generalized anxiety subsection of the PARS symptom checklist
- Pediatric Anxiety Rating Scale severity score of ≥15
- Clinical Global Impression of Severity rating of ≥4
- presence of significant social, academic, and/or familial dysfunction as determined by the CGAS score of ≤60

Early in the implementation of the study, a trend was observed in patients not meeting baseline symptom severity inclusion criteria on the primary efficacy measure (PARS severity for GAD–13 patients). An additional 12 patients were randomized to account for the potentially reduced effect size from the 13 patients not meeting PARS GAD severity inclusion criteria, which increased the original sample size from 260 to 272. At the time the sponsor proposed this strategy, our statistical reviewer, Eiji Ishida, MS, recommended that the sponsor conduct a sensitivity analysis to assess the impact of patients who did not meet the severity inclusion criterion on results of primary ITT efficacy analysis. The results of the sensitivity analysis were consistent with the primary analysis.

Key Exclusion Criteria

- Current or previous diagnosis of bipolar disorder, psychotic depression, schizophrenia or other psychotic disorder, anorexia, bulimia, obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, or pervasive development disorder.
- Any Axis II disorder that would interfere significantly with protocol compliance.
- DSM-IV-TR-defined substance abuse or dependence within the previous year.
- Current primary diagnosis of any DSM IV Axis I disorder except GAD, or a current secondary DSM-IV-TR Axis I disorder that required any pharmacologic treatment. “Primary” was defined as the disorder that was the primary focus of treatment.
- One or more first-degree relatives with diagnosed bipolar I disorder.
- Significant suicide attempt within 1 year of Visit 1 or were at risk of suicide in the opinion of the investigator.
- Weight less than 20 kg at any Screening Period visit.
- Lack of response to two or more adequate trials of antidepressants at a clinically appropriate dose for a minimum of 4 weeks for the GAD episode at the time of Screening or, in the judgment of the investigator, the patient had treatment-resistant GAD.
- Change to psychotherapy (start, stop, or change in type, intensity, or frequency) in six weeks prior to study or during Study Period II.
- History of seizure disorder (other than febrile seizures).
- History of electroconvulsive therapy (ECT) within 1 year of Visit 1.
- Had a positive urine drug screen for any substances of abuse or excluded medication.

- Known hypersensitivity to duloxetine or its inactive ingredients, or had frequent or severe allergic reactions to multiple medications.
- Uncontrolled narrow-angle glaucoma.
- Acute liver injury (eg, hepatitis) or severe cirrhosis (Child-Pugh Class C).
- Serious or unstable medical illness, psychological condition, or clinically significant laboratory or ECG result that, in the opinion of the investigator, would compromise participation in the study or be likely to lead to hospitalization during the course of the study.
- Abnormal TSH concentration.
- Initiated or discontinued hormone therapy within 3 months prior to screening.
- Female patients who were either pregnant, nursing, or had recently given birth.
- Patients for whom the primary focus of treatment was separation anxiety or social phobia (patients with secondary separation anxiety or social phobia were allowed to participate).
- Patients with a diagnosis of MDD at the time of screening.

Study Design

The study consisted of four periods:

Study Period I—Screening

- 1-week screening period (not less than 5 days, not to exceed 30 days)

Study Period II—Acute Treatment

- 10-week double-blind acute treatment period
- Subjects were randomized 1:1 to receive either
  - once-daily duloxetine, flexible dosing (60, 90, or 120 mg), or
  - once-daily placebo.
- Dose adjustments will occur as described in Table 1, below.
- At Visit 8, all patients had their investigative product (IP) adjusted to duloxetine 60 mg QD dose. This was done to ensure all patients were at the same dose prior to starting open-label IP.

Table 1: HGMI Study Period II Dose Adjustments

Safety and Tolerance[a]	Tolerating Current Dose	Not Tolerating Current Dose
Response		
CGI-Severity >2 (Mildly ill, Moderately ill, Markedly ill, Severely ill, or Among the most extremely ill patients)	Dose should be increased.	Dose should be decreased.
CGI-Severity ≤ 2 (Normal, not at all ill or Borderline ill)	Dose should be maintained.	Dose should be decreased.

Abbreviations: CGI-Severity = Clinical Global Impressions of Severity.
[a] Safety and tolerance based on investigator's clinical judgment.
(source: HGMI protocol, Table HGMI.9.3, page 35)

Study Period III—Open Label Treatment

- 18-week treatment period, of which 16 weeks are open-label

Study Period IV—Taper

- 2-week taper prior to discontinuing IP, as outlined in Table 2, below.

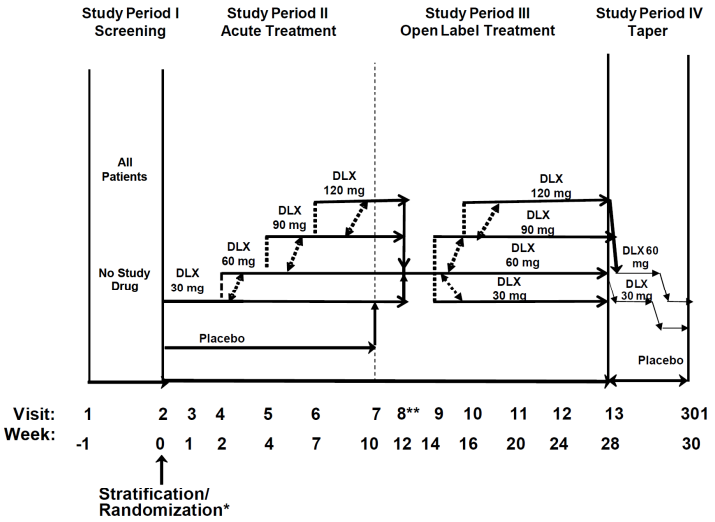
Table 2: HGMI Taper Schedule

Dose Prior to Taper	Taper Week 1 Dose	Taper Week 2 Dose
30 mg duloxetine (Visits 4-8)	Placebo	Placebo
30 mg duloxetine (After Visit 9)	no taper required	no taper required
60 mg duloxetine	30 mg QD	Placebo
90 mg duloxetine	60 mg QD	30 mg QD
120 mg duloxetine	60 mg QD	30 mg QD
Placebo (Study Period II only)	Placebo	Placebo

Abbreviation: QD = once daily.
(source: HGMI protocol, Table HGMI.9.4, page 35)

See Figure 1, below, for a schematic of the study design.

Figure 1. HGMI Study Design



Abbreviations: DLX=duloxetine
* Patients were stratified by age (children aged 7-11 years or adolescents aged 12-17 years) before randomization into the 2 treatment arms. Enrollment was monitored to achieve no less than 40% total complement of children.
** After Visit 8 and prior to Visit 9, if necessary due to tolerability, a dose decrease may have occurred at an unscheduled visit.

(source: HGMI clinical study report body, Figure HGMI.9.1, page 31)

Assessments

Efficacy Measures

- Pediatric Anxiety Rating Scale (PARS)
- Clinical Global Impression of Severity (CGI-S)
- Children's Global Assessment Scale (CGAS)

Efficacy Analyses

The primary efficacy endpoint was mean change from baseline to endpoint (10 weeks) as measured by the Pediatric Anxiety Rating Scale (PARS) severity rating score evaluated for symptoms identified on the generalized anxiety subsection of the PARS symptom checklist. The PARS was completed at every study visit.

The PARS is an interview-based scale, with both parents and children interviewed by a clinician. The PARS has 2 sections: a symptom checklist and seven severity/impairment/interference items. The symptom checklist is used to determine the child's repertoire of symptoms during the past week. This checklist includes six subsections (Social Interactions or Performance Situations; Separation; Generalized; Specific Phobia; Acute Physical Signs and Symptoms; Other) with a total of 50 symptoms. The primary efficacy measure for this study was the PARS severity rating for GAD. This score was derived by summing five of the seven severity/impairment/interference items (2, 3, 5, 6, and 7); the severity score ranged from 0 to 25. Items 1 (overall number of anxiety symptoms) and 4 (overall severity of physical symptoms) were not included in the severity score calculation. This method conforms to published instructions on PARS scoring for clinical trials.

Efficacy analyses were conducted on an ITT basis. The ITT analysis was an analysis of data by the groups to which patients were assigned by random allocation, even if the patient did not take the assigned treatment, did not receive the correct treatment, or did not follow the protocol. For each efficacy variable, the analysis included patients with baseline and post-baseline observations. However, as noted in Section 3.2 above, the nine subjects at Site 190 were excluded from the ITT population and all efficacy analyses due to breach of GCP.

The primary efficacy analysis was the contrast between duloxetine and placebo at the last visit in Study Period II (Visit 7, Week 10) from a MMRM analysis on change from baseline in the PARS severity score for GAD. The model for this analysis included the fixed, categorical effects of treatment, pooled investigator, visit, treatment-by-visit interaction, age category (children aged 7 through 11 years, adolescents aged 12 through 17 years), age category-by-visit interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction.

Determination of Sample Size

To detect an effect size of at least 0.37 between duloxetine and placebo at 80% power and a significance level of 0.05 (two-sided) using a two-sample t-test with equal allocation to treatment groups, the sponsor calculated that it was necessary to screen approximately 372 patients in order to enroll approximately 260 patients with approximately 130 randomized to each of 2 treatment arms (duloxetine or placebo). Allowing for 10% of patients to have missing postbaseline data, it was assumed that 117 patients per treatment arm would have at least 1 postbaseline assessment.

As noted above, some patients were enrolled despite not meeting the severity criteria for inclusion. The estimation of effect size and power above were based on the assumption that all randomized patients would have adequate severity of GAD symptoms at baseline in accordance with the study inclusion criteria. The sponsor assumed that the randomization of patients who did not meet the minimum GAD severity criteria at baseline would decrease the effect size. To ensure sufficient power for a decreased effect size, the number of enrolled patients could exceed 260 patients by approximately 10 to 15%; a total of 272 patients were enrolled.

Results

Demographics and Baseline Characteristics

The median age of the ITT population was 12.21 years. A total of 47.1% of patients were aged 7 through 11 years and 52.9% were aged 12 through 17 years. Among children (7 through 11 years), 52.3% were male and 47.7% were female. Among adolescents (12 through 17 years), 41.7% were male and 58.3% were female. A total of 49.7% of female patients had reached menarche at baseline. Overall, 46.7% of ITT patients were male (53.3% were female) and 82.0% of patients were White. The mean (SD) weight was 53.21 (23.519) kg, the mean height was 151.83 (16.033) cm, and the mean BMI was 22.28 (7.256) kg/m2. There were no statistically significant (p≤.05) differences between treatment groups for any of the baseline patient demographics (see Table 3, below).

Table 3: Patient Demographic Characteristics at Baseline, ITT Population, Double-Blind Treatment Phase (Study Period II)

	Duloxetine (N=135)	Placebo (N=137)	Total (N=272)	p-Value
Age (years)				
n	135	137	272	0.334*a
Mean (SD)	12.55(2.956)	12.20(2.904)	12.37(2.929)	
Median	12.21	12.21	12.21	
Minimum - Maximum	7.0 - 17.6	7.1 - 17.8	7.0 - 17.8	
Age Category (n (%))				
7-11 years	62(45.93)	66(48.18)	128(47.06)	0.717*b
12-17 years	73(54.07)	71(51.82)	144(52.94)	
Gender (n (%))				
Male	65(48.15)	62(45.26)	127(46.69)	0.715*b
Female	70(51.85)	75(54.74)	145(53.31)	
Achieved Menses Prior to Study Entry (n(%))*c	36(51.43)	36(48.00)	72(49.66)	0.741*b
Ethnicity (n (%))				
Hispanic or Latino	37(29.60)	40(31.25)	77(30.43)	0.786*b
Not Hispanic or Latino	88(70.40)	88(68.75)	176(69.57)	
Not Applicable	10	9	19	
Race (n (%))				
American Indian or Alaska Native	7 (5.19)	6 (4.38)	13 (4.78)	0.952*b
Asian	1 (0.74)	1 (0.73)	2 (0.74)	
Black or African American	9 (6.67)	10 (7.30)	19 (6.99)	
White	112(82.96)	111(81.02)	223(81.99)	
Multiracial	6 (4.44)	9 (6.57)	15 (5.51)	

Weight (kg)				
n	135	137	272	0.662*a
Mean (SD)	52.83(23.838)	53.59(23.282)	53.21(23.519)	
Median	47.80	52.20	50.20	
Minimum - Maximum	22.7 - 165.1	21.2 - 126.0	21.2 - 165.1	
Height (cm)				
n	135	137	272	0.966*a
Mean (SD)	151.79(16.130)	151.88(15.995)	151.83(16.033)	
Median	153.50	152.40	153.00	
Minimum - Maximum	102.0 - 189.0	116.5 - 188.0	102.0 - 189.0	
BMI (kg/m2)				
n	135	137	272	0.790*a
Mean (SD)	22.25(7.905)	22.31(6.583)	22.28(7.256)	
Median	19.99	21.31	20.83	
Minimum - Maximum	13.3 - 65.7	14.0 - 46.7	13.3 - 65.7	
Country (n (%))				
Mexico	26(19.26)	26(18.98)	52(19.12)	>.999*b
South Africa	11 (8.15)	12 (8.76)	23 (8.46)	
United States	98(72.59)	99(72.26)	197(72.43)	

Abbreviation: cm = centimeter; kg = kilogram; kg/m2 = kilogram per square meter; N = number of randomized patients in each treatment group; n= number of patients in the specified category.
Note: Percentage and p-value calculations exclude patients who did not provide answer.
*a: From ANOVA model including terms: treatment and pooled investigator.
*b: From Fisher's exact test.
*c The denominator is Female only.

(source: HGMI clinical study report body, page 88-89)

Patients also had similar baseline clinical characteristics (see

Table 4, below). More than half of the patients in each treatment group (>59%) did not have a previous diagnosis of GAD, and a large majority (>90%) of patients in each treatment group did not have a previous diagnosis of social anxiety disorder or separation anxiety disorder. Among patients with a previous diagnosis of GAD, the mean duration of time since the previous GAD diagnosis was 2.4 years in both treatment groups. The mean time since the first observation of any anxiety symptoms that caused significant distress or impairment was 4.2 years for the duloxetine group and 4.5 years for the placebo group. There were no statistically significant ($p \leq .05$) differences for any baseline illness characteristics between groups. In addition, there were no statistically significant differences between treatment groups with regard to percentage of patients reporting any specific historical illnesses, or family psychiatric history. With the exception of exercise-induced asthma in 4.4% of patients randomized to duloxetine and 0% of patients randomized to placebo ($p=.014$), there were no statistically significant differences between treatment groups with regard to the percentage of patients reporting with preexisting conditions. No patients reported current alcohol use, and 1 patient reported current tobacco use at baseline.

Table 4: Psychiatric History, ITT Population, Double-Blind Treatment Phase (Study Period II)

Variable	Duloxetine (N=135) n(%)	Placebo (N=137) n(%)	p-Values
Previous Diagnosis of GAD			
Yes	47(34.81)	55(40.15)	0.383*a
No	88(65.19)	82(59.85)	
Previous Diagnosis of Social Anxiety Disorder			
Yes	3 (2.22)	10 (7.30)	0.085*a
No	132(97.78)	127(92.70)	
Previous Diagnosis of Separation Anxiety			
Yes	5 (3.70)	5 (3.65)	>.999*a
No	130(96.30)	132(96.35)	
Time Since Previous Diagnosis of GAD (years)			>.999*b
Number of Patients n (%)	47 (34.8)	55 (40.1)	
Mean (SD)	2.4 (2.66)	2.4 (2.51)	
Median	1.5	1.4	
Minimum-Maximum	0 - 10	0 - 10	
Time Since Previous Diagnosis of Social Anxiety (years)			0.983*b
Number of Patients n (%)	3 (2.2)	10 (7.3)	
Mean (SD)	1.2 (1.40)	3.2 (3.23)	
Median	0.4	2.3	
Minimum-Maximum	0 - 3	0 - 11	
Time Since Previous Diagnosis of Separation Anxiety (years)			0.459*b
Number of Patients n (%)	5 (3.7)	5 (3.6)	
Mean (SD)	3.6 (2.28)	4.6 (4.44)	
Median	4.1	2.7	
Minimum-Maximum	0 - 6	1 - 11	
Time Since First Observation of any Anxiety Symptom (years) that Caused Significant Distress or Impairment			0.431*b
Number of Patients n (%)	135 (100.0)	137 (100.0)	
Mean (SD)	4.2 (2.96)	4.5 (2.93)	
Median	3.7	4.1	
Minimum-Maximum	0 - 16	0 - 13	

Abbreviation: GAD = generalized anxiety disorder; N = number of randomized patients in each treatment group; n= number of patients in the specific category.
*a: From Fisher's Exact test.
*b: From ANOVA model including terms: treatment and pooled investigator.

(source: HGMI clinical study report body, page 90-91)

Baseline severity of illness as measured by PARS GAD Severity score, CGI-S score, and CGAS score is summarized in Table 5, below. The mean PARS GAD Severity score at baseline was 17.4 (median 17.0), and the mean CGI-S score at baseline was 4.5 (median 4.0), indicating moderate severity of illness, on average, at baseline. A total of 13 patients were randomized without meeting baseline severity criteria on the PARS GAD severity, and 1 patient was randomized without meeting baseline severity criteria on the CGI-S. The mean CGAS raw score at baseline was 49 (median 50), indicating, on average, “a moderate degree of impairment in most social areas of functioning” in the study population. There were no statistically significant (p≤.05) differences for baseline severity of illness between treatment groups for any of the baseline severity measures. Approximately 19% of patient population had separation anxiety disorder and approximately 18% of the patient population had social anxiety disorder at baseline based on clinical examination. There were no statistically significant differences between treatment groups in the proportion of patients with separation anxiety disorder; however, there was a statistically significantly (p=.038) greater proportion of patients with social anxiety disorder in the placebo group (23%) compared with the duloxetine group (13%).

Table 5: Baseline Illness Characteristics and Current Medical Status, ITT Population, Double-Blind Treatment Phase (Study Period II)

Variable	Duloxetine (N=135)	Placebo (N=137)	Total (N=272)	p-Values
Baseline Severity of Illness				
Baseline PARS Severity Total Score				
Number of Patients n (%)	135	137	272	0.516*a
Mean (SD)	17.3 (2.24)	17.2 (2.36)	17.2 (2.30)	
Median	17.0	17.0	17.0	
Minimum-Maximum	11 - 24	10 - 24	10 - 24	
PARS Severity Score for GAD				
Number of Patients n (%)	135	137	272	0.547*a
Mean (SD)	17.5 (1.98)	17.4 (2.25)	17.4 (2.12)	
Median	17.0	17.0	17.0	
Minimum-Maximum	13 - 23	10 - 24	10 - 24	
CGAS Raw Score				
Number of Patients n (%)	135	137	272	0.886*a
Mean (SD)	48.8 (5.88)	48.6 (6.06)	48.7 (5.96)	
Median	50.0	50.0	50.0	
Minimum-Maximum	35 - 60	30 - 60	30 - 60	
CGAS Transformed Score				
Number of Patients n (%)	135	137	272	0.905*a
Mean (SD)	5.2 (0.70)	5.2 (0.65)	5.2 (0.68)	
Median	5.0	5.0	5.0	
Minimum-Maximum	4 - 6	3 - 6	3 - 6	
CGI-S Score				
Number of Patients n (%)	135	137	272	0.762*a
Mean (SD)	4.5 (0.66)	4.5 (0.62)	4.5 (0.64)	
Median	4.0	4.0	4.0	
Minimum-Maximum	3 - 6	4 - 6	3 - 6	
Current Medical Status				
Generalized Anxiety Disorder				
Number of Patients n (%)	135 (100)	137 (100)	272 (100)	
Yes	135 (100)	137 (100)	272 (100)	
Separation Anxiety Disorder				
Number of Patients n (%)	135 (100)	137 (100)	272 (100)	0.214*b
Yes	21(15.56)	30(21.90)	51(18.75)	
No	114(84.44)	107(78.10)	221(81.25)	
Social Anxiety Disorder				
Number of Patients n (%)	135 (100)	137 (100)	272 (100)	0.038*b
Yes	17(12.59)	31(22.63)	48(17.65)	
No	118(87.41)	106(77.37)	224(82.35)	

Abbreviation: CGAS = children's global assessment scale; CGI-S = clinical global impressions of severity; GAD = generalized anxiety disorder; ITT = intent-to-treat; PARS = pediatric anxiety rating scale; SD = standard deviation.
*a: From ANOVA model including terms: treatment and pooled investigator.
*b: From Fisher's Exact test.

(source: HGMI clinical study report body, page 92-93)

Subject Disposition

Of the 281 randomized subjects, 272 subjects were included in the Intent-to-Treat (ITT) population; because of a major quality issue at Site 190, all nine randomized patients from the site were excluded from the ITT population.

Several sensitivity analyses (a total of 4) were performed to address the impact of different patient populations on the results of the primary analysis. These sensitivity analyses were conducted specifically to assess the impact of patients not meeting the PARS severity for GAD study inclusion criteria (N = 13), as well as the impact of patients from Site 190 with significant quality issues (N = 9). The results of all 4 of these sensitivity analyses were consistent with the primary analysis. See

Table 6 below for additional details related to these analyses.

Table 6: Summary of Primary and Sensitivity Analyses Population

Primary and Sensitivity Analyses	Group 1 Number of original randomized patients, excluding 9 patients from Site 190 and 13 patients with PARS severity score for GAD <15 at Visits 1 or 2 (N = 238)*	Group 2 9 patients from Site 190 (N = 9)*	Group 3 13 patients with PARS severity score for GAD <15 at Visits 1 or 2 (N = 13)*	Group 4 9 patients randomized with randomization date ordered at 261st to 269th (N = 9)*	Group 5 12 last randomized patients (N = 12)*
Primary analyses (ITT population) (N = 272)*	Included	Not Included	Included	Included	Included
Sensitivity analyses with selection model (ITT population) (N = 272)*	Included	Not Included	Included	Included	Included
Sensitivity Analysis 1 (N = 259)*	Included	Not Included	Not Included	Included	Included
Sensitivity Analysis 2 (N=281)*	Included	Included	Included	Included	Included
Sensitivity Analysis 3 (N = 251)*	Included	Not Included	Included	Not Included	Not Included
Sensitivity Analysis 4 (N = 260)*	Included	Not Included	Included	Included	Not Included

Abbreviations: GAD = generalized anxiety disorder; ITT = intent-to-treat population; N = total number of patients; PARS = Pediatric Anxiety Rating Scale.
*Note, the capital Ns in this table only account for randomized patients; however, in the real analyses, only randomized patients with nonmissing baseline and at least 1 postbaseline measure were included.

(source: HGMI clinical study report body, Figure HGMI.9.1, page 63)

A total of 77.0 % of duloxetine-treated patients completed Study Period II compared with 77.4% for placebo. The most common reasons that patients discontinued the study were as follows: withdrawal by patient (5.9%); AE (4.8%); parent or caregiver decision (4.0%); protocol violation (3.7%); lost to follow-up (3.3%); and lack of efficacy (1.1%). Overall, there were no statistically significant ($p \leq .05$) differences for treatment discontinuation for duloxetine-treated patients compared with placebo-treated patients.

This was an international multicenter study with most patients enrolled from the US (72.4%) followed by Mexico (19.1%), and South Africa (8.5%).

Concomitant Treatment

Concomitant therapies with reported frequency ≥2% of patients were: ibuprofen (19.1%); paracetamol (18.8%); loratadine (5.5%); EMLA (5.2%); amoxicillin (4.4%); azithromycin (4.4%); cetirizine (4.4%); salbutamol (4.0%); all other therapeutic products (3.7%), which included counseling, and other nonpharmacologic psychiatric or psychological therapy; fluticasone (3.7%); diphenhydramine (2.9%); multivitamins (2.9%); bismuth (2.6%); and montelukast (2.2%). With the exception of salbutamol used by 6.7% of patients randomized to duloxetine and 1.5% of patients randomized to placebo (p=.034), there were no statistically significant differences between groups for reported concomitant therapies.

Important Protocol Violations

Of the 272 patients in the ITT population, 77 (28%) had at least one protocol violation; this includes 39 (29%) of the duloxetine-treated patients and 38 (28%) patients who received placebo. The most frequent protocol deviations were: (1) key measurements not collected; (2) visit interval outside specified limits; and (3) protocol inclusion/exclusion criteria violations. There were no statistically significant ($p \leq .05$) differences in the number of significant protocol violations for duloxetine-treated patients compared with placebo-treated patients (see Table 7, below).

Table 7: Summary of Significant Protocol Violations, ITT Population, Double-Blind Treatment Phase

Important Protocol Violation	Duloxetine (N=135) n (%)	Placebo (N=137) n (%)	Total (N=272) n (%)	p-Value*a
Patients with >=1 Protocol Violation	39 (0.29)	38 (0.28)	77 (0.28)	0.984
Key measurements not collected	17 (0.13)	15 (0.11)	32 (0.12)	0.910
Study visit interval outside specified limits	11 (0.08)	13 (0.09)	24 (0.09)	0.941
Protocol inclusion/exclusion criteria violations	9 (0.07)	13 (0.09)	22 (0.08)	0.688
Prohibited concomitant medications	5 (0.04)	8 (0.06)	13 (0.05)	0.701
Study Drug Non-Compliance	5 (0.04)	1 (0.01)	6 (0.02)	0.252
Discontinuation due to protocol violation*b	1 (0.01)	1 (0.01)	2 (0.01)	>.999
Improper administration of ICF	0 (0.00)	0 (0.00)	0 (0.00)	

Abbreviation: ITT = intent-to-treat.
*a: From Fisher's exact test.
*b: This category only captures the patients who reported "discontinued due to protocol violation" in the disposition eCRF at a visit other than the visit that protocol violation actually happened .
(source: HGMI clinical study report body, Table HMGI.10.2, page 83)

With regard to the deviation of "key measurements not collected," this includes patients with missing measurements at the discontinuation visit, even if the patients were discontinued without completing study procedures for documented reasons such as withdrawal of consent. Of the 32 patients with deviations related to key measurements not collected, about half were included due to missing procedures at the discontinuation visit when the patients were discontinued without completing study procedures.

Efficacy Findings

The primary objective for Study HMGI was to assess the efficacy of duloxetine in the treatment of pediatric patients with GAD, based on the mean change from baseline to endpoint on the Pediatric Anxiety Rating Scale (PARS) severity score for GAD. The primary efficacy analysis was the contrast between duloxetine and placebo at the last visit in Study Period II (Visit 7, Week 10) from a Mixed-effects and model repeated measures (MMRM) analysis on change from baseline in the PARS severity score for GAD. The model for this analysis included the fixed, categorical effects of treatment, pooled investigator, visit, treatment-by-visit interaction, age category (children aged 7 through 11 years, adolescents aged 12 through 17 years), age category-by-visit interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. Mean PARS severity scores for GAD at baseline were similar

across groups. Mean improvement in GAD symptom severity was observed for both treatment groups over the 10-week course of acute treatment. Statistically significantly greater improvement for the duloxetine group compared with the placebo group started at Week 2 (p=.012) and continued to endpoint with p<.001 at Week 10. The observed effect size [LSMean change difference/standard deviation (SD) estimate] at Visit 7 (Week 10) was 0.50. See

Table 8 and

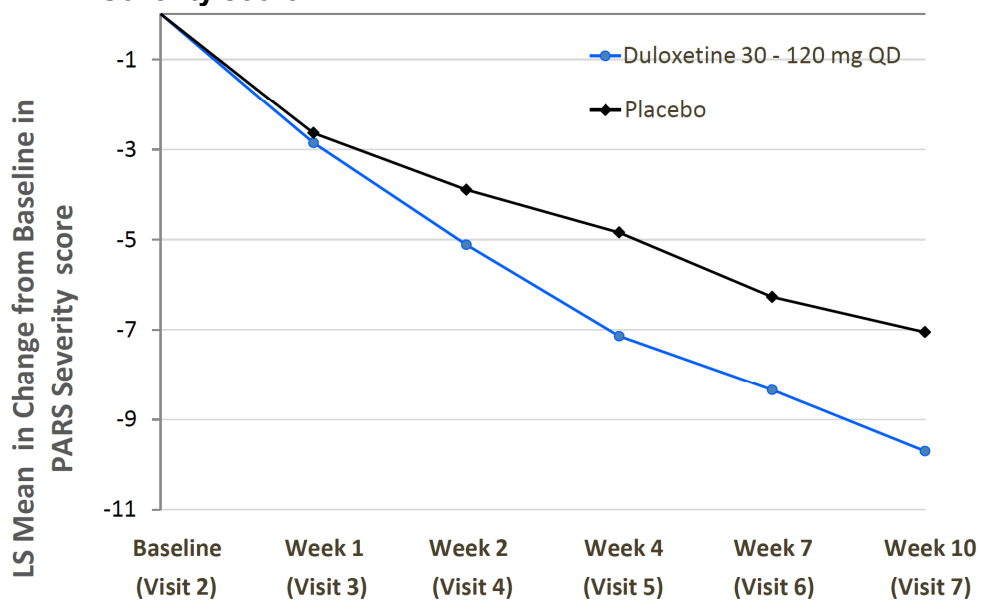
Figure 2 below.

Table 8: Change from Baseline in PARS Severity Score for Generalized Anxiety Disorder Repeated Measures Analysis–ITT Population, Double-Blind Treatment Phase

			MMRM Analysis Results					
Visit (Week)	Treatment	N	LS Mean*a	LS Mean Change (SE)*b	Within Group p-value*b,c	LS Mean Change Difference (SE)*b	95% CI for Difference*b	p-value*b
3 (1)	Duloxetine	135	14.67	-2.85 (0.306)	<0.001	-0.22 (0.421)	(-1.05, 0.61)	0.605
	Placebo	133	14.89	-2.63 (0.307)	<0.001			
4 (2)	Duloxetine	130	12.41	-5.11 (0.349)	<0.001	-1.22 (0.485)	(-2.18, -0.27)	0.012
	Placebo	127	13.63	-3.89 (0.351)	<0.001			
5 (4)	Duloxetine	121	10.38	-7.14 (0.405)	<0.001	-2.30 (0.561)	(-3.40, -1.19)	<0.001
	Placebo	124	12.68	-4.84 (0.400)	<0.001			
6 (7)	Duloxetine	117	9.18	-8.34 (0.455)	<0.001	-2.07 (0.634)	(-3.32, -0.82)	0.001
	Placebo	117	11.25	-6.27 (0.453)	<0.001			
7 (10)	Duloxetine	107	7.82	-9.70 (0.502)	<0.001	-2.65 (0.700)	(-4.03, -1.27)	<0.001
	Placebo	108	10.47	-7.05 (0.500)	<0.001			
Overall	Duloxetine	135	10.89	-6.63 (0.312)	<0.001	-1.69 (0.428)	(-2.54, -0.85)	<0.001
	Placebo	133	12.58	-4.94 (0.311)	<0.001			

Abbreviation: CI = confidence interval; ITT = intent-to-treat; LS = least square; MMRM = mixed model repeated measure; N = number of patients in each treatment group with a baseline and post-baseline result in each treatment group at the specific visit; PARS = pediatric anxiety rating scale; SE = standard error.
Note: Baseline is defined as the last nonmissing value at 1<=Visit<=2.
*a. LS Means are from the MMRM model: Score = Treatment + Pooled investigator + Visit + Baseline + Age category +Treatment*Visit + Baseline*Visit + Age category*Visit; Covariance structure = Unstructured; Denominator degrees of freedom were estimated using the Kenward - Roger method.
*b: From the MMRM model: Change = Treatment + Pooled investigator + Visit + Baseline + Age category +Treatment*Visit + Baseline*Visit + Age category*Visit; Covariance structure = Unstructured; Denominator degrees of freedom were estimated using the Kenward - Roger method.
*c: Within group p-values are from t-tests of LS Mean change from the MMRM model of *b.
(source: HGMI clinical study report body, Table HMGI.11.5, page 100)

Figure 2: Duloxetine 30 - 120 mg QD versus Placebo: Visit-wise efficacy profile in PARS Severity score



Note: Week 10 is the efficacy endpoint.

(source: analyses conducted by Eiji Ishida, MS)

6.1.3 Cross-Cutting Issues

Subgroup Analyses

Age

The treatment-by-age category interaction was not statistically significant. In the subgroup of children (aged 7 through 11 years), the LSMean improvement for the duloxetine treatment group was statistically significantly greater than the LSMean improvement in the placebo treatment group (p=.002). In the subgroup of adolescents (aged 12 through 17 years), the LSMean improvement for the duloxetine treatment group was greater than the LSMean improvement in the placebo treatment group; however, the difference was not statistically significant (p=.100).

Sex

The treatment-by gender interaction was not statistically significant. In the subgroup of males, the LSMean improvement for the duloxetine treatment group was statistically significantly greater than the LSMean improvement in the placebo treatment group (p=.005). In the subgroup of females, the LSMean improvement for the duloxetine treatment group was greater than the LSMean improvement in the placebo treatment group; however, the difference was not statistically significant (p=.060).

Baseline Severity of Illness

The treatment-by-baseline severity interaction was not statistically significant. In the subgroup of patients with high baseline GAD severity (PARS severity for GAD score

≥median), the LSMean improvement for the duloxetine treatment group was statistically significantly greater than the LSMean improvement in the placebo treatment group (p<.001). In the subgroup of patients with low baseline GAD severity (PARS severity for GAD score <median), the LSMean improvement for the duloxetine treatment group was greater than the LSMean improvement in the placebo treatment group; however, the difference was not statistically significant (p=.071).

Race and Ethnicity
The treatment-by-race and treatment-by-ethnicity interactions were not statistically significant. In the subgroup of White patients, the LSMean improvement for the duloxetine treatment group was statistically significantly greater than the LSMean improvement in the placebo treatment group (p=.003). In the subgroup of all other races combined, the LSMean improvement for the duloxetine treatment group was greater than the LSMean improvement in the placebo treatment group; however, the difference was not statistically significant (p=.106).

In the subgroup of Hispanic or Latino patients, the LSMean improvement for the duloxetine treatment group was statistically significantly greater than the LSMean improvement in the placebo treatment group (p=.004). In the subgroup of Non-Hispanic or Latino patients, the LSMean improvement for the duloxetine treatment group was statistically significantly greater than the LSMean improvement in the placebo treatment group (p=.020).

Region
The treatment- by-country interaction was not statistically significant. In the subgroup of patients from the US, the LSMean improvement for the duloxetine treatment group was statistically significantly greater than the LSMean improvement in the placebo treatment group (p=.004). In the subgroup of patients from Mexico, the LSMean improvement for the duloxetine treatment group was statistically significantly greater than the LSMean improvement in the placebo treatment group (p=.037). In the subgroup of patients from South Africa, the LSMean improvement for the duloxetine treatment group was greater than the LSMean improvement in the placebo treatment group; however, the difference was not statistically significant (p=.138).

6.1.4 Conclusions Regarding Efficacy Claim

Results of the primary efficacy analysis show that the duloxetine treatment group demonstrated a statistically significant difference from placebo in the overall main effect of treatment analysis (p<.001). Although some subgroup analyses appear to suggest that duloxetine may be more likely to be effective in certain demographic groups, these analyses were not pre-specified, and were not adequately powered to draw any definitive conclusions.

7 Review of Safety

Safety Summary

In general, the safety profile of duloxetine as demonstrated in study HMGI is similar to the overall safety profile described in the original NDA review and in current labeling.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This safety review is focused on the safety of duloxetine for the treatment of pediatric patients with generalized anxiety disorder (GAD) as derived from study HMGI. All safety analyses were based on the intent-to-treat (ITT) population.

Study HMGI consisted of a double-blind acute treatment period and an open-label extension. Site 190 was excluded from all analyses due to quality issues at that site. For the double-blind period, 281 patients were randomized, all 9 patients from Site 190 were excluded, leaving an ITT population of 272 patients for the safety analyses. Of those patients, 210 entered the open-label extension.

The sponsor submitted safety analyses for the acute treatment and open-label phases both separately and combined, as well as an Integrated Summary of Safety (ISS) which includes data from 822 pediatric patients (age 7-17 years) exposed to duloxetine in four completed clinical trials [F1JMC-HMFN (HMFN), F1J-MC-HMCK (HMCK), F1J-MC-HMCL (HMCL), and F1J-MCHMGI (HMGI)]. The data cut-off date for the ISS was August 16, 2013.

Given that one cannot draw meaningful safety conclusions from an open-label study, this safety review is focused on the data derived from the acute treatment phase of Study HMGI, as well as the pooled data from the acute treatment phase of HMCK, HMCL, and HMGI. However, information regarding adverse events at the more serious end of the spectrum (deaths, non-fatal serious adverse events, and adverse events that led to dropout) from the open-label phase of Study HMGI was also examined.

7.1.2 Categorization of Adverse Events

The JMP files for adverse events were reviewed with an emphasis on the verbatim to preferred term coding. In general, it appeared that most verbatim terms were appropriately coded to preferred terms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

See 7.1.1

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In adults, the safety and efficacy of duloxetine for the acute treatment of generalized anxiety disorder (GAD) in doses ranging from 60mg to 120mg daily was established in one 9-week and two 10-week trials in adults, ages 18-83 years. Maintenance efficacy was demonstrated in a randomized withdrawal trial (26 weeks of open-label treatment followed by 10 weeks of double-blind treatment). In this supplement, the sponsor is proposing to expand the approved GAD patient population to include children and adolescents ages 7-17 years.

This supplement includes new data from a single study, Study HMGI. All safety analyses were conducted on the Intent to Treat (ITT) population, which included 272 pediatric patients, ages 7-17 years, 135 of whom were exposed to duloxetine in doses up to 120mg daily for up to 10 weeks. Following the acute treatment phase, this trial also included a 16-week open-label extension phase and a 2-week taper phase.

In addition to the pediatric data submitted in this supplement, the sponsor previously submitted data from a Phase 2 open-label pharmacokinetic (PK) study (HMFN) and two 10-week placebo-controlled trials (HMCL and HMCK) in children and adolescents, ages 7-17 years, with major depressive disorder (MDD). The maximum dose in each of these trials was also 120mg daily. Thus, the primary placebo-controlled population includes 475 pediatric patients exposed to duloxetine in two MDD trials and one GAD trial. The integrated pediatric safety database (three placebo-controlled trials, three open-label extensions, one PK trial) consists of 822 pediatric patients exposed to duloxetine (see Table 9, below).

Table 9: Patients Included in the Pediatric Safety Population Datasets

Datasets	Placebo N	Duloxetine N	Total N
Primary Placebo-Controlled Population (10-weeks [HMCK, HMCL, HMGI])			
Overall (7-17 years)	362	476	838
Children (7-11 years)	153	202	355
Adolescents (12-17 years)	209	274	483
GAD Placebo-Controlled Population (10-weeks [HMGI])			
Overall (7-17 years)	137	135	272
Children (7-11 years)	66	62	128
Adolescents (12-17 years)	71	73	144
Overall Exposure Population (treatment up to 36 weeks [HMFN, HMCK, HMCL, HMGI])			
Overall (7-17 years)	n/a	822	822
Children (7-11 years)	n/a	343	343
Adolescents (12-17 years)	n/a	479	479

(source: Table 2.7.4.3, Summary of Clinical Safety, page 15.)

The mean duloxetine total dispensed dose was 53.6mg. The last prescribed dose for duloxetine patients during Study Period II was 30mg (27.4% of patients), 60mg (30.4%), 90mg (29.6%), and 120mg (12.6%). During Study Period II, the modal dose (most frequently prescribed dose) for duloxetine was 30mg (35.6%), 60mg (34.8%), 90mg (20.7%), and 120mg (8.9%).

Among children (aged 7 through 11 years), the mean duloxetine total dispensed dose was 50.3mg, and among adolescents (aged 12 through 17 years), the mean duloxetine total dispensed dose was 56.4mg.

7.2.2 Explorations for Dose Response

The flexible-dose design of this study precludes any meaningful dose-response conclusions.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

The clinical trials programs included usual routine clinical testing at screening, baseline, at various time points during studies and at the end of study.

Clinical monitoring of adverse events, vital signs (with height at Visits 2, 7, and 13), Columbia Suicide Severity Rating Scale, and concomitant medications were assessed at every study visit. Additional safety assessments included ECGs (Visits 6, 7, and 10), hematology and clinical chemistry (Visits 5, 7, 9, 11, and 13), and urinalysis and hemoglobin A1c (Visits 7 and 13). Physical exam, medical and psychiatric history, pregnancy test, TSH, and urine drug screen were assessed only at Visit 1 during the Screening Period.

7.2.5 Metabolic, Clearance, and Interaction Workup

None.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Some of the relevant safety issues for the SNRI antidepressants include suicidal ideation and behavior, serotonin syndrome, hypertension, activation of mania, and discontinuation syndrome. The clinical trials included appropriate assessments for these adverse events.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in Study HMGI.

7.3.2 Nonfatal Serious Adverse Events

Acute Treatment
One adolescent male patient (130-01308) experienced two serious adverse events (SAEs) during the study. This patient experienced suicidal ideation and self-injurious behavior, both of which were deemed related to the study drug. The patient had a prior history of attempted overdose (eight ibuprofen), as well as wish to be dead/non-specific suicidal ideation at baseline. The patient began experiencing suicidal ideation 20 days after starting duloxetine. The suicidal ideation lasted 6 days, and then the patient experienced self-injurious ideation 26 days after starting duloxetine. During an argument with his father, the patient picked up a knife, pointed it towards his chest, and said that he should kill himself. The patient was taking duloxetine 60 mg at the time of both events. Study drug was stopped, and the patient was discontinued from the study 1 day after the event of self-injurious ideation.

Open-Label Extension
One male child (250-2502) experienced the SAE of acute psychosis during Study Period III after transitioning from placebo to duloxetine. The patient began experiencing suicidal ideation and psychosis 33 days after starting duloxetine (approximately 2 days after a dose increase to 90 mg), and made several suicide attempts (two aborted, one interrupted). He had no prior history of suicidal ideation or behavior, psychiatric hospitalization, bipolar disorder, or substance abuse. The patient was hospitalized and discontinued from the study due to the AE of suicidal ideation.

One female adolescent (370-3702) experienced the SAE of bipolar disorder during Study Period III after transitioning from placebo to duloxetine, 92 days after starting duloxetine and while the patient was taking 30 mg daily. The patient began exhibiting bizarre behavior and was hospitalized. The patient had a history of sleep disorder, attention deficit hyperactivity disorder combined type, and oppositional defiant disorder. She was discontinued from the study due to the SAE of bipolar disorder.

One male adolescent (280-2808) experienced the SAE of suicidal ideation during Study Period III, 173 days after starting duloxetine and while the patient was taking 60 mg daily. The suicidal ideation occurred after a dose reduction from 90 mg QD to 60 mg QD due to irritability. The patient had not experienced suicidal ideation during the study prior to the SAE and did not have a history of previous suicidal behavior/attempts. The patient was discontinued from Study Period III due to the SAE of suicidal ideation.

One male adolescent (340-3413) experienced two SAEs of severe tonsillitis and severe adenoiditis during Study Period III, four days after stopping duloxetine. This patient

received duloxetine during both Study Period II and III. He was hospitalized and discontinued from Study Period III due to the SAE of severe adenoiditis.

Taper
One male adolescent (280-2803) experienced the SAE of suicidal ideation during Study Period IV after discontinuing duloxetine treatment in Study Period III due to the AE of apathy. The SAE of suicidal ideation occurred one day after discontinuing duloxetine and while the patient was taking placebo. The patient did not have a history of suicidal ideation or previous suicidal behavior/attempts.

7.3.3 Dropouts and/or Discontinuations

Acute Treatment
Thirteen subjects were discontinued from investigational product due to an AE [7 (5.2%) patients in the duloxetine treatment group, 6 (4.4%) patients in the placebo treatment group]. Treatment-emergent adverse events within the duloxetine group that led to discontinuation of investigational product were nausea (2 patients), vomiting, pharyngeal inflammation, somnolence, and vaginal hemorrhage (1 patient each), as well as the SAEs noted above.

One female child (110-01106) discontinued from the study due to nausea with moderate severity which began 33 days after starting duloxetine. The duloxetine dose was 60 mg at the time of the event. In the opinion of the investigator, the nausea was possibly related to the study drug.

One female adolescent (140-1402) discontinued from the study due to nausea with moderate severity which began 2 days after starting duloxetine. The duloxetine dose was 30 mg at the time of the event. In the opinion of the investigator, the nausea was possibly related to the study drug.

One female adolescent (170-1700) discontinued from the study due to somnolence with moderate severity which began 28 days after starting duloxetine. The duloxetine dose was 60 mg at the onset of the event and was increased to 90 mg and the event persisted. In the opinion of the investigator, the somnolence was possibly related to the study drug.

One female child (280-2802) discontinued from the study due to severe vomiting which began 45 days after starting duloxetine. The duloxetine dose was 30 mg at the time of the event. In the opinion of the investigator, the vomiting was possibly related to the study drug.

One female adolescent (290-2913) discontinued from the study due to pharyngeal inflammation with moderate severity which began 27 days after starting duloxetine. The duloxetine dose was 60 mg at the time of the event. In the opinion of the investigator, the pharyngeal inflammation was not related to the study drug.

One female child (360-3614) discontinued from the study due to vaginal hemorrhage (actual term: vaginal bleeding) with mild severity. The child had not reached menarche prior to entering the study, and experienced vaginal bleeding which began 10 days after starting duloxetine. The duloxetine dose was 30 mg at the time of the event. The vaginal bleeding resolved after stopping the study drug. In the opinion of the investigator, the vaginal hemorrhage was possibly related to the study drug. The patient recovered from the event after stopping duloxetine, and prior to discontinuing from the study.

Open-Label Extension
A total of 15 patients discontinued the study due to an AE [8 (7.7%) patients in the DLX/DLX group, 7 (6.6%) patients in the PLA/DLX group]. The only AEs that led to discontinuation in more than one patient during Study Period III were suicidal ideation [3 (1.4%) patients] and nausea [2 (1.0%) patients]. The SAEs leading to discontinuation are described in 7.3.2, above. Other AEs leading to discontinuation, each in a single patient, include irritability, upper abdominal pain, blepharospasm, fatigue, dyspepsia, abnormal behavior, and initial insomnia.

7.3.4 Significant Adverse Events

Except as noted above, no other clinically significant adverse events were reported.

7.3.5 Submission Specific Primary Safety Concerns

Antidepressants carry a boxed warning for suicidal ideation and behavior in children, adolescents, and young adults. Reports of suicidal ideation and behavior in study HGMI are reviewed in 7.3.2 above, and 7.7.1 below.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common (>5% and 2x placebo) AEs in HGMI included nausea (20.7%), vomiting (16.3%), decreased appetite (14.8%), dizziness (7.4%), and oropharyngeal pain (7.4%); in the pediatric primary placebo-controlled population, the most common AEs were nausea (18.3%), dizziness (8.2%), and diarrhea (5.9%). The labeled most common AEs (derived from adult placebo-controlled trials) include nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.

All common AEs (≥2%) in the pediatric primary placebo-controlled population are presented in

Table 10, below. Those that occurred in a statistically significantly greater proportion of duloxetine-treated patients are presented in Table 11.

Table 10: Treatment-Emergent Adverse Events Occurring in ≥2% of Duloxetine-Treated Pediatric Patients, Primary Placebo-Controlled Population, Ages 7-17 years.

MedDRA Preferred Term	Duloxetine	Placebo	p-value
Overall (ages 7 – 17 years)	**N = 476**	**N = 362**	
Headache	85 (17.9%)	48 (13.3%)	.062
Nausea	87 (18.3%)	30 (8.3%)	<.001
Decreased appetite	46 (9.7%)	18 (5.0%)	.005
Vomiting	41 (8.6%)	16 (4.4%)	.005
Abdominal pain upper	40 (8.4%)	25 (6.9%)	.507
Dizziness	39 (8.2%)	13 (3.6%)	.011
Somnolence	37 (7.8%)	21 (5.8%)	.191
Fatigue	30 (6.3%)	15 (4.1%)	.125
Diarrhoea	28 (5.9%)	10 (2.8%)	.026
Insomnia	24 (5.0%)	13 (3.6%)	.190
Oropharyngeal pain	18 (3.8%)	7 (1.9%)	.080
Influenza	15 (3.2%)	11 (3.0%)	.769
Nasopharyngitis	13 (2.7%)	20 (5.5%)	.064
Upper respiratory tract infection	13 (2.7%)	11 (3.0%)	.655
Cough	12 (2.5%)	3 (0.8%)	.087
Dysmenorrhoea [a]	6 (2.5%)	5 (2.6%)	.933
Abdominal discomfort	11 (2.3%)	5 (1.4%)	.269
Sedation	11 (2.3%)	0 (0.0%)	.005
Irritability	10 (2.1%)	10 (2.8%)	.616
Dry mouth	10 (2.1%)	3 (0.8%)	.173

[a] % based on denominator of female patients
(source: Table 2.7.4.9, Summary of Clinical Safety, pages 32)

Table 11: Treatment-Emergent Adverse Events Occurring in a Statistically Significantly Greater Proportion of Duloxetine-Treated Pediatric Patients, Primary Placebo-Controlled Population.

MedDRA Preferred Term	Duloxetine	Placebo	p-value
Overall (ages 7 – 17 years)	**N = 476**	**N = 362**	
Nausea	87 (18.3%)	30 (8.3%)	<.001
Decreased appetite	46 (9.7%)	18 (5.0%)	.005
Vomiting	41 (8.6%)	16 (4.4%)	.005
Dizziness	39 (8.2%)	13 (3.6%)	.011
Diarrhoea	28 (5.9%)	10 (2.8%)	.026
Sedation	11 (2.3%)	0 (0.0%)	.005
Hyperhidrosis	8 (1.7%)	1 (0.3%)	.041
Weight decreased	7 (1.5%)	1 (0.3%)	.049
Palpitations	7 (1.5%)	0 (0.0%)	.010
Nightmare	5 (1.1%)	0 (0.0%)	.047
Children (ages 7 – 11 years)	**N = 202**	**N = 153**	
Nausea	36 (17.8%)	11 (7.2%)	.002
Decreased appetite	26 (12.9%)	9 (5.9%)	.009
Vomiting	22 (10.9%)	6 (3.9%)	.004
Diarrhoea	16 (7.9%)	3 (2.0%)	.027
Weight decreased	4 (2.0%)	0 (0.0%)	.037
Adolescents (ages 12 – 17 years)	**N = 274**	**N = 209**	
Headache	56 (20.4%)	25 (12.0%)	.013
Nausea	51 (18.6%)	19 (9.1%)	.005
Dizziness	26 (9.5%)	9 (4.3%)	.037
Anxiety	6 (2.2%)	0 (0.0%)	.034
Pharyngitis	5 (1.8%)	0 (0.0%)	.037
Palpitations	4 (1.5%)	0 (0.0%)	.046

(source: Table 2.7.4.10, Summary of Clinical Safety, pages 33)

7.4.2 Laboratory Findings

No clinically meaningful trends were observed in laboratory results over time in Study HMGI. However, statistically significant within-group baseline to endpoint changes were observed in the duloxetine and placebo treatment groups for some laboratory analytes (see Table 12, below). No patient had an SAE related to abnormal laboratory values or discontinued Study Period II due to abnormal laboratory values. No patient in the study had a treatment-emergent ALT ≥3X ULN during Study Period II.

Table 12: Mean Change from Baseline to Endpoint (LOCF), Study HGMI, ITT Population, Ages 7-17 Years.

Lab Parameter	Duloxetine	Placebo	p value
Direct Bilirubin	-0.2 (0.9)	0.1 (0.8)	0.022
Chloride	-0.3 (2.4)	0.6 (2.1)	<0.001
Cholesterol	0 (0.6)	-0.1 (0.5)	0.022
Lymphocytes	-0.2 (0.7)	0 (0.6)	0.036

(source: extracted from Table HMGI.14.27, HMGI Clinical Study Report, page 440.)

In the primary placebo-controlled population (two MDD trials and one GAD trial, N=475), statistically significant within-group baseline to endpoint changes were observed in the duloxetine and placebo treatment groups for some laboratory analytes (see

Table 13, below). Again, there were no clinically meaningful trends.

Table 13: Mean Change from Baseline to Endpoint (LOCF), Primary Placebo-Controlled Population, Ages 7-17 Years.

Lab Parameter	Duloxetine	Placebo	p value
Bicarbonate	1.26	0.75	0.018
Chloride	-0.59	-0.15	0.021
Cholesterol	0.0	-0.11	0.017
gGTP	-1.28	-0.58	0.002
Uric Acid[1]	-14.15	1.78	<0.001
Hemoglobin	0.01	-0.01	0.005
Basophils	0.0	-0.00	0.036
Lymphocytes	-0.12	0.01	0.014
UA-pH	0.01	-0.10	0.044

[1]At baseline, mean (SD) uric acid in the duloxetine group was 283.69 (78.63) and in placebo was 276.47 (73.77).
(source: Clinical Summary of Safety, pages 44-45.)

7.4.3 Vital Signs

In the pediatric primary placebo-controlled population, duloxetine was associated with statistically significantly greater increases in pulse and diastolic blood pressure, and decrease in weight, compared to placebo. The results of MMRM analyses of mean change in vital signs and weight from baseline to endpoint (10 weeks) are summarized in Table 14, below. These changes are consistent with the known effects of SNRIs, and the labeled side effect profile of this product.

Table 14: Summary LS Mean Change from Baseline to Endpoint (10 weeks) in Vital Signs and Weight, Primary Placebo-Controlled Population, Ages 7-17 Years.

	LS Mean Change (MMRM)		
	Duloxetine	**Placebo**	**p-value**
Overall (ages 7 – 17 years)	**N = 467**	**N = 354**	
Pulse (bpm)	**2.4**	**0.5**	**.018**
Systolic BP (mmHg)	1.0	0.1	.179
Diastolic BP (mmHg)	**2.0**	**0.6**	**.021**
Weight (kg)	**-0.1**	**0.9**	**<.001**

N = Number of patients with a baseline and at least one non-missing post-baseline measurement.
(source: Table 2.7.4.9, Summary of Clinical Safety, page 32)

There were no statistically significant differences in the incidence of potentially clinically significant (PCS) changes in blood pressure or pulse at any time in duloxetine-treated patients compared to placebo-treated patients. In the pediatric primary placebo-controlled population PCS weight loss at any time was the only parameter that occurred in a statistically significantly greater proportion of duloxetine-treated patients compared with placebo-treated patients. PCS was defined as follows:

- **Systolic BP PCS High**: systolic BP >95th percentile and an increase from baseline ≥5 mmHg
- **Systolic BP treatment-emergent Low**: systolic BP as ≤ 80 mmHg and a decrease from baseline ≥15 mmHg for children; ≤90 and a decrease from baseline ≥20 for adolescents
- **Diastolic BP PCS High**: diastolic BP >95th percentile and an increase from baseline ≥5 mmHg
- **Diastolic BP treatment-emergent Low**: diastolic BP ≤50 mmHg and a decrease from baseline ≥10 mmHg
- **Pulse PCS High**: pulse >140 bpm and an increase from baseline ≥15 bpm for children; >120 bpm and an increase from baseline ≥15 bpm for adolescents
- **Pulse PCS Low**: pulse <60 bpm and a decrease from baseline ≥25 bpm for children; <50 bpm and a decrease from baseline ≥15 bpm for adolescents

- **Weight (kg) PCS Low**: a decrease from baseline ≥3.5%

Treatment-emergent PCS abnormal vital signs at any time in the acute treatment period and at endpoint are summarized in

Table 15 and

Table 16, respectively, below.

Table 15: Treatment-Emergent Potentially Clinically Significant and Abnormal Values at Any Time Age Subgroup, Primary Placebo-Controlled Population

Vital Signs and Weight
Treatment-Emergent Potentially Clinically Significant and Treatment-Emergent Abnormal Values at Any Time
All Randomized Patients
Pediatric Placebo-Controlled Analyses Set
HMCK, HMCL and HMGI Acute Phase

		DLX				PLA				DLX vs PLA	
Vital Signs Abnormal Criteria	Direction	N1	N2	n	PCT	N1	N2	n	PCT	CMH	Fisher's
Sitting Diastolic BP	PCS High	420	46	40	9.5	328	26	26	7.9	.392	.516
	Low	445	22	9	2.0	332	22	8	2.4	.774	.806
Sitting Pulse	PCS High	467	0	1	0.2	354	0	1	0.3	.972	1.000
	PCS Low	454	13	1	0.2	346	8	1	0.3	.952	1.000
Sitting Systolic BP	PCS High	410	56	43	10.5	304	50	25	8.2	.355	.367
	Low	450	17	3	0.7	342	12	3	0.9	.580	1.000
Weight (kg) (3.5%)	PCS Loss	467	0	65	13.9	354	0	20	5.6	<.001	<.001

DLX: Duloxetine; PLA: Placebo; PCT=Percent
N1=Number of patients who did not meet the PCS/abnormal criteria at baseline and had at least one nonmissing postbaseline measure.
N2=Number of patients who met the PCS/abnormal criteria at baseline and had at least one nonmissing postbaseline measure.
n = Number of patients with a PCS postbaseline measurement. PCT is (n/N1)*100
baseline: VISSTD 1-99, postbaseline: VISSTD 100-199

(source: Table 2.7.4.18, Summary of Clinical Safety, page 54)

Table 16: Treatment-Emergent Potentially Clinically Significant and Abnormal Values at Endpoint, Primary Placebo-Controlled Population

Vital Signs and Weight
Treatment-Emergent Potentially Clinically Significant and Treatment-Emergent Abnormal Values at Endpoint
All Randomized Patients
Pediatric Placebo-Controlled Analyses Set
HMCK, HMCL and HMGI Acute Phase

		DLX				PLA				DLX vs PLA	
Vital Signs Abnormal Criteria	Direction	N1	N2	n	PCT	N1	N2	n	PCT	CMH	Fisher's
Sitting Diastolic BP	PCS High	420	46	17	4.0	328	26	9	2.7	.284	.422
	Low	445	22	3	0.7	332	22	2	0.6	.822	1.000
Sitting Pulse	PCS High	467	0	1	0.2	354	0	1	0.3	.972	1.000
	PCS Low	454	13	0	0	346	8	1	0.3	.297	.433
Sitting Systolic BP	PCS High	410	56	15	3.7	304	50	7	2.3	.281	.383
	Low	450	17	0	0	342	12	1	0.3	.176	.432
Weight (kg) (3.5%)	PCS Loss	467	0	42	9.0	354	0	8	2.3	<.001	<.001

DLX: Duloxetine; PLA: Placebo; PCT=Percent
N1=Number of patients who did not meet the PCS/abnormal criteria at baseline and had at least one nonmissing postbaseline measure.
N2=Number of patients who met the PCS/abnormal criteria at baseline and had at least one nonmissing postbaseline measure.
n = Number of patients with a PCS postbaseline measurement. PCT is (n/N1)*100
baseline: VISSTD 1-99, postbaseline: VISSTD 100-199

(source: Table 2.7.4.19, Summary of Clinical Safety, page 55)

7.4.4 Electrocardiograms (ECGs)

LSMean changes in heart rate from baseline to endpoint were 5.96 bpm for the duloxetine treatment group and -0.16 bpm for the placebo treatment group (p<.001). LSMean changes from baseline to endpoint for the QTcB interval were 1.36 msec for the duloxetine treatment group and -0.01 msec for the placebo treatment group. The difference in QTcB interval between the duloxetine and placebo treatment groups was not statistically significant. LSMean changes from baseline to endpoint for the QTcF interval were -4.84 msec for the duloxetine treatment group and -1.19 msec for the

placebo treatment group (p=.017). There were no statistically significant differences between treatment groups for the PR interval or the QRS interval. There were no statistically significant differences between the duloxetine and placebo treatment groups at any time or at endpoint in any ECG parameter during Study Period II.

In the pediatric primary placebo-controlled population, statistically significant between-group differences were observed for mean change in heart rate, QT interval and QTcF interval. LSMean changes in heart rate from baseline to endpoint were 3.8 bpm for the duloxetine treatment group and -0.6 bpm for the placebo treatment group (p<.001). LSMean changes from baseline to endpoint for the QT interval were -9.1 msec for the duloxetine treatment group and 0.2 msec for the placebo treatment group (p<0.001); for the QTcF interval, LSMean changes from baseline to endpoint were -3.6 msec for the duloxetine treatment group and -0.7 msec for the placebo treatment group (p=0.002). The mean decreases in QT and QTcF intervals are consistent with results in duloxetine-treated adults. No other statistically significant ECG differences were observed between the duloxetine and the placebo treatment groups.

Current labeling notes that duloxetine appears to be associated with concentration-dependent but not clinically meaningful QT shortening.

7.4.5 Special Safety Studies/Clinical Trials

No special clinical safety studies were conducted to support this supplement.

7.4.6 Immunogenicity

No evaluations of immunogenicity were reported under this supplement. In HMGI, there were no significant differences between duloxetine and placebo in the number of subjects who experienced AEs in the skin and subcutaneous tissue disorders SOC.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No analysis was conducted.

7.5.2 Time Dependency for Adverse Events

No analysis was conducted.

7.5.3 Drug-Demographic Interactions

No analysis was conducted.

7.5.4 Drug-Disease Interactions

No new information on drug-disease interactions was submitted with this sNDA.

7.5.5 Drug-Drug Interactions

No new information on drug-drug interactions was submitted with this sNDA.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new information on human carcinogenicity was submitted with this sNDA.

7.6.2 Human Reproduction and Pregnancy Data

No new information on human reproduction and pregnancy was submitted with this sNDA.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not included in this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not included in this submission.

7.7 Additional Submissions / Safety Issues

7.7.1 Suicidal Ideation and Behavior and Other Psychiatric Adverse Events

The C-SSRS was used in this study to capture the occurrence, severity, and frequency of suicidal ideation and behavior.

During Study Period II, 5.9% of duloxetine-treated patients and 6.0% of placebo-treated patients experienced suicidal ideation; no statistically significant differences were observed between treatment groups. No patients in either the duloxetine or placebo treatment groups experienced serious suicidal ideation (Category 4 or 5 on the C-SSRS) during Study Period II. No patients in either the duloxetine or placebo treatment groups experienced a suicidal behavior during Study Period II.

Compared to lifetime baseline, 3.7% of duloxetine-treated patients and 2.2% of placebo-treated patients experienced treatment-emergent suicidal ideation; no statistically significant differences were observed between treatment groups. Compared to lead-in baseline (study screening period), 5.9% of duloxetine-treated patients and 5.2% of

placebo-treated patients experienced treatment-emergent suicidal ideation; this difference was also not statistically significant.

Among patients with no suicidal ideation or behavior during lifetime baseline, 4 (3.0%) patients in the duloxetine treatment group, and 2 (1.5%) patients in the placebo treatment group shifted to a higher category (suicidal ideation) during treatment. From the lead-in baseline, 8 (5.9%) patients in the duloxetine treatment group, and 7 (5.2%) patients in the placebo treatment group shifted from no suicidal ideation or behavior to a higher category (suicidal ideation) during treatment.

Among patients with suicidal ideation during lifetime baseline or lead-in baseline, no patients in either the duloxetine or placebo treatment groups shifted to a higher category (suicidal behavior) during treatment, and no patients in either treatment group reported suicidal behavior during treatment. Regardless of lifetime or lead-in baseline severity of suicidal ideation, no patients in either the duloxetine or placebo treatment groups shifted to the categories (4 or 5) of serious suicidal ideation during treatment.

8 Postmarket Experience

The sponsor did not submit any new information on the postmarket experience with this sNDA.

9 Appendices

9.1 Literature Review/References

The sponsor did not include references from an exhaustive or systematic search of the published generalized anxiety disorder (GAD) literature in this submission. The references included in this submission were those cited in various sections of the submission to support the specific information presented in those sections. This supplement (S-043) references the published literature search submitted as part of the Cymbalta NDA Annual Report on 27 September 2013 (Sequence Number 0181, Module 5.3.6, Periodic Safety Update Report 2013). The sponsor notes that automated literature reviews are conducted on a weekly basis via Lilly's Link Library, using criteria noted in the sponsor's response to our filing letter question (Sequence Number 0190, Module 1.11.3, Regulatory Response Pediatric). The search strategy was implemented by (b) (4), and the resultant abstracts are delivered to the surveillance associates ((b) (4)) who review them weekly to determine potentially important findings. The review of published literature revealed no new potential adverse safety findings associated with Cymbalta and as such, the current benefit-risk profile of Cymbalta remains unchanged.

9.2 Labeling Recommendations

The sponsor submitted labeling related to Supplements 43 and 44 concurrently. Relevant to this supplement, the sponsor has added language throughout the label specifying data or other information that is only applicable to adults. In addition, the sponsor is proposing changes to the following sections of the label:

Boxed Warning

(b) (4)

(b) (4)

(b) (4)

Generalized Anxiety Disorder

Adults — For most patients, the recommended starting dose for Cymbalta is 60 mg administered once daily. For some patients, it may be desirable to start at 30 mg once daily for 1 week, to allow patients to adjust to the medication before increasing to 60 mg once daily. While a 120 mg once daily dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit. Nevertheless, if a decision is made to increase the dose beyond 60 mg once daily, dose increases should be in increments of 30 mg once daily. The safety of doses above 120 mg once daily has not been adequately evaluated *[see Clinical Studies (14.2)]*.

Children and Adolescents (7 to 17 years of age) — (b) (4) at a dose of 30 mg once daily for 2 weeks before considering an increase to 60 mg. The recommended dose range is 30 to 60 mg once daily. Some patients may benefit from doses above 60 mg once daily. The maximum dose studied (b) (4) 120 mg per day. The safety of doses above 120 mg once daily has not been evaluated *[see Clinical Studies (14.2)]*.

6 Adverse Reactions

The sponsor has added information describing adverse reactions in pediatric clinical trials, to include data from the pediatric GAD trial. The sponsor proposed the following criteria to identify AEs to be included in the United Stated Package Insert (USPI):

(b) (4)

8.4 Pediatric Use

This section has been modified to include efficacy information in pediatric GAD, (b) (4)

12.3 Pharmacokinetics

Pediatric PK data added.

14.2 Generalized Anxiety Disorder

The efficacy of Cymbalta in the treatment of pediatric patients 7 to 17 years of age with generalized anxiety disorder (GAD) was established in 1 flexible-dose randomized, double-blind, placebo-controlled trial in pediatric outpatients (b) (4) (b) (4)

In this study, the starting dose was 30 mg once daily for 2 weeks (b) (4) 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 (b) (4) the 10-week acute treatment phase was 57.6 mg/day. In this study, Cymbalta (N=135) demonstrated superiority over placebo (N=137) from baseline to endpoint as measured by greater improvement in the Pediatric Anxiety Rating Scale (PARS) for GAD severity score.

17. (b) (4)

Pediatric Use — Safety and efficacy of Cymbalta in patients 7 to 17 years of age have been established for the treatment of GAD. The types of adverse reactions observed with Cymbalta in children and adolescents were generally similar to those observed in adults. The safety and effectiveness of Cymbalta has not been established in pediatric patients less than 18 years of age with other indications *[see Use in Specific Populations (8.4)]*.

With regard to the specific changes noted above, we have few objections to the labeling changes proposed by the sponsor. A number of editorial changes were made to update the label to reflect current standards (e.g., simplification of Indications and Usage to remove population and clinical study details). (b) (4)

The Division sent preliminary labeling comments to the sponsor on August 14, 2014. These comments were relevant to both Supplement 43 and 44 (GAD in geriatric patients), and many of the comments related to content and format of currently approved labeling rather than the changes noted above. The suggested changes were intended to update the label to reflect current Agency and Division standards for prescribing information. With regard to comments specific to this supplement, we asked the sponsor to change the title of the table listing pediatric adverse reactions (ARs), and to include a separate table for ARs that occurred with an incidence of greater than 2% and greater than placebo in the pediatric GAD trial.

The sponsor replied to our request and submitted revised labeling on September 5, 2014. The sponsor agreed to some of the requested changes, (b) (4) . At the time this review was filed, labeling negotiations were still ongoing. Complete labeling recommendations will be provided in a separate Word document using track changes.

9.3 Advisory Committee Meeting

Not applicable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIFFANY R FARCHIONE
09/18/2014

MITCHELL V Mathis
09/19/2014