CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-427/S-015, S-017

Trade Name: Cymbalta

Generic Name: duloxetine hydrochloride

Sponsor: Eli Lilly

Approval Date: November 28, 2007

Indications: Cymbalta® is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for: Major Depressive Disorder, Diabetic Peripheral Neuropathic Pain, Generalized Anxiety Disorder.

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APPLICATION NUMBER:

21-427/S-015, S-017

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-427/S-015/S-017

Eli Lilly and Company
Attention: Bryan Boggs, Pharm.D.
Manager, U.S. Regulatory Affairs
Eli Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Boggs:

Please refer to your supplemental new drug applications dated October 31, 2006 (S-015), and May 17, 2007 (S-017), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cymbalta (duloxetine hydrochloride) Delayed-Release 20mg, 30mg and 60mg capsules.

We acknowledge receipt of your submissions to S-015 dated September 28, 2007, and October 29, 2007. Your submission dated September 28, 2007, constituted a complete response to our action letter dated August 28, 2007.

Reference is also made to Agency letters dated May 18, 2007, and July 30, 2007, requesting information on overdose as well as revisions to the labeling pertaining to serious skin reactions and hyponatremia. We also acknowledge your responses dated August 17, 2007 and November 27, 2007.

The above supplemental applications provide for the following changes to product labeling:

S-015

- Revisions throughout labeling to provide for the results of your maintenance data in adult patients with Major Depressive Disorder.

S-017

- Revisions to the Precautions-Discontinuation of Treatment with Cymbalta and Adverse Reactions-Postmarketing Spontaneous Reports sections.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Request for Safety Data and Follow-Up Monitoring

1. We are requesting that you conduct an analysis of serious skin reactions in the placebo-controlled clinical trials database.
2. We are requesting an enhanced pharmacovigilance program by submitting to the Agency of 15-days expedited reports for any serious skin or hypersensitivity reaction with the expectation that these reports would have better collection of information and follow up of these cases.

We are waiving the requirements of 21 CFR 201.157(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

The final printed labeling (FPL) must be identical to the enclosed labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission **"SPL for approved supplements NDA 21-427/S-015 and S-017"**.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirements for children aged 0 to 17 years for this application since it is often difficult to perform long term studies within this age group.

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call CDR Bill Bender, Regulatory Project Manager, at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Thomas Laughren
11/28/2007 04:39:35 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427/S-015, S-017

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-427/S-015/S-017

Eli Lilly and Company
Attention: Bryan Boggs, Pharm.D.
Manager, U.S. Regulatory Affairs
Eli Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Boggs:

Please refer to your supplemental new drug applications dated October 31, 2006 (S-015), and May 17, 2007 (S-017), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cymbalta, (duloxetine Hydrochloride) Delayed-Release 20mg, 30mg and 60mg capsules.

We acknowledge receipt of your submissions to S-015 dated December 18, 2006, January 10, 2007, February 27, 2007, April 27, 2007, May 4 and 15, 2007, June 4 and 21, 2007, and August 13, 2007.

Reference is also made to Agency letters dated May 18, 2007, and July 30, 2007, requesting information on overdose as well as revisions to the labeling pertaining to serious skin reactions and hyponatremia.

The above supplemental applications provide for the following changes to product labeling:

S-015

- Maintenance data in adult patients with Major Depressive Disorder.

S-017

- Revisions to Precautions-Discontinuation of treatment with Cymbalta and Adverse Reactions-Postmarketing Spontaneous Reports sections.

We have completed our review of these applications, as amended, and they are approvable. Before these applications may be approved, however, you must submit final printed labeling identical in content to the enclosed labeling.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL, as soon as it is available but no more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material.

Your updated labeling should also incorporate the labeling changes approved in our letter dated August 2, 2007.

Within 10 days after the date of this letter, you are required to amend these application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, call CDR Bill Bender, Regulatory Project Manager, at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Thomas Laughren
8/28/2007 08:56:39 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427/S-015, S-017

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Cymbalta safely and effectively. See full prescribing information for Cymbalta.

Cymbalta (duloxetine hydrochloride) Delayed-Release Capsules for Oral use.
Initial U.S. Approval: 2004

WARNING: Suicidality and Antidepressants
See full prescribing information for complete boxed warning.
Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders. Cymbalta is not approved for use in pediatric patients (5.1).

----------RECENT MAJOR CHANGES----------

WARNING: Suicidality and Antidepressants *(Boxed Warning)*	6/2007
Indications and Usage, Generalized Anxiety Disorder *(1.3)*	2/2007
Warnings and Precautions, Abnormal Bleeding (5.5)	MM/2007
Warnings and Precautions, Clinical Worsening and Suicide Risk *(5.1)*	6/2007
Warnings and Precautions, Orthostatic Hypotension and Syncope *(5.3)*, Serotonin Syndrome *(5.4)*, Effect on Blood Pressure *(5.9)*, Hyponatremia *(5.11)*	10/2006

----------INDICATIONS AND USAGE----------
Cymbalta® is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for:
- Major Depressive Disorder (1.1)
- Diabetic Peripheral Neuropathic Pain (1.2)
- Generalized Anxiety Disorder (1.3)

----------DOSAGE AND ADMINISTRATION----------
- Cymbalta should generally be administered once daily without regard to meals. Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the capsule be opened and its contents be sprinkled on food or mixed with liquids (2.1).

Indication	Recommended Dose
MDD (2.1, 2.2)	Acute Treatment: 40 mg/day (20 mg twice daily) to 60 mg/day (once daily or as 30 mg twice daily); Maintenance Treatment: 60 mg/day
DPNP (2.1)	60 mg/day (once daily)
GAD (2.1)	60 mg/day (once daily)

- Some patients may benefit from starting at 30 mg once daily.
- There is no evidence that doses greater than 60 mg/day confers additional benefit, while adverse reactions such as dizziness, fatigue, somnolence, constipation, and decreased appetite were observed to be dose-dependent.
- Discontinuing Cymbalta: a gradual dose reduction is recommended.

----------DOSAGE FORMS AND STRENGTHS----------
- 20, 30, and 60 mg capsules (3)

----------CONTRAINDICATIONS----------
- Use of a monoamine oxidase inhibitor concomitantly or in close temporal proximity (4.1)
- Use in patients with uncontrolled narrow-angle glaucoma (4.2)

----------WARNINGS AND PRECAUTIONS----------
- Suicidality: Monitor for clinical worsening and suicide risk (5.1).
- Hepatotoxicity: Elevated transaminases, bilirubin and alkaline phosphatase, some severe, have occurred. Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease (5.2).
- Orthostatic hypotension and syncope: Cases have been reported with duloxetine therapy (5.3).
- Serotonin Syndrome: Serotonin syndrome has been reported with SSRIs and SNRIs (5.4, 7.14).
- Abnormal bleeding: Cymbalta may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation (5.5, 7.4).
- Abrupt discontinuation: may result in symptoms, including dizziness, paresthesia, irritability, and headache (5.6).
- Activation of mania or hypomania has occurred (5.7).
- Seizures: prescribe with care in patients with a history of seizure disorder (5.8).
- Blood Pressure: Monitor blood pressure prior to initiating treatment and periodically throughout treatment (5.9).
- Inhibitors of CYP1A2 or thioridazine: Should not administer with Cymbalta (5.10).
- Hyponatremia: Cases of hyponatremia have been reported (5.11).
- Hepatic Insufficiency and Severe Renal Impairment: Should ordinarily not be administered to these patients (5.12).
- Controlled narrow-angle glaucoma: Use cautiously in these patients (5.12).
- Glucose control in diabetes: In diabetic peripheral neuropathic pain patients, small increases in fasting blood glucose, HbA1c, and total cholesterol have been observed (5.12).
- Conditions that slow gastric emptying: Use cautiously in these patients (5.-12).
- Urinary Hesitation and Retention (5.13)

----------ADVERSE REACTIONS----------
- Most common adverse reactions (≥5% and at least twice the incidence of placebo patients): nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis (6.3).
- To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Potent inhibitors of CYP1A2 should be avoided (7.1).
- Potent inhibitors of CYP2D6 may increase duloxetine concentrations (7.2).
- Duloxetine is a moderate inhibitor of CYP2D6 (7.9).

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy and nursing mothers: use only if the potential benefit justifies the potential risk to the fetus or child (2.3, 8.1, 8.3).

See 17 for PATIENT COUNSELING INFORMATION and the FDA approved Medication Guide (17.1)

Revised: MM/YYYY

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients. *[see Warnings and Precautions (5.1) Use in Specific Populations (8.4) and Information for Patients (17.2).]*

1 INDICATIONS AND USAGE

1.1 Major Depressive Disorder

Cymbalta is indicated for the acute and maintenance treatment of major depressive disorder (MDD) [*see Clinical Studies (14.1)*].

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

1.2 Diabetic Peripheral Neuropathic Pain

Cymbalta is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy [*see Clinical Studies (14.2)*].

1.3 Generalized Anxiety Disorder

Cymbalta is indicated for the acute treatment of generalized anxiety disorder (GAD) [*see Clinical Studies (14.3)*].

Generalized anxiety disorder is defined by the DSM-IV as excessive anxiety and worry, present more days than not, for at least 6 months. The excessive anxiety and worry must be difficult to control and must cause significant distress or impairment in normal functioning. It must be associated with at least 3 of the following 6 symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and/or sleep disturbance.

2 DOSAGE AND ADMINISTRATION

Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the capsule be opened and its contents sprinkled on food or mixed with liquids. All of these might affect the enteric coating. Cymbalta should be given without regard to meals.

2.1 Initial Treatment

Major Depressive Disorder - Cymbalta should be administered at a total dose of 40 mg/day (given as 20 mg twice daily) to 60 mg/day (given either once daily or as 30 mg twice 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/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer any additional benefits. The safety of doses above 120 mg once daily has not been adequately evaluated [*see Clinical Studies (14.1)*].

Diabetic Peripheral Neuropathic Pain - Cymbalta should be administered at a total dose of 60 mg/day given once a day.

While a 120 mg/day dose was shown to be safe and effective, there is no evidence that doses higher than 60 mg confer additional significant benefit, and the higher dose is clearly less well tolerated [*see Clinical Studies (14.2)*]. For patients for whom tolerability is a concern, a lower starting dose may be considered. Since diabetes is frequently complicated by renal disease, a lower starting dose and gradual increase in dose should be considered for patients with renal impairment [*see Clinical Pharmacology (12.3) and Dosing in Special Populations (2.3)*].

Generalized Anxiety Disorder - 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 (14.3)*]

2.2 Maintenance/Continuation/Extended Treatment

Major Depressive Disorder — It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy. Cymbalta should be administered at a total dose of 60 mg once daily. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment [*see Clinical Studies (14.1)*].

Diabetic Peripheral Neuropathic Pain — As the progression of diabetic peripheral neuropathy is highly variable and management of pain is empirical, the effectiveness of Cymbalta must be assessed individually. Efficacy beyond 12 weeks has not been systematically studied in placebo-controlled trials.

Generalized Anxiety Disorder — Generalized anxiety disorder is recognized as a chronic condition. The efficacy of Cymbalta in the treatment of GAD, that is, beyond 10 weeks, has not been systematically studied. The physician who elects to use Cymbalta for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

2.3 Dosing in Special Populations

Hepatic Insufficiency —It is recommended that Cymbalta should ordinarily not be administered to patients with any hepatic insufficiency [*see Warnings and Precautions (5.12) and Use in Specific Populations (8.9)*].

Severe Renal Impairment — Cymbalta is not recommended for patients with end-stage renal disease or severe renal impairment (estimated creatinine clearance <30 mL/min) [*see Warnings and Precautions (5.12) and Use in Specific Populations (8.10)*].

Elderly Patients — No dose adjustment is recommended for elderly patients on the basis of age. As with any drug, caution should be exercised in treating the elderly. When individualizing the dosage in elderly patients, extra care should be taken when increasing the dose [*see Use in Specific Populations (8.5)*].

Pregnant Women — There are no adequate and well-controlled studies in pregnant women; therefore, Cymbalta should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [*see Use in Specific Populations (8.1)*].

Nursing Mothers — Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended [*see Use in Specific Populations (8.3)*].

2.4 Discontinuing Cymbalta

Symptoms associated with discontinuation of Cymbalta and other SSRIs and SNRIs have been reported. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible [*see Warnings and Precautions (5.6)*].

2.5 Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI [*see Contraindications (4.1) and Warnings and Precautions (5.4)*].

3 DOSAGE FORM AND STRENGTHS

Cymbalta is available as:
20mg opaque green capsules imprinted with “Lilly 3235 20mg”
30mg opaque white and blue capsules imprinted with “Lilly 3240 30mg”
60mg opaque green and blue capsules imprinted with “Lilly 3237 60mg”

4 CONTRAINDICATIONS

4.1 Monoamine Oxidase Inhibitors

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome [*see Dosage and Administration, (2.5)* and *Warnings and Precautions (5.4)*].

4.2 Uncontrolled Narrow-Angle Glaucoma

In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma [*see Warnings and Precautions (5.12)*].

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Dosage and Administration (2.4) and Warnings and Precautions (5.6)* for descriptions of the risks of discontinuation of Cymbalta].

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder — A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Cymbalta (duloxetine) is not approved for use in treating bipolar depression.

5.2 Hepatotoxicity

Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.3% (73/23,983) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled trials in any indication, elevation of ALT >3 times the upper limit of normal occurred in 1.1% (75/6871) of Cymbalta-treated patients compared to 0.3% (13/5036) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively. Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. In clinical trials, three Cymbalta patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

5.3 Orthostatic Hypotension and Syncope

Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors [*see Warnings and Precautions (5.10) and Drug Interactions (7.1)*] and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

5.4 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated [*see Contraindications (4.1)*].

If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [*see Drug Interactions (7.15)*].

The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not recommended [*see Drug Interactions (7.14)*].

5.5 Abnormal Bleeding

SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

5.6 Discontinuation of Treatment with Cymbalta

Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis and vertigo.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate [*see Dosage and Administration (2.4)*].

5.7 Activation of Mania/Hypomania

In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2327) of duloxetine-treated patients and 0.1% (1/1460) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP or GAD placebo-controlled trials. Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania.

5.8 Seizures

Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.04% (3/8504) of patients treated with duloxetine and 0.02% (1/6123) of patients treated with placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

5.9 Effect on Blood Pressure

In clinical trials across indications, relative to placebo, duloxetine treatment was associated with a mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg BID. At the highest 200 mg BID dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment [*see Adverse Reactions (6.6)*]

5.10 Clinically Important Drug Interactions

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

<u>Potential for Other Drugs to Affect Cymbalta</u>

CYP1A2 Inhibitors — Co-administration of Cymbalta with potent CYP1A2 inhibitors should be avoided [*see Drug Interactions (7.1)*].

CYP2D6 Inhibitors — Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 60%) of duloxetine [*see Drug Interactions (7.2)*].

Potential for Cymbalta to Affect Other Drugs

Drugs Metabolized by CYP2D6 — Co-administration of Cymbalta with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered [*see Drug Interactions (7.9)*].

Other Clinically Important Drug Interactions

Alcohol —Use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should ordinarily not be prescribed for patients with substantial alcohol use [*see Warnings and Precautions (5.2) and Drug Interactions (7.16)*].

CNS Acting Drugs — Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action [*see Warnings and Precautions (5.10) and Drug Interactions (7.17)*].

5.11 Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Cymbalta. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/Lhave been reported and appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk [*see Use in Specific Populations (8.5)*]. Discontinuation of Cymbalta should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated hallucination, syncope, seizure, coma, respiratory arrest, and death.

5.12 Use in Patients with Concomitant Illness

Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

Hepatic Insufficiency - Cymbalta should ordinarily not be used in patients with hepatic insufficiency [*see Dosage and Administration (2.3), Warnings and Precautions (5.2), and Use in Specific Populations (8.9)*].

Severe Renal Impairment - Cymbalta should ordinarily not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis).[*see Dosage and Administration (2.3) and Use in Specific Populations (8.10)*].

Controlled Narrow-Angle Glaucoma - In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma [*see Contraindications (4.2)*].

Glycemic Control in Patients with Diabetes - As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline

hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, Cymbalta was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the Cymbalta and by 0.2% in the routine care groups.

5.13 Urinary Hesitation and Retention

Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related.

In post marketing experience, cases of urinary retention have been observed. In some instances of urinary retention associated with duloxetine use, hospitalization and/or catheterization has been needed.

5.14 Laboratory Tests

No specific laboratory tests are recommended.

6 ADVERSE REACTIONS

6.1 Clinical Trial Data Sources

The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2327), DPNP (N=568) and GAD (N=668). The population studied was 17 to 89 years of age; 64.8%, 38.7%, and 64.7% female; and 85.5%, 77.6%, and 84.6% Caucasian for MDD, DPNP, and GAD, respectively. Most patients received doses of a total of 60 to 120 mg per day [*see Clinical Studies (14)*].

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Reactions reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.2 Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials

Major Depressive Disorder — Approximately 9% (209/2327) of the patients who received duloxetine in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.7% (68/1460) of the patients receiving placebo. Nausea (duloxetine 1.3%, placebo 0.5%) was the only common adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Diabetic Peripheral Neuropathic Pain — Approximately 14.3% (81/568) of the patients who received duloxetine in placebo-controlled trials for DPNP discontinued treatment due to an adverse reaction, compared with 7.2% (16/223) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) were nausea (duloxetine 3.5%, placebo 0.4%), dizziness (duloxetine 1.6%, placebo 0.4%), somnolence (duloxetine 1.6%, placebo 0.0%), and fatigue (duloxetine 1.1%, placebo 0.0%).

Generalized Anxiety Disorder — Approximately 15.3% (102/668) of the patients who received duloxetine in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction, compared with 4.0% (20/495) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.7%, placebo 0.2%), vomiting (duloxetine 1.3%, placebo 0.0%), and dizziness (duloxetine 1.0%, placebo 0.2%).

6.3 Adverse Reactions Occurring at an Incidence of 5% or More among Duloxetine-Treated Patients in Placebo-Controlled Trials

Table 2 gives the incidence of treatment-emergent adverse reactions in placebo-controlled trials for approved indications that occurred in 5% or more of patients treated with duloxetine and with an incidence greater than placebo. The most commonly observed adverse reactions in duloxetine-treated patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.

Table 2: Treatment-Emergent Adverse Reactions: Incidence of 5% or More in Placebo-Controlled Trials of Approved Indications[1]

	Percentage of Patients Reporting Reaction	
Adverse Reaction	Cymbalta (N=3563)	Placebo (N=2178)
Nausea	25	9
Dry mouth	14	6
Diarrhea	10	7
Dizziness*	11	6
Insomnia[a]	10	6
Fatigue*[b]	10	6
Somnolence*[c]	11	4
Constipation*	10	4
Decreased appetite*[d]	8	2
Hyperhidrosis	7	2

[1] Events reported by at least 5% of patients treated with Cymbalta and more often than with placebo.
* Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.
[a] Also includes middle insomnia, early morning awakening, and initial insomnia
[b] Also includes asthenia
[c] Also includes hypersomnia and sedation
[d] Also includes anorexia

6.4 Adverse Reactions Occurring at an Incidence of 2% or More among Duloxetine-Treated Patients in Placebo-Controlled Trials

Pooled MDD and GAD trials

Table 3 gives the incidence of treatment-emergent adverse reactions in MDD and GAD placebo-controlled trials for approved indications that occurred in 2% or more of patients treated with duloxetine and with an incidence greater than placebo. The most commonly observed adverse reactions in duloxetine-treated MDD/GAD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were nausea, dry mouth, constipation, somnolence, decreased appetite, and hyperhidrosis.

Table 3: Treatment-Emergent Adverse Reactions: Incidence of 2% or More in MDD and GAD Placebo-Controlled Trials[1]

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	Cymbalta (N=2995)	Placebo (N=1955)
Cardiac Disorders		
Palpitations	2	2
Eye Disorders		
Vision blurred	3	2
Gastrointestinal Disorders		
Nausea	25	9
Dry mouth	15	6
Diarrhea	10	7
Constipation*	10	4
Abdominal pain[a]	4	4
Vomiting	5	2
General Disorders and Administration Site Conditions		
Fatigue[b]	10	6
Investigations		
Weight decreased*	2	<1
Metabolism and Nutrition Disorders		
Decreased appetite[c]	7	2
Nervous System Disorders		
Dizziness	10	6
Somnolence[d]	10	4
Tremor	3	<1
Psychiatric Disorders		
Insomnia[e]	10	6
Agitation[f]	5	3
Anxiety	3	2
Libido decreased[g]	4	1
Orgasm abnormal[h]	3	<1
Abnormal dreams[i]	2	1
Reproductive System and Breast Disorders		
Erectile dysfunction[j]	5	1
Ejaculation delayed*[j]	3	<1
Ejaculation disorder[j,k]	2	<1
Respiratory, Thoracic, and Mediastinal Disorders		
Yawning	2	<1
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	6	2
Vascular Disorders		
Hot flush	2	<1

[1] Events reported by at least 2% of patients treated with Cymbalta and more often than with placebo.
* Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.
[a] Also includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain
[b] Also includes asthenia
[c] Also includes anorexia

[d] Also includes hypersomnia and sedation
[e] Also includes middle insomnia, early morning awakening, and initial insomnia
[f] Also includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation
[g] Also includes loss of libido
[h] Also includes anorgasmia
[i] Also includes nightmare
[j] Males patients only
[k] Also includes ejaculation failure and ejaculation dysfunction

Diabetic Peripheral Neuropathic Pain

Table 4 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of DPNP placebo-controlled trials (doses of 20 to 120 mg/day) and with an incidence greater than placebo. The most commonly observed adverse events in Cymbalta-treated DPNP patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia (*see* Table 4).

Table 4: Treatment-Emergent Adverse Reactions Incidence of 2% or More in DPNP Placebo-Controlled Trials

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction			
	Cymbalta 60 mg BID (N=225)	Cymbalta 60 mg QD (N=228)	Cymbalta 20 mg QD (N=115)	Placebo (N=223)
Gastrointestinal Disorders				
Nausea	30	22	14	9
Constipation	15	11	5	3
Diarrhea	7	11	13	6
Dry mouth	12	7	5	4
Vomiting	5	5	6	4
Dyspepsia	4	4	4	3
Loose stools	2	3	2	1
General Disorders and Administration Site Conditions				
Fatigue	12	10	2	5
Asthenia	8	4	2	1
Pyrexia	3	1	2	1
Infections and Infestations				
Nasopharyngitis	9	7	9	5
Metabolism and Nutrition Disorders				
Decreased appetite	11	4	3	<1
Anorexia	5	3	3	<1
Musculoskeletal and Connective Tissue Disorders				
Muscle cramp	4	4	5	3
Myalgia	4	1	3	<1
Nervous System Disorders				
Somnolence	21	15	7	5
Headache	15	13	13	10
Dizziness	17	14	6	6
Tremor	5	1	0	0
Psychiatric Disorders				
Insomnia	13	8	9	7
Renal and Urinary Disorders				
Pollakiuria	5	1	3	2
Reproductive System and Breast Disorders				

Erectile dysfunction[1]	4	1	0	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	5	3	6	4
Pharyngolaryngeal pain	6	1	3	1
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis	8	6	6	2

1-Male patients only

6.5 Effects on Male and Female Sexual Function

Changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment. Because adverse sexual reactions are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, as shown in Table 5 below, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. Negative numbers signify an improvement from a baseline level of dysfunction, which is commonly seen in depressed patients. Physicians should routinely inquire about possible sexual side effects.

Table 5: Mean Change in ASEX Scores by Gender in MDD Placebo-Controlled Trials

	Male Patients[a]		**Female Patients[a]**	
	Cymbalta (n=175)	**Placebo (n=83)**	**Cymbalta (n=241)**	**Placebo (n=126)**
ASEX Total (Items 1-5)	0.56[b]	-1.07	-1.15	-1.07
Item 1 — Sex drive	-0.07	-0.12	-0.32	-0.24
Item 2 — Arousal	0.01	-0.26	-0.21	-0.18
Item 3 — Ability to achieve erection (men); Lubrication (women)	0.03	-0.25	-0.17	-0.18
Item 4 — Ease of reaching orgasm	0.40[c]	-0.24	-0.09	-0.13
Item 5 — Orgasm satisfaction	0.09	-0.13	-0.11	-0.17

a n=Number of patients with non-missing change score for ASEX total

b p=0 013 versus placebo

c p<0 001 versus placebo

6.6 Vital Sign Changes

In clinical trials across indications, relative to placebo, duloxetine treatment was associated with a mean increase of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure [*see Warnings and Precautions (5.3 and 5.9)*].

Duloxetine treatment, for up to 13-weeks in placebo-controlled trials typically caused a small increase in heart rate compared to placebo of up to 3 beats per minute.

6.7 Weight Changes

In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10-weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13-weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.

6.8 Laboratory Changes

Cymbalta treatment in placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients [*see Warnings and Precautions (5.2)*].

6.9 Electrocardiogram Changes

Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13-weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg BID, no prolongation of the corrected QT interval was observed.

6.10 Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine

Following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in clinical trials. In clinical trials of all indications, 23,983 patients were treated with duloxetine. Of these, 6,702 took duloxetine for at least 6 months, and 3,006 for at least one year. The following listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

Cardiac Disorders — *Frequent:* palpitations; *Infrequent:* myocardial infarction and tachycardia.

Ear and Labyrinth Disorders — *Frequent:* vertigo; *Infrequent:* ear pain.

Endocrine Disorders — *Infrequent:* Hypothyroidism.

Eye Disorders — *Frequent:* vision blurred; *Infrequent:* diplopia and visual disturbance.

Gastrointestinal Disorders — *Frequent:* flatulence; *Infrequent:* eructation, gastritis, halitosis, and stomatitis; *Rare:* gastric ulcer, hematochezia, and melena.

General Disorders and Administration Site Conditions — *Frequent:* chills/rigors; *Infrequent:* feeling abnormal, feeling hot and/or cold, malaise, and thirst.

Infections and Infestations — *Infrequent:* gastroenteritis and laryngitis.

Investigations — *Frequent:* weight increased; *Infrequent:* blood cholesterol increased.

Metabolism and Nutrition Disorders — *Infrequent:* dehydration and hyperlipidemia; *Rare:* dyslipidemia.

Musculoskeletal and Connective Tissue Disorders — *Frequent:* musculoskeletal pain; *Infrequent:* muscle tightness and muscle twitching.

Nervous System Disorders — *Frequent:* dysgeusia, lethargy, and parasthesia/hypoesthesia; *Infrequent:* disturbance in attention, dyskinesia, and myoclonus; *Rare:* dysarthria.

Psychiatric Disorders — *Frequent:* abnormal dreams and sleep disorder; *Infrequent:* apathy, bruxism, disorientation/confusional state, irritability, mood swings, and suicide attempt; *Rare:* completed suicide.

Renal and Urinary Disorders — *Infrequent:* dysuria, micturition urgency, nocturia, and urine odor abnormal.

Reproductive System and Breast Disorders — *Frequent:* anorgasmia/orgasm abnormal; *Infrequent:* menopausal symptoms.

Respiratory, Thoracic and Mediastinal Disorders — *Frequent:* yawning; *Infrequent:* throat tightness.

Skin and Subcutaneous Tissue Disorders —*Infrequent:* cold sweat, erythema, increased tendency to bruise, night sweats, and photosensitivity reaction; *Rare:* ecchymosis.

Vascular Disorders — *Frequent:* hot flush; *Infrequent:* flushing, orthostatic hypotension, and peripheral coldness.

6.11 Postmarketing Spontaneous Reports

The following adverse reactions have been identified during postapproval use of Cymbalta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, angioneurotic edema, erythema multiforme, extrapyramidal disorder, glaucoma, hallucinations, hyperglycemia, hypersensitivity, hypertensive crisis, rash, supraventricular arrhythmia, trismus, and urticaria.

Serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine.

7 DRUG INTERACTIONS

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

7.1 Inhibitors of CYP1A2

When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the C_{max} was increased about 2.5-fold, and duloxetine $t_{1/2}$ was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin [*see Warnings and Precautions (5.10)*].

7.2 Inhibitors of CYP2D6

Concomitant use of duloxetine (40 mg QD) with paroxetine (20 mg QD) increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine) [*see Warnings and Precautions (5.10)*].

7.3 Dual Inhibition of CYP1A2 and CYP2D6

Concomitant administration of duloxetine 40 mg BID with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and C_{max}.

7.4 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued [*see Warnings and Precautions (5.5)*].

7.5 Lorazepam

Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

7.6 Temazepam

Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

7.7 Drugs that Affect Gastric Acidity

Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta

in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption [*see Warnings and Precautions (5.12)*].

7.8 Drugs Metabolized by CYP1A2

In vitro drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%-27%) when co-administered with duloxetine (60 mg BID).

7.9 Drugs Metabolized by CYP2D6

Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg BID) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold [*see Warnings and Precautions (5.10)*].

7.10 Drugs Metabolized by CYP2C9

Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

7.11 Drugs Metabolized by CYP3A

Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

7.12 Drugs Metabolized by CYP2C19

Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

7.13 Monoamine Oxidase Inhibitors

[*see Dosage and Administration (2.5), Contraindications (4.1), and Warnings and Precautions (5.4)*].

7.14 Serotonergic Drugs

Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta, and the potential for serotonin syndrome, caution is advised when Cymbalta is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort. The concomitant use of Cymbalta with other SSRIs, SNRIs or tryptophan is not recommended [*see Warnings and Precautions (5.4)*].

7.15 Triptans

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [*see Warnings and Precautions (5.4)*].

7.16 Alcohol

When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol.

In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen [*see Warnings and Precautions (5.2 and 5.10)*].

7.17 CNS Drugs

[*see Warnings and Precautions (5.10)*].

7.18 Drugs Highly Bound to Plasma Protein

Because duloxetine is highly bound to plasma protein, administration of Cymbalta to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C — In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m^2 basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m^2 basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m^2 basis in rat; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects — Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.4)*].

When treating pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester [*see Dosage and Administration (2.3)*].

8.2 Labor and Delivery

The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the

benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics.

The disposition of duloxetine was studied in 6 lactating women who were at least 12 weeks postpartum. Duloxetine 40 mg BID was given for 3.5 days. Like many other drugs, duloxetine is detected in breast milk, and steady state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 µg/day while on 40 mg BID dosing. The excretion of duloxetine metabolites into breast milk was not examined. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended [(*see Dosing and Administration (2.3)*].

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established [*see Boxed Warning and Warnings and Precautions (5.1)*]. Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

8.5 Geriatric Use

Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD and DPNP studies, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.SSRIs and SNRIs, including Cymbalta have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [*see Warnings and Precautions (5.11)*].

The pharmacokinetics of duloxetine after a single dose of 40 mg were compared in healthy elderly females (65 to 77 years) and healthy middle-age females (32 to 50 years). There was no difference in the C_{max}, but the AUC of duloxetine was somewhat (about 25%) higher and the half-life about 4 hours longer in the elderly females. Population pharmacokinetic analyses suggest that the typical values for clearance decrease by approximately 1% for each year of age between 25 to 75 years of age; but age as a predictive factor only accounts for a small percentage of between-patient variability. Dosage adjustment based on the age of the patient is not necessary [*see Dosage and Administration (2.3)*].

8.6 Gender

Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

8.7 Smoking Status

Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

8.8 Race

No specific pharmacokinetic study was conducted to investigate the effects of race.

8.9 Hepatic Insufficiency

Patients with clinically evident hepatic insufficiency have decreased duloxetine metabolism and elimination. After a single 20-mg dose of Cymbalta, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although C_{max} was similar to normals in the cirrhotic patients, the half-life was about 3 times longer [*see Dosage and Administration (2.3) and Warnings and Precautions (5.12)*].

8.10 Severe Renal Impairment

Limited data are available on the effects of duloxetine in patients with end-stage renal disease (ESRD). After a single 60-mg dose of duloxetine, C_{max} and AUC values were approximately 100% greater in patients with end-stage renal disease receiving chronic intermittent hemodialysis than

in subjects with normal renal function. The elimination half-life, however, was similar in both groups. The AUCs of the major circulating metabolites, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate, largely excreted in urine, were approximately 7- to 9-fold higher and would be expected to increase further with multiple dosing. Population PK analyses suggest that mild to moderate degrees of renal dysfunction (estimated CrCl 30-80 mL/min) have no significant effect on duloxetine apparent clearance [*see Dosage and Administration (2.3) and Warnings and Precautions (5.12)*].

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse

In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential.

While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

9.3 Dependence

In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

10 OVERDOSAGE

10.1 Signs and Symptoms

In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension and vomiting.

10.2 Management of Overdose

There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

An adequate airway, oxygenation, and ventilation should be assured, and cardiac rhythm and vital signs should be monitored. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

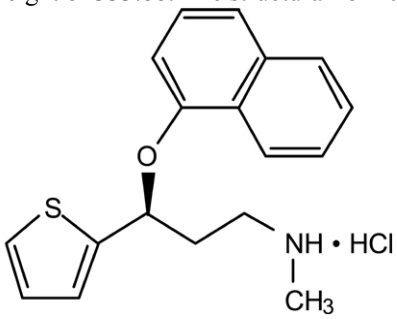
Activated charcoal may be useful in limiting absorption of duloxetine from the gastrointestinal tract. Administration of activated charcoal has been shown to decrease AUC and C_{max} by an average of one-third, although some subjects had a limited effect of activated charcoal. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial.

In managing overdose, the possibility of multiple drug involvement should be considered. A specific caution involves patients who are taking or have recently taken Cymbalta and might ingest excessive quantities of a TCA. In such a case, decreased clearance of the parent tricyclic and/or its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation [*see Warnings and Precautions (5.4) and Drug Interactions (7)*]. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

11 DESCRIPTION

Cymbalta® (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(*S*)-*N*-methyl-γ-(1-

naphthyloxy)-2-thiophenepropylamine hydrochloride. The empirical formula is $C_{18}H_{19}NOS{\bullet}HCl$, which corresponds to a molecular weight of 333.88. The structural formula is:



Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

Each capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include FD&C Blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 20 and 60 mg capsules also contain iron oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.2 Pharmacodynamics

Preclinical studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors *in vitro*. Duloxetine does not inhibit monoamine oxidase (MAO).

Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related.

12.3 Pharmacokinetics

Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and its pharmacokinetics are dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Elimination of duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP1A2 and CYP2D6.

Absorption and Distribution — Orally administered duloxetine hydrochloride is well absorbed. There is a median 2-hour lag until absorption begins (T_{lag}), with maximal plasma concentrations (C_{max}) of duloxetine occurring 6 hours post dose. Food does not affect the C_{max} of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%. There is a 3-hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose.

The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α_1-acid glycoprotein. The interaction between duloxetine and other highly protein bound drugs has not been fully evaluated. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

Metabolism and Elimination — Biotransformation and disposition of duloxetine in humans have been determined following oral administration of ^{14}C-labeled duloxetine. Duloxetine comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring

followed by conjugation and further oxidation. Both CYP1A2 and CYP2D6 catalyze the oxidation of the naphthyl ring *in vitro*. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the feces. Duloxetine undergoes extensive metabolism, but the he major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis — Duloxetine was administered in the diet to mice and rats for 2 years.

In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m^2 basis).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m^2 basis) did not increase the incidence of tumors.

Mutagenesis — Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility — Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m^2 basis) did not alter mating or fertility.

14 CLINICAL STUDIES

14.1 Major Depressive Disorder

The efficacy of Cymbalta as a treatment for depression was established in 4 randomized, double-blind, placebo-controlled, fixed-dose studies in adult outpatients (18 to 83 years) meeting DSM-IV criteria for major depression. In 2 studies, patients were randomized to Cymbalta 60 mg once daily (N=123 and N=128, respectively) or placebo (N=122 and N=139, respectively) for 9 weeks; in the third study, patients were randomized to Cymbalta 20 or 40 mg twice daily (N=86 and N=91, respectively) or placebo (N=89) for 8 weeks; in the fourth study, patients were randomized to Cymbalta 40 or 60 mg twice daily (N=95 and N=93, respectively) or placebo (N=93) for 8 weeks. There is no evidence that doses greater than 60 mg/day confer additional benefits.

In all 4 studies, Cymbalta demonstrated superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score.

In all of these clinical studies, analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

In another study, 533 patients meeting DSM-IV criteria for MDD received Cymbalta 60 mg once daily during an initial 12-week open-label treatment phase. Two hundred and seventy-eight patients who responded to open label treatment (defined as meeting the following criteria at weeks 10 and 12: a HAMD-17 total score ≤9, Clinical Global Impressions of Severity (CGI-S) ≤2, and not meeting the DSM-IV criteria for MDD) were randomly assigned to continuation of Cymbalta at the same dose (N=136) or to placebo (N=142) for 6 months. Patients on Cymbalta experienced a statistically significantly longer time to relapse of depression than did patients on placebo. Relapse was defined as an increase in the CGI–S score of ≥2 points compared with that obtained at week 12, as well as meeting the DSM-IV criteria for MDD at 2

consecutive visits at least 2 weeks apart, where the 2-week temporal criterion had to be satisfied at only the second visit. The effectiveness of Cymbalta in hospitalized patients with major depressive disorder has not been studied.

14.2 Diabetic Peripheral Neuropathic Pain

The efficacy of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy was established in 2 randomized, 12-week, double-blind, placebo-controlled, fixed-dose studies in adult patients having diabetic peripheral neuropathic pain for at least 6 months. Study 1 and 2 enrolled a total of 791 patients of whom 592 (75%) completed the studies. Patients enrolled had Type I or II diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for at least 6 months. The patients had a baseline pain score of ≥4 on an 11-point scale ranging from 0 (no pain) to 10 (worst possible pain). Patients were permitted up to 4 g of acetaminophen per day as needed for pain, in addition to Cymbalta. Patients recorded their pain daily in a diary.

Both studies compared Cymbalta 60 mg once daily or 60 mg twice daily with placebo. Study 1 additionally compared Cymbalta 20 mg with placebo. A total of 457 patients (342 Cymbalta, 115 placebo) were enrolled in Study 1 and a total of 334 patients (226 Cymbalta, 108 placebo) were enrolled in Study 2. Treatment with Cymbalta 60 mg one or two times a day statistically significantly improved the endpoint mean pain scores from baseline and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figures 1 and 2 show the fraction of patients achieving that degree of improvement. The figures are cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

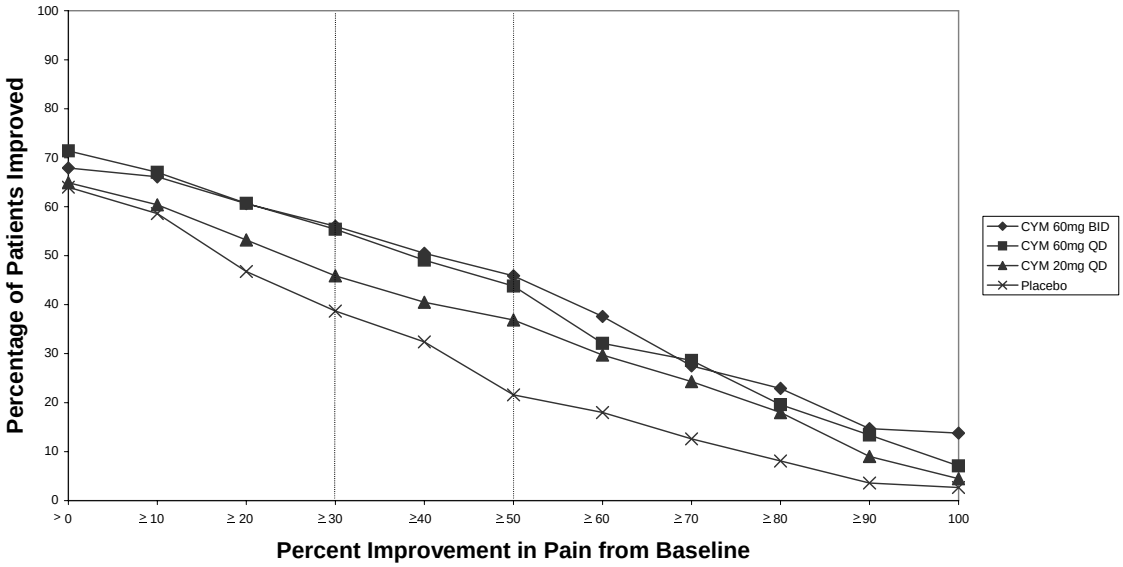


Figure 1: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 1

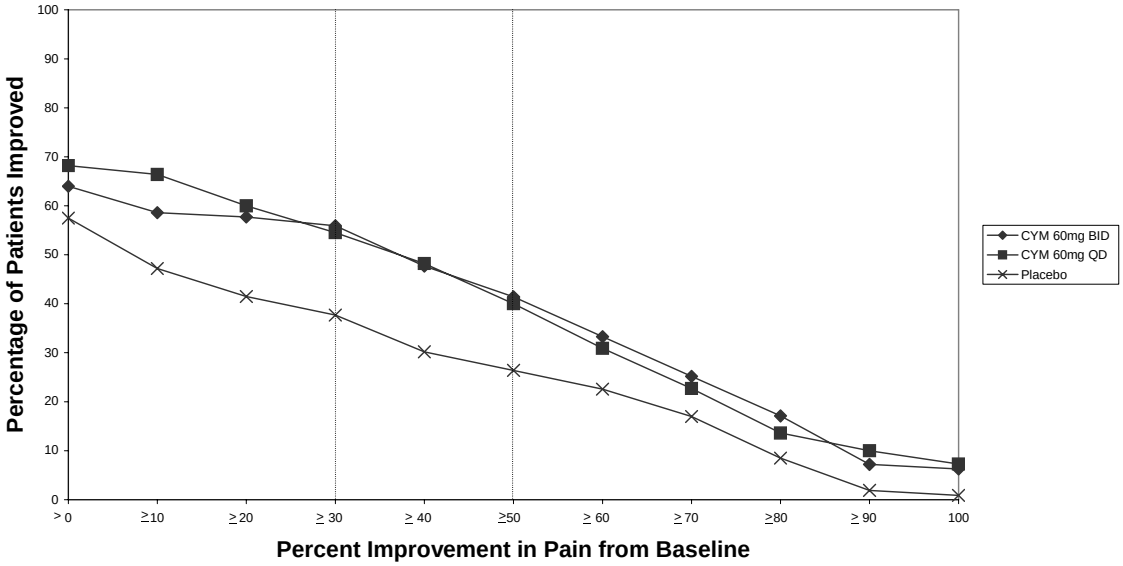


Figure 2: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 2

14.3 Generalized Anxiety Disorder

The efficacy of Cymbalta in the treatment of generalized anxiety disorder (GAD) was established in 1 fixed-dose randomized, double-blind, placebo-controlled trial and 2 flexible-dose randomized, double-blind, placebo-controlled trials in adult outpatients between 18 and 83 years of age meeting the DSM-IV criteria for GAD.

In 1 flexible-dose study and in the fixed-dose study, the starting dose was 60 mg once daily where down titration to 30 mg once daily was allowed for tolerability reasons before increasing it to 60 mg once daily. Fifteen percent of patients were down titrated. One flexible-dose study had a starting dose of 30 mg once daily for 1 week before increasing it to 60 mg once daily.

The 2 flexible-dose studies involved dose titration with Cymbalta doses ranging from 60 mg once daily to 120 mg once daily (N=168 and N=162) compared to placebo (N=159 and N=161) over a 10-week treatment period. The mean dose for completers at endpoint in the flexible-dose studies was 104.75 mg/day. The fixed-dose study evaluated Cymbalta doses of 60 mg once daily (N=168) and 120 mg once daily (N=170) compared to placebo (N=175) over a 9-week treatment period. While a 120 mg/day dose was shown to be effective, there is no evidence that doses greater than 60 mg/day confer additional benefit.

In all 3 studies, Cymbalta demonstrated superiority over placebo as measured by greater improvement in the Hamilton Anxiety Scale (HAM-A) total score and by the Sheehan Disability Scale (SDS) global functional impairment score. The SDS is a widely used and well-validated scale that measures the extent emotional symptoms disrupt patient functioning in 3 life domains: work/school, social life/leisure activities and family life/home responsibilities.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Cymbalta® is available as capsules in the following strengths, colors, imprints, and presentations:

Features	**Strengths**		
	20 mg*	**30 mg***	**60 mg***
Body color	Opaque green	Opaque white	Opaque green

Cap color	Opaque green	Opaque blue	Opaque blue
Cap imprint	Lilly 3235	Lilly 3240	Lilly 3237
Body imprint	20mg	30mg	60mg
Capsule number	PU3235	PU3240	PU3237
Presentations and NDC Codes			
Bottles of 30	NA	0002-3240-30	0002-3237-30
Bottles of 60	0002-3235-60	NA	NA
Bottles of 90	NA	0002-3240-90	0002-3237-90
Bottles of 1000	NA	0002-3240-04	0002-3237-04
Blisters ID†100	0002-3235-33	0002-3240-33	0002-3237-33

* equivalent to duloxetine base
† Identi-Dose® (unit dose medication, Lilly)

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide

17.1 Information on Medication Guide

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Cymbalta and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for Cymbalta. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Cymbalta.

17.2 Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication [*see Boxed Warning, and Warning and Precautions (5.1)*].

17.3 Medication Administration

Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the capsule be opened and its contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating.

17.4 Continuing the Therapy Prescribed

While patients may notice improvement with Cymbalta therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

17.5 Abnormal Bleeding

Patients should be cautioned about the concomitant use of duloxetine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding [*see Warnings and Precautions, (5.5)*].

17.6 Concomitant Medications

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter medications, since there is a potential for interactions [*see Dosage and Administration (2.5), Contraindications (4.1), Warnings and Precautions (5.4 and 5.10), and Drug Interactions (7)*].

17.7 Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of Cymbalta and triptans, tramadol or other serotonergic agents [*see Warnings and Precautions (5.4) and Drug Interactions (7.14)*].

17.8 Pregnancy and Breast Feeding

Patients should be advised to notify their physician if they

- become pregnant during therapy
- intend to become pregnant during therapy
- are breast-feeding [*see Dosage and Administration (2.3) and Use in Specific Populations (8.1, 8.2, and 8.3)*].

17.9 Alcohol

Although Cymbalta does not increase the impairment of mental and motor skills caused by alcohol, use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should ordinarily not be prescribed for patients with substantial alcohol use [*see Warnings and Precautions (5.2) and Drug Interactions (7.16)*].

17.10 Orthostatic Hypotension and Syncope

Patients should be advised of the risk of orthostatic hypotension and syncope, especially during the period of initial use and subsequent dose escalation, and in association with the use of concomitant drugs that might potentiate the orthostatic effect of duloxetine [*see Warnings and Precautions (5.3)*].

17.11 Interference with Psychomotor Performance

Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies Cymbalta has not been shown to impair psychomotor performance, cognitive function, or memory, it may be associated with sedation and dizziness. Therefore, patients should be cautioned about operating hazardous machinery including automobiles, until they are reasonably certain that Cymbalta therapy does not affect their ability to engage in such activities.

Literature revised: mmm dd, yyyy

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Indianapolis, IN 46285, USA
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A NL 5901 AMP PRINTED IN USA

Medication Guide

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability

- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the US Food and Drug Administration for all antidepressants.

Patient Information revised June 21, 2007

PV 5083 AMP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427/S-015, S-017

OFFICE DIRECTOR MEMO

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 28, 2007

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approvable action for Cymbalta (duloxetine) for the maintenance treatment of major depressive disorder (MDD)

TO: File NDA 21-427/S-015
[Note: This overview should be filed with the 10-31-06 original submission of this supplemental NDA.]

1.0 BACKGROUND

Cymbalta (duloxetine) is an SNRI that is approved for the treatment of MDD, diabetic peripheral neuropathic pain, and GAD. This supplement seeks a claim for the maintenance treatment of MDD, at a dose of 60 mg/day. The study supporting this claim was conducted under IND 38,838, and a pre-supplemental NDA meeting was held with the sponsor on 10-5-05.

2.0 CHEMISTRY

There were no CMC issues that required a review, other than environmental assessment. This was done and found to be acceptable.

3.0 PHARMACOLOGY

There were no pharmacology/toxicology issues that required a review.

4.0 BIOPHARMACEUTICS

There were no biopharmaceutics issues that required a review.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Study F1J-MC-HMBC

This was a randomized withdrawal study that began with a 12-week, open-label run-in period in adult patients with acutely symptomatic MDD. They were treated with duloxetine 60 mg/day (Note: Patients could be reduced to 30 mg/day for tolerability problems, but not beyond week 4. After week 4, patients who could not tolerate 60 mg/day were dropped.) "Response" for the purposes of randomization was defined as meeting the following criteria for a minimum of 2 weeks at the end of the study, i.e., weeks 10 through 12 (visits 7 and 8):

-No longer meeting criteria for MDD
-HAMD17 $\leq$ 9
-CGI-S $\leq$ 2.

Patients meeting this definition of "response" were randomized to either continue on duloxetine 60 mg/day or switch to placebo. They were then observed for "relapse" for a period of up to 26 weeks, on a double-blind basis. "Relapse" was defined as follows:

-An increase in CGI-S of $\geq$ 2 points (relative to the value at week 12), for 2 consecutive visits, and
-Meeting criteria for MDD, for 2 consecutive visits
-In addition, the primary analysis included patients meeting a second definition of "relapse associated with reemergence," i.e., patients who had a total of 6 visits with a HAMD17 total score $\geq$ 12.

The sponsor had a second definition of "response" at any point during the run-in phase, i.e., $\geq$ 50% reduction of the HAMD17 total score. However, this definition had nothing to do with randomization and its purpose was not clear.

A total of 278 patients met "response" criteria for randomization and were randomized (136 to duloxetine 60 mg/day and 142 to placebo). The log rank test for time to relapse was highly statistically significant (p=0.004), and was associated with relapse rates of 17% for duloxetine vs 29% for placebo. Exploratory analyses were done to detect subgroup interactions on the basis primarily of age, gender, and race. There was no indication of any difference in effectiveness based on these subgroups.

(b) (4)

(b) (4) In addition, we also noted in our minutes for that meeting that "the exact wording of labeling will be a matter of review." Clearly, we have the prerogative to make final decisions about labeling after seeing and reviewing all the data. (b) (4) Dr. Khin has suggested 5 weeks as a (b) (4) reasonable time period, since this captured 88% of the total randomized population. I am not inclined to accept these post-hoc analyses. Not only is this post-hoc, but in addition, this approach does not require that patients continuously meet this criterion, e.g., a patient would qualify if this criterion were met at weeks 2, 3, 4, 5, 6, but not 7, 8, 9, and 10. I would prefer instead to simply state in labeling that patients were in a "responder " status for at least 2 weeks, and leave it at that, since apparently it is not possible to determine the average length of time patients were in a "responder" status, as defined for randomization.

5.1.2 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of the maintenance efficacy of Cymbalta in the treatment of MDD. We differ with the sponsor on how to characterize this finding in labeling.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review and Overview of Findings

The safety data for this supplement came entirely from the 278 patients randomized in study HMBC. Of the 278 randomized patients, 136 received duloxetine and 142 received placebo. The profile of AEs observed with duloxetine was as expected, given what is already known about this drug.

5.2.2 Conclusions Regarding Safety of Cymbalta

There were no new safety findings for Cymbala revealed for this supplement. However, we have been reviewing duloxetine safety data from other sources, and we will ask for labeling updates regarding these other events (e.g., serious skin reactions, hyponatremia) in our draft labeling.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have asked the sponsor to make a number of changes, and in some cases, provide new information.

6.0 WORLD LITERATURE

The sponsor provided literature references that were reviewed by Dr. Glass. These provided no new information that would change conclusions about the approvability of this application.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Cymbalta is not approved anywhere at this time for the maintenance treatment of MDD.

8.0 DSI INSPECTIONS

Inspections were conducted at 2 sites, and data from both sites were deemed to be acceptable.

10.0 LABELING AND APPROVABLE LETTER

10.1 Labeling

As noted, we have drafted an alternative version of labeling that we will forward with the approvable letter.

10.2 Foreign Labeling

To my knowledge, Cymbalta is not approved anywhere at this time for the maintenance treatment of MDD.

10.3 Approvable Letter

The approvable letter includes our draft of labeling.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Lilly has submitted sufficient data to support the conclusion that Cymbalta is effective and acceptably safe in the maintenance treatment of MDD. We have drafted a version of labeling that we will attach to an approvable letter, in anticipation of final approval.

cc:
Orig NDA 21-427/S-015
HFD-130
HFD-130/TLaughren/MMathis/NKhin/RGlass/WBender
DOC: Cymbalta_MDD_LT_Laughren_AE_Memo.doc

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

/s/

Thomas Laughren
8/28/2007 08:47:48 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427/S-015, S-017

CROSS DISCIPLINE TEAM LEADER REVIEW

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 28, 2007

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products

TO: File NDA 21-427/SE1-015 (This overview should be filed with the 09-28-2007 submission.)

SUBJECT: Recommendation of Approval Action for Cymbalta (duloxetine) for the Maintenance Treatment of Major Depressive Disorder (MDD)

Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI). It is approved in the U.S. since August 3, 2004, for the treatment of major depressive disorder (MDD) at doses up to 60 mg per day. It is also approved for the treatment of diabetic peripheral neuropathic pain at doses up to 120 mg/day (HFD-170). Recently, duloxetine is approved for its use in the treatment of Generalized Anxiety Disorder. Duloxetine capsules are available in 20, 30, 40 and 60 mg strengths.

The sponsor has submitted the above referenced supplemental NDA on October 31, 2006. The application included the efficacy results from a randomized withdrawal trial: study F1J-MC-HMBC. This submission contains revised labeling in a new PLR format. The clinical data was reviewed by Roberta Glass, M.D., Medical Officer, DPP, and an approvable letter (AE) for S-015 was sent on August 28, 2007.

In the AE letter, the sponsor was informed that the following labeling issues would need to be addressed before this supplement could be approved:

1) Labeling changes in Dosage and Administration: include a sentence stating that the capsule should not be opened and its contents sprinkled on food; reinserted part of approved language for (b) (4) .
2) (b) (4)
3) We asked the sponsor to incorporate recent class labeling changes regarding adult suicidality, and hyponatremia subsections under Warnings/Precautions.
4) (b) (4)
5) Based on post-marketing experience, there were cases of urinary retention in which some needed hospitalization and/or catheterization. We've proposed that this subsection should be moved from the AE section to part of Warnings/Precautions.

6) The sponsor should provide justification on their proposal to (b) (4) .

The sponsor submitted their responses to the labeling issues stated above on September 28, 2007. The sponsor has adequately addressed the labeling issues cited in the AE letter.

During this review cycle, Drs. Villalba and Hughes from the safety team who reviewed the OSE report on serious skin reactions cases, also reviewed arguments and supporting documents submitted by Lilly on this topic. It was concluded that we do not yet have strong enough evidence to add the risk of SJS as a Warning/Precaution. We added a statement regarding SJS cases with duloxetine which required hospitalization in the post-marketing reports section for now (email dated 11/20/2007). Additionally, we asked that a new section under Warnings/Precautions, that described the risk of abnormal bleeding with SSRI/SNRIs including Cymbalta and the sponsor agreed to do so.

All these labeling changes were negotiated with the sponsor. Now that we have reached agreement on labeling language with the sponsor, I recommend we consider approval of this NDA supplement. A copy of final labeling should be included in the approval letter.

cc: HFD-130/Laughren/Mathis/Glass/Bender

File: NDA\21427\Memo_SE1015_AEresponse_112007

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/s/

Ni Aye Khin
11/28/2007 08:02:19 AM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 12, 2007

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products

TO: File NDA 21-427/SE1-015 (This overview should be filed with the 10-31-2006 submission.)

SUBJECT: Recommendation of Approval Action for Cymbalta (duloxetine) for the Maintenance Treatment of Major Depressive Disorder (MDD)

1. BACKGROUND

Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI). It is approved in the U.S. since August 3, 2004, for the treatment of major depressive disorder (MDD) at doses up to 60 mg per day. It is also approved for the treatment of diabetic peripheral neuropathic pain at doses up to 120 mg/day (HFD-170). Recently, duloxetine is approved for its use in the treatment of generalized anxiety disorder. Duloxetine capsules are available in 20, 30, 40 and 60 mg strengths.

Currently, Prozac (fluoxetine), Zoloft (sertraline), Paxil (paroxetine), Celexa (citalopram), Lexapro (escitalopram), Effexor XR (venlafaxine)], Remeron (mirtazapine), Serzone (nefazodone) and EMSAM (selegiline transdermal system) are labeled for maintenance of efficacy for MDD claim with some variation in language to convey the stabilization period.

The sponsor has submitted the above referenced supplemental NDA on October 31, 2006. The application included the efficacy results from a randomized withdrawal trial: study F1J-MC-HMBC.

This supplemental NDA has been reviewed by Roberta Glass, M.D., Medical Officer, DPP (review dated 6/26/2007) and Yeh Fong Chen Ph.D., from the Office of Biostatistics (review dated /2007). An Environmental Assessment Review was conducted by Raanan A. Bloom, Ph.D., Chemistry reviewe (memo dated 6/15/2007).

2.0 CHEMISTRY

No new CMC information submitted in this sNDA except environmental assessment issues. A finding of no significant impact was recommended.

3.0 PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology issues submitted in this sNDA.

4.0 CLINICAL PHARMACOLOGY

There was no OCP issues submitted that would require a review.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of one randomized withdrawal study (study F1J-MC-HMBC) to evaluate the efficacy and safety of duloxetine in the maintenance treatment of MDD.

5.1.2 Summary of Study Pertinent to Efficacy Claim

Study F1J-MC-HMBC

This study consisted of a 12- week open-label acute therapy phase in which adult patients who met a DSM-IV diagnosis of MDD without psychotic features were treated with duloxetine 60 mg po once daily. Patients who had difficulty tolerating duloxetine 60 mg QD (two capsules) had, at the investigator's discretion, the number of capsules reduced to 30 mg QD (one capsule) at any time up to Visit 5 (week 4). The dose was returned to 60 mg QD no later than Visit 5 or the patient was discontinued. Those patients who fulfilled requirements of response criteria were randomized (Visit 8, week 12) into the 26 week, double-blind, placebo-controlled, continuation therapy phase of the study, in which time to relapse during the continuation phase was assessed as primary efficacy variable.

The protocol-defined "Response" for determining eligibility for randomization in the continuation therapy phase was defined as, at Visit 7 and Visit 8:

- No longer meeting the diagnostic criteria for DSM-IV-defined MDD, and
- $HAMD_{17} \leq 9$, and
- CGI-Severity ≤ 2.

"Response" during the study at any point was also defined as 50% reduction of $HAMD_{17}$ total score from baseline.

In general, the time period that patients were considered responders up to the beginning of the placebo controlled portion of the study is considered to be the stabilization period. There was no definition of stabilization period in the protocol.

According to the protocol, "relapse" during the continuation therapy phase was defined as:

- An increase in the CGI-Severity score of at least two points relative to the rating at Visit 8 for two consecutive visits; and

- Meeting the criteria for major depressive episode for two consecutive visits, as determined by the depression module of the MINI. However, the temporal criterion (2 weeks) had to be met at only the second visit.

The 'Relapse associated with reemergence' was defined as:

- Six visits of any kind (weekly or regularly scheduled, consecutive or nonconsecutive) during the continuation phase with a HAMD score ≥ 12.

The study was conducted at 30 centers located in the U.S., France, Spain and Italy. A total of 681 patients were screened for the study. Of these 681 patients, 148 failed to meet entry criteria or declined to participate in the study. The remaining 533 patients were enrolled into the acute therapy phase and received duloxetine 60 mg once daily (QD) at Visit 2. A total of 278 patients continued in the study at the end of the acute therapy phase and were randomized to receive either duloxetine 60 mg qd (136 subjects) or placebo (142 subjects) at Visit 8. A total of 74 subjects (54.4%) in duloxetine group, and 47 subjects (33.1%) in placebo group, completed the study. 29 duloxetine patients and 58 placebo patients entered the optional rescue phase of the study. 70 subjects discontinued (33 subjects from duloxetine and 37 subjects from placebo group). The reasons for discontinuation from the study included protocol violations (more dropouts due to this reason in duloxetine group 7.4% vs. 4.9% in placebo), adverse events (similar numbers between duloxetine treatment 3.7% and placebo groups 3.5%), lack of efficacy (2.1% in placebo vs. 0.7% in duloxetine), patient decision, and lost to follow up.

The subjects enrolled were mostly Caucasian (93.5%) and women (72%). Mean age was approximately 45 yrs. There seemed to be no significant differences in demographic characteristics among the treatment groups.

The primary efficacy analysis compared the time to relapse during the continuation phase between treatment groups using the log rank test. Dr. Chen confirmed the efficacy results. Dr. Chen noted in her statistical review that relapses associated with reemergence were also included as relapse events for the analysis. Survival curves were constructed using the Kaplan-Meier method. Time to relapse was the time from Visit 8 to the first visit during the continuation therapy phase at which the patient met the relapse criteria. For patients who did not relapse during the continuation phase, the time to censoring was the time from Visit 8 to the patient's endpoint visit during the continuation therapy phase.

(b) (4)

As stated in both Drs. Glass and Chen in their reviews, from the protocol design, it appears that patients were only required to have two weeks of stabilization at Visits 7 and 8 (Week 10 & 12) prior to randomization into the double-blind phase. It was noted that the HAMD assessments were done baseline and at weeks 1 (V3), 2 (V4), 4 (V5), 7 (V6), 10 (V7) and 12 (V8) during the open label acute phase.

Dr. Chen conducted an alternative analysis to describe the stabilization period using the response criteria of 50% reduction of $HAMD_{17}$ total score from baseline during the study at any time point, in addition to the protocol-defined "response" criteria two weeks prior to randomization (i.e., at Visit 7 and Visit 8: no longer meeting the diagnostic criteria for DSM-IV-defined MDD, and $HAMD_{17} \leq 9$, and CGI-Severity ≤ 2. Based on Dr. Chen's analysis, the study results were noted below.

Table 1: Summary of percent of patients who have achieved stabilization at each time point assessed prior to randomization.

Stabilization Period (Weeks prior to randomization)	2	5	8	10	11
Number of Patients Stabilized (%) (total randomized n=278)	32 (12%)	62 (22%)	77 (28%)	67 (24%)	40 (14%)
Accumulative percent of patients achieving stabilization prior to randomization	(100%)	(88%)	(66%)	(38%)	(14%)

Table 2: Duration of Response and corresponding relapse rate

Duration of Response (weeks)	≥5	≥8	≥10	≥11
Relapse rate Duloxetine placebo	 0.16(=19/116) 0.26(=32/122)	 0.17(=14/84) 0.25(=24/94)	 0.1=(5/50) 0.3(=16/53)	 0.11(=2/18) 0.33(=7/21)
p-value	0.0054	0.0163	0.0032	0.0852

Regarding patients' duration of continuous response and the average of time that patients have response (defined by ≥50% decrease from baseline in the $HAMD_{17}$ before 2 weeks prior to randomization), the average was found to be 5.55 weeks (i.e. continuous response for 7.55 weeks before randomization on average). In other words, the majority of patients (66% of randomized subjects) would have stabilization period of at least 8 weeks; 88% of randomized patients would have stabilization period of at least 5 weeks.

Based on all randomized ITT population, 23 out of 132 patients (17.4%) who were randomized to duloxetine 60 mg QD and 39 out of 137 patients (28.5%) who were randomized to placebo relapsed during the continuation therapy phase. Both the unstratified and country-stratified analyses demonstrated that the differences between duloxetine 60 mg QD and placebo were statistically significant (p=0.004 and p=0.002, respectively). Patients in duloxetine 60 mg QD groups had

longer time to relapse than patients in placebo as can be seen in the Kaplan-Meier Plot of time to relapse (Figure 6.1.4 in Dr. Glass' clinical review).

Comment: Both Drs. Glass and Chen considered this a positive study for duloxetine, and I agree with them. We would be able to adequately describe the stabilization period in the labeling.

5.1.3 Comments on Other Important Clinical Issues

Subgroup analyses on baseline disease characteristics and treatment effect
The sponsor performed exploratory subgroup analyses in order to detect subgroup interactions on the basis of gender (M, F), age (<55 yrs, ≥55 yrs) and race (Caucasian, non-Caucasian). Dr. Chen confirmed the sponsor's analysis. No statistically significant treatment by subgroup interactions was observed. Baseline HAMD scores were similar between the treatment groups.

Secondary efficacy variable
In order to be eligible to be considered a key secondary variable in the labeling, the results would need to be replicated in a second study, and a hypothesis testing plan would need to be pre-specified in the protocol. This application is based on results from a single study. Therefore, there will be no issue of secondary efficacy variable claim the labeling.

Dose response relationship
In this study, only 60 mg dose of duloxetine was used as compared to placebo.

5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analyses of HMBC supported the maintenance efficacy claim of duloxetine in the treatment of MDD.

5.2 Safety Data

5.2.1 Satety Database

As stated by Dr. Glass in her review, the safety review of this sNDA is limited to the safety data from study HMBC with the data cut-off date of 4/26/2006 for this sNDA submission, and of 10/31/2006 for the safety update (with listing of deaths cut-off date 1/28/2007), respectively.

Out of a total of 278 subjects who entered the 26 week double-blind placebo controlled phase of the study, 136 were treated with duloxetine 60 mg qd and 142 subjects received placebo. Based on the sponsor's calculation, the mean days of exposure was 125±69 days. There were 32 (24%) that had an exposure of ≤181 days and 45 (33%) subjects had an exposure of ≥182 days.

There was no death reported during the placebo-controlled, continuous treatment phase of the study. Serious adverse events were available from this double-blind phase. 5 out of 7 subjects who experienced SAE were the duloxetine treated patients. The events listed were cholelithiasis, GI reflux disease, suicidal ideation, vaginal hemorrhage and wrist fracture. The AE dropout rates were comparable for both the placebo (3.5%) and the duloxetine (3.7%) groups.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk). Based on the limited information provided by the sponsor in this application, the AEs occurring in ≥5% of patients in the duloxetine 60 mg qd treatment group included headaches, dizziness, nausea and arthralgia.

It was noted by Dr. Glass in her review that the sponsor only provided common AEs incidence for the first two weeks and did not cover the entire 26 week period of the study. Although it is not anticipated to see any new common AEs during this period, prior to taking final action, we should ask the sponsor to update any common AE in the proposed labeling if they are different from those already in the labeling.

5.2.2.2 Vital Signs Data

A statistically significant mean increase (+1.03 mmHg) from baseline in supine diastolic blood pressure was observed in duloxetine (N=97) group as compared to placebo (N=99). One subject (0.75%) in the duloxetine treated group who demonstrated a sustained elevation in blood pressure (defined as either systolic or diastolic BP>140 mm Hg and an increase from baseline >10 mm Hg at three consecutive visits) as compared to no placebo-treated patients. The vital sign findings are adequately described in the current labeling.

5.2.2.3 Laboratory Tests

There were statistically significant difference in mean changes from baseline to endpoint in abnormal laboratory parameters including alkaline phosphatase (-2.4 U/L), GGT (0.3) and CPK (-34.8 U/L) between duloxetine and placebo.

5.2.2.4 Post-Marketing Safety Evaluations

The Office of Surveillance and Epidemiology (OSE) has reviewed the post marketing reports on serious skin reactions such as EM and SJS, and recommended labeling changes that serious skin reaction be added to the Precautions section of the labeling.

Duloxetine was the first drug which was used in the CDER pilot study to assess the post marketing safety evaluation of new molecular entities. Our DNP/DPP safety group and the OSE have been working on safety issues during this pilot study. At present, we have received completed reviews from 1) DMETS on medication errors (3/8/07), 2) a safety review by Dr. Villalba on post marketing cases of loss of consciousness (5/22/07), and 3) a safety review by Dr. Stone on hepatic cases (5/16/07). We have requested the sponsor to provide additional information regarding post marketing hepatic cases and overdose events. Dr. Stone will continue working on duloxetine hepatic cases, and Dr. Villalba will review the data when the requested information on overdose cases is received. The OSE has just completed their reviews of post marketing cases with urinary retention that resulted in hospitalization and/or catheterization and recommended that DPP consider adding this information to the precaution section. The OSE is currently working on their reviews of post marketing cases of bleeding disorders and drug interactions, and expect to receive the reviews in

August 2007. The safety team MO Dr. Villalba and safety team leader Dr. Hughes has been working on modification of hyponatremia language as part of class labeling. We should evaluate and consider incorporating any of these recommended labeling changes when we negotiate labeling with the sponsor during this review cycle of the pending efficacy supplement.

5.2.3 Conclusion Regarding Safety Data

Overall, this supplemental NDA submission revealed no new or specific safety concerns. We should evaluate and further follow up on any post-marketing safety issues with this drug as the completed reviews from the safety team and the OSE as part of the pilot NME post marketing safety evaluation project are received.

6.0 WORLD LITERATURE

The sponsor has provided a brief literature review in this submission. Based on Dr. Glass' review, the submitted materials did not mention any unknown adverse events.

7.0 FOREIGN REGULATORY ACTION

Based on the sponsor's submission list, as of February 2006, this drug has been approved in 35 countries for MDD, 2 countries for diabetes neuropathic pain, and in 14 countries for stress urinary incontinence.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 2 study sites. DSI recommended that data from these inspected sites appear acceptable in support of this NDA. Inspectional findings did not seem to raise any major concern on integrity of study data.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

This submission contains revised labeling in a new PLR format. The sponsor's proposed language in this submission has been modified. We plan to incorporate part of the labeling changes proposed by the safety team and the OSE. All these labeling changes will be negotiated with the sponsor. A copy of final labeling should be included in the action letter.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to demonstrate a longer time to relapse comparing duloxetine to placebo in the maintenance treatment of MDD. While I note both Drs. Chen and Glass' concerns regarding determination of the length of stabilization period during the open-label

treatment with duloxetine based on the study design, I believe we would be able to adequately describe the stabilization period in the labeling. I recommend we consider approval of this NDA supplement provided that we reach an agreement with the sponsor regarding the language in the labeling.

cc: HFD-130/Laughren/Mathis/Glass/Bender

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/s/

Ni Aye Khin
7/16/2007 05:31:51 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427/S-015, S-017

MEDICAL REVIEW(S)

Review of Clinical Data

NDA:	21-427 (S-015)
Drug Name:	Generic Name: Duloxetine Trade Name: Cymbalta®
Sponsor:	Lilly
Material Reviewed:	Proposed labeling revision
Reviewer:	Marc Stone, MD
Date Completed:	30 July 2007

As part of its application for an indication for maintenance of effect for duloxetine, Lilly has submitted changes to the product label regarding hepatotoxicity. The changes consist of 1) revised numbers for the incidence of discontinuation due to elevated liver transaminase levels and the incidence of ALT levels above three times the upper limit of normal that include clinical trials completed since the original labeling and no longer show separate numbers by indication

(b) (4)

The revised numbers for the incidence of discontinuation are shown in this table:

Transaminase elevations leading to discontinuation			
	No	Yes	
Original label	8423	31	0.37%
Subsequent Trials	15487	42	0.27%
Total	23910	73	0.30%

The difference in incidence between the original label and subsequent trials is not statistically significant (p=0.22). The next table compares the incidence of ALT elevations:

ALT elevation	>3xULN						
	Duloxetine			Placebo			
	No	Yes		No	Yes		Odds ratio
MDD	922	8	0.86%	650	2	0.31%	2.82
DPN	469	8	1.68%	187	0	0.00%	Inf
Other	2302	23	0.99%	1725	4	0.23%	4.31
Total Original Label	3693	39	1.05%	2562	6	0.23%	4.51
Subsequent Trials	3103	36	1.15%	2461	7	0.28%	4.08
Total	6796	75	1.09%	5023	13	0.26%	4.26

The difference in incidence among indications in the original label is not statistically significant for duloxetine (p=0.33) or placebo (p=0.79). Similarly, there is no significant difference in incidence between the original label and subsequent trials for duloxetine (p=0.73) or placebo (p=0.79). The odds ratios also remain quite similar. In summary, these revisions do not alter the impression given in the original label but, due to the larger sample size, strengthen it.

(b) (4)

(b) (4)

Lilly has also changed the statement under section 5.4 “Patients with Hepatic Insufficiency” (b) (4) from “Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and Cymbalta should not be administered to these patients.” This change removes the explanation for why Cymbalta should be avoided but the reader is referred to a better explanation in section 8.9 while removing “It is recommended that duloxetine not be administered to patients with any hepatic insufficiency” from that section. These changes constitute an acceptable reduction in redundancy.

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/s/

Marc Stone
8/6/2007 03:08:11 PM
MEDICAL OFFICER

Reference to 5.4 added

Alice T. Hughes
8/6/2007 03:23:39 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 21-427
Submission Number	S 015
Submission Code	SE-1
Letter Date	10/31/06
Stamp Date	10/31/06
PDUFA Goal Date	9/1/07
Reviewer Name	Roberta Glass, M.D.
Review Completion Date	6/26/07
Established Name	Duloxetine
(Proposed) Trade Name	Cymbalta
Therapeutic Class	Serotonin and norepinephrine re-uptake inhibitor
Applicant	Eli Lilly & Co.
Priority Designation	S
Formulation	Capsule
Dosing Regimen	20 mg, 30 mg, 40 mg & 60 mg qd
Indication	Major Depressive Disorder, maintenance of efficacy
Intended Population	Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The sponsor was able to demonstrate a longer time to relapse comparing a duloxetine treatment group to placebo in a 26 week placebo controlled study, HMBC. The difficulty lies in determining the length of stabilization in the open label duloxetine treated phase prior to randomization into the placebo controlled portion of the study. It is recommended that the sponsor claim with certainty that patients had a stabilization period of 2 weeks prior to randomization into the portion of the study assessing relapse.

If it is deemed acceptable that a stabilization period be defined by a response criteria that was assessed infrequently (i.e. every 2-3 weeks), then the data suggests that approximately 66% of patients had a stabilization period of 8 weeks, while 88% achieved a stabilization period of 5 weeks prior to randomization into the portion of the study assessing relapse.

On the other hand, if utilizing a response criteria that was measured infrequently is not acceptable, it is recommended that the sponsor conduct a study which includes a well defined 12 week stabilization period, and then pursue this claim for maintenance of effect. This recommendation is made in light of the fact that a two week stabilization period is not clinically significant in the treatment of major depressive disorder, and does not support a claim for long term treatment.

Please see the labeling section for further recommendations.

1.2 Recommendation on Postmarketing Actions

There have been many post-marketing reports regarding safety issues with duloxetine. Duloxetine was the first drug assessed in the CDER pilot study examining the post-marketing evaluation of new molecular entities. There were many safety issues identified that are actively being followed by the safety group of HFD-130, and the Office of Surveillance and Epidemiology (ODE). Please refer to Section 7.2.7 for a listing of significant adverse events being followed.

1.2.1 Risk Management Activity

The HFD-130 safety group and the Office of Surveillance and Epidemiology (ODE) will be following the recommendations made during the CDER pilot New Molecular Entity initiative.

1.2.2 Required Phase 4 Commitments

In this submission, the sponsor states that they are preparing to assess duloxetine in the pediatric population in response to FDA's pediatric written request. It would be helpful if the sponsor also conducted a relapse prevention study in the pediatric population for the indication of major depressive disorder.

1.2.3 Other Phase 4 Requests

Because of post marketing reports describing adverse events occurring as a result of patients opening the available capsules (See DMETS Memo), it is recommended that the sponsor develop a formulation (e.g. sprinkles, oral solution) specifically designed for the pediatric population as part of their fulfilling the pediatric written request. This would allow for a safer and more palatable delivery system for duloxetine as the sponsor pursues their pediatric drug development program.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Duloxetine is a selective serotonin and norepinephrine uptake inhibitor (SSRNI), and has been marketed since 2004. It is currently indicated for the treatment of patients with major depressive disorder, diabetic peripheral neuropathy, and generalized anxiety disorder.

This submission consists one study, **HMBC**, to support labeling changes to include a maintenance of efficacy claim for the use of duloxetine to treat major depressive disorder. Prior to being assigned to a randomized placebo controlled portion of the study, patients are required to be stabilized on a treatment with study medication for a period of time in an open label treatment. Determination of efficacy depends on the rate of relapse in the placebo controlled portion of the study.

There were 136 patients diagnosed with major depressive disorder who were exposed to duloxetine in the placebo controlled portion of this study. The sponsor calculates that the mean days of exposure in this 26 week placebo controlled portion of the study was 125±69 days of exposure to duloxetine 60 mg daily. There were 32 (24%) patients that had an exposure of ≤ 181 days, and 45 (33%) patients had an exposure of ≥ 182 days.

The majority of patients were Caucasians (93.5%) and women (72.7%). Non-Caucasians are underrepresented in the study population.

1.3.2 Efficacy

(b) (4)

The response criteria used for randomization into the placebo controlled portion of the study included 100% of the patients randomized, but patients were only required to have two weeks of stabilization using this criteria.

Using an alternative response criteria ($HAMD_{17}$ scores) in the protocol, the data could suggest that approximately 66% of patients had a stabilization period of 8 weeks, while 88% achieved a stabilization period of 5 weeks prior to randomization; however, there is a significant flaw in using this alternative criteria as it was not assessed weekly, but rather at infrequent intervals (2-3 week intervals) during the 12 week open label portion of the study preceding randomization into the placebo controlled portion phase of the study (when relapse rate is assessed).

1.3.3 Safety

The safety data base for this review was limited to the placebo-controlled portion of Study HMBC. Overall, the safety profile in this supplement was consistent with current labeling. However, it is difficult to identify and comment on the common and drug-related adverse events, as the sponsor only provided data from the first two weeks of the 26 week randomized placebo-controlled portion of study HMBC.

1.3.4 Dosing Regimen and Administration

Duloxetine (Cymbalta ™) is currently labeled for the indications of major depressive disorder diabetic peripheral neuropathic pain, and generalized anxiety disorder.

For **major depressive disorder**, the recommended dose is 40 mg/day (given as 20 mg bid) to 60 mg/day (given as 60 mg qd or 30 mg bid) without regard to meals. It has also been noted that doses > 60 mg/day have not shown any additional benefit.

For **diabetic peripheral neuropathic pain**, the recommended dose is 60 mg/day, without regard to meals. Again, there was no evidence that doses > 60 mg/day have shown any additional benefit.

For **generalized anxiety disorder**, the dose range is 60 mg/day to a maximum dose of 120 mg daily.

For **special populations**, the labeling states that duloxetine is not recommended for patients with end-stage renal disease, severe renal impairment, or hepatic insufficiency.

The dosage used in Study HMDC to support the **maintenance of efficacy for major depressive disorder** was 60 mg daily.

1.3.5 Drug-Drug Interactions

As stated in the marketed labeling, duloxetine has the potential to inhibit CYP1A2, thus increasing the concentration of drugs such as fluvoxamine and quinolone antibiotics. Because of duloxetine's inhibition of CYP2D6, concomitant use may result in higher concentration of drugs such as paroxetine, fluoxetine, quinidine, tricyclic antidepressnats (e.g.nortriptyline, amitryptline, and imiprmaine), phenothiazines and Type 1C antiarrhythmics (e.g. propafenone, flecainide).

1.3.6 Special Populations

The marketed labeling states that duloxetine is not recommended for patients with end-stage renal disease, severe renal impairment, or hepatic insufficiency. Dosages do not need to be adjusted for elderly patient; however, care should be taken when increasing the dose. Class labeling for SSRIs or SNRIs includes that neonates exposed in the late third trimester have developed complications requiring hospitalization, respiratory support, and tube feeding. Administration to nursing mothers is not recommended as no data is available. It is noted that duloxetine has a pregnancy category C due to adverse effects seen on embryo/fetal and postnatal development in laboratory animals.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Duloxetine is a selective serotonin and norepinephrine uptake inhibitor (SSRNI), and has been approved for marketing in the United States since August 2004. It is currently indicated for the treatment of patients with major depressive disorder, diabetic peripheral neuropathy, and generalized anxiety disorder. (b) (4)

This submission includes one study to support labeling changes to include a maintenance of efficacy claim for the use of duloxetine to treat major depressive disorder.

2.2 Currently Available Treatment for Indications

Table 2.2, below, lists the drugs which currently have a maintenance of efficacy claim for major depressive disorder (MDD) in the marketed labeling. It is noted that there is a wide array of wording to convey the supporting stabilization period.

Table 2.2 Summary drugs with maintenance of efficacy claims for MDD and the label phasing to convey this indication claim.

DRUGS WITH MDD MAINTENANCE CLAIM	WORDING IN LABELING FOR CLAIM OF MAINTENANCE OF EFFICACY UNDER INDICATIONS SECTION OF LABELING
Effexor XR:	The efficacy of Effexor in maintaining a response in patients with recurrent major depressive disorder who had responded and continued to be improved during an initial 26 weeks of treatment and were then followed for a period of up to 52 weeks was demonstrated in a second placebo-controlled trial
Ensam	The benefit of maintaining patients with major depressive disorder on therapy with **EMSAM** after achieving a responder status for an average duration of about 25 days was demonstrated in a controlled trial .
Lexapro	The efficacy of Lexapro in maintaining a response, in patients with major depressive disorder who responded during an 8-week, acute-treatment phase while taking Lexapro and were then observed for relapse during a period of up to 36 weeks, was demonstrated in a placebo-controlled trial
Prozac	The efficacy of Prozac Weekly once weekly in maintaining a response in major depressive disorder has been demonstrated in a placebo-controlled trial for up to 25 weeks following open-label acute treatment of 13 weeks with Prozac 20 mg daily for a total treatment of 38 weeks.
Paxil	The efficacy of PAXIL in maintaining a response in major depressive disorder for up to 1 year was demonstrated in a placebo-controlled trial
Celexa	The efficacy of Celexa in maintaining an antidepressant response for up to 24 weeks following 6 to 8 weeks of acute treatment was demonstrated in two placebo-controlled trials .
Zoloft	The efficacy of ZOLOFT in maintaining an antidepressant response for up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) was demonstrated in a placebo-controlled trial.
Remeron	Systematic evaluation of REMERON has demonstrated that its efficacy in major depressive disorder is maintained for periods of up to 40 weeks following 8–12 weeks of initial treatment at a dose of 15–45 mg/day
Serzone	The efficacy of Nefazodone in reducing relapse in patients with major depression who were judged to have had a satisfactory clinical response to 16 weeks of open-label Nefazodone treatment for an acute depressive episode has been demonstrated in a randomized placebo-controlled trial (see CLINICAL PHARMACOLOGY). Although remitted patients were followed for as long as 36 weeks in the study cited (i.e., 52 weeks total),…
Proposed maintenance claim for Duloxetine in the current submission	
Duloxetine	**Under indications section:** (b) (4)

DRUGS WITH MDD MAINTENANCE CLAIM	WORDING IN LABELING FOR CLAIM OF MAINTENANCE OF EFFICACY UNDER INDICATIONS SECTION OF LABELING
	Under Clinical trials section: In another study, 533 patients meeting DSM-IV criteria for MDD received Cymbalta 60 mg once daily during an initial 12-week open-label treatment phase (b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

Duloxetine (Cymbalta™) has been marketed in the United States since 2004.

2.4 Important Issues With Pharmacologically Related Products

Duloxetine shares class label warnings with the SSRIs, SNRIs, and general warnings of anti-depressants. (please refer to the current labeling for more details).

2.5 Presubmission Regulatory Activity

Duloxetine was first marketed for the indication of major depressive disorder in 2004, and has since been labeled for the use in patients with diabetic peripheral neuropathic pain and generalized anxiety disorder.

Since the time that the pivotal protocol for this supplement, HMBC, was submitted, the agency has more clearly defined requirements for length of stabilization period prior to randomization into a placebo controlled (relapse assessment portion of the study); an FDA advisory meeting held on **October 25, 2005**, recommended a stabilization period of 3 months, and a 2 month period for an add on study.

In detail, the sponsor submitted protocol HMBC which proposed assessing relapse prevention for duloxetine's treatment of major depressive disorder on **March 8, 2002**; Study HMBC was conducted from **March, 2002** through **July, 2003**. In **August, 2005**, meeting minutes show that the sponsor came in to discuss (b) (4) during this meeting, they were informed that an advisory meeting would be conducted in October, 2005 to make clarify the time requirements for a stabilization period, and that the requirements would most likely be 3 to 4 months. Meeting minutes show that on **October 5, 1005** (20 days prior to the scheduled advisory meeting), the sponsor returned to discuss findings of Study HMDC, (b) (4)

(b) (4)

Also, the minutes of the October 5, 2005 meeting state that "the exact wording of labeling would be a matter of review after the supplement is submitted, and…that this issue of how to characterize the findings from the randomized withdrawal studies in labeling will be a topic for discussion at the October 25th PDAC meeting."

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No new information was submitted in this NDA.

3.2 Animal Pharmacology/Toxicology

No animal studies were submitted with this NDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of data in this review are the clinical trial submitted by the sponsor (10/31/06:), revised labeling in PLR format (e-mail: 5/1/07).

Also considered were the following FDA reviews and documents:

Statistical Review and Evaluation by Yeh-Fong Chen, Ph.D. (draft).

DMETS Medication Error Postmarketing Safety Review by Richard Abate, R.Ph., MS, Safety Evaluation (Memo: 3/8/07)

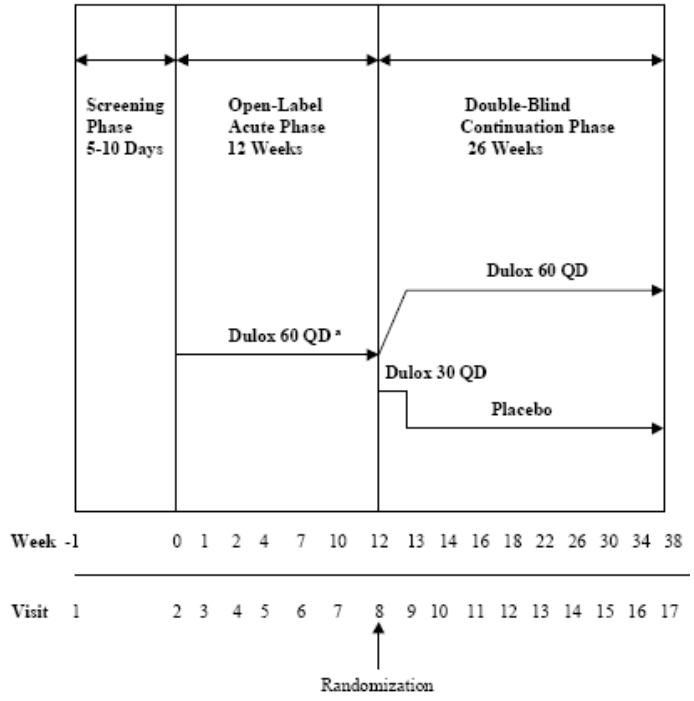
OND Safety Review: Follow_Up of Safety Concerns Identified During NME Evaluation by Lordes Villalba, M.D. (5/22/07).

Environmental Assessment Review by Raanan A. Bloom, Ph.D. (Memo: 6/15/07).

Clinical Inspection Summary by Antoine E-Hage, Ph.D. (Memo: 6/13/07).

4.2 Tables of Clinical Studies

There was only one study, HMBC, reviewed to support claims regarding the maintenance of effect for the treatment of major depressive disorder. Study HMBC provided a relapse prevention design in which patients who were able to be stabilized on a dose of duloxetine in an open label setting, were randomized to either duloxetine or placebo treatment for 24 weeks to determine a rate of relapse. Please refer to the following segment of the sponsor's schematic of study HMBC which was used to support their new proposed labeling.



4.3 Review Strategy

For the purpose of evaluating the data to support the sponsor's claim of maintenance of effect for the treatment of major depressive disorder, there was only one study reviewed, Study HMB C (please refer to section 4.2. above).

4.4 Data Quality and Integrity

A DSI report investigated two investigators, and concluded that there were no significant problems that would compromise the data collected for this supplement NDA. Please refer to Clinical Inspection Summary by Antoine E-Hage, Ph.D. (Memo: 6/13/07).

4.5 Compliance with Good Clinical Practices

The DSI report investigating two principle investigators did not find violations that would compromise the efficacy findings of Study HMBC.

4.6 Financial Disclosures

The sponsor submitted certifications of Financial Interests and Arrangements of Clinical Investigators for Study HMBC. Form **3455**, signed by the Medical Director of Eli Lily and Company, listed two investigators who had received significant payments from the sponsor; the sponsor's attachment to form 3455 is summarized below:

1. (b) (6): principal investigator of Site (b) (6) (Study HMBC) received (b) (6) payment of $85,600.00 during the time period of (b) (6) for (b) (6) to Study HMBC. According to the sponsor, (b) (6) site enrolled (b) (6) patients of the 533 patients (or (b) (6) %) of patients enrolled in Study HMBC.

2. (b) (6): study coordinator of Site (b) (6) (principal investigator: (b) (6)): reports that (b) (6) This site enrolled (b) (6) patients of the 533 patients (or (b) (6) %) of patient enrolled in Study HMBC.

The sponsor states that they conducted a re-analysis excluding these two sites (b) (6) and (b) (6)), and that the results of the primary efficacy variable (time to relapse) remained unchanged.

Otherwise, the Medical Director at Eli Lilly and Company signed the Form **3454** testifying that, to his knowledge, there were no financial arrangements made with the remaining investigators that could affect the outcome of the Study HMBC as defined in 21 CFR 54.2 (a), and that no listed investigator (attached to the form) was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

There was no new pharmacokinetic data included in this submission.

Duloxetine has an elimination half-life of 12 hours (range 8-17 hrs.). Pharmacokinetics are dose proportional over the therapeutic range. Steady state concentrations are achieved after 3 days of dosing. Elimination of duloxetine is mainly hepatic involving two P450 isozymes, CYP2D6 and CYP1A2. Cmax is achieved at 6 hours post dose. Food does not affect the Cmax, but does delay the time to reach peak concentration from 6 to 10 hours. Evening doses appear to have a 3 hour delay in absorption and a one-third increase in clearance of duloxetine compared to morning dosing. Duloxetine is excreted primarily through urine as metabolites (70%), and excreted in feces (20%).

5.2 Pharmacodynamics

There was no new pharmacodynamic data included in this submission.

Animal studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to add to the pharmacologic activity of duloxetine.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication for this NDA is for the **maintenance of efficacy treatment for major depressive disorder (MDD**) in the adult population. This becomes an important consideration in treatment, as many antidepressants are used beyond what is considered acute treatment.

6.1.1 Methods

Prior to being assigned to a randomized placebo controlled portion of the study, patients are required to be stabilized on a treatment with study medication for a period of time in an open label treatment. Determination of efficacy depends on the rate of relapse in the placebo controlled portion of the study.

The sponsor has submitted one study, HMBC, which has a design that would potentially fulfill requirements to assess the efficacy of maintenance treatment for MDD (see design section below for schematic). Of the 278 patients entering the **26 week double blind placebo controlled (continuation phase) portion of the study**, 142 patients were randomized to placebo, while 136 patients were randomized to treatment with duloxetine 60 mg qd.

The study was completed by 47 (or 33%) placebo patients, and 74 (or 54%) patients in the duloxetine 60 mg qd group. Patients discontinuing from the continuation phase due to relapse either discontinued completely (placebo: n=47 or 33%; duloxetine: n=33 or 24%) or entered the rescue phase of the study (placebo: n=58 41%; duloxetine: n=29 or 21%).

Table XX Reasons for withdrawal during the 26 week placebo controlled continuation phase of Study HMBC

Reasons for Withdrawal	Duloxetine (60 mg qd) N= 136	Placebo N=142
Adverse events	5 (3.7)	5 (3.5%)
Lack of efficacy	1 (0.7)	3 (2.1)
Patient decision	11 (8.1)	15 (10.6)
Lost to follow up	6 (4.4)	7 (4.9)
Protocol violation	10 (7.4)	7 (4.9)
Total relapsed	62 (45.6)	95 (66.9)
Total completed	74 (54.4)	47 (33.1)

6.1.2 General Discussion of Endpoints

In order to be eligible to enter the placebo controlled randomized portion of the study, patients were required to fulfill the following three criteria by weeks 10 and 11 (visit 7 and 8) of the acute open label phase of the study (i.e. one and two weeks prior to randomization):

- $HAMD_{17} \leq 9$,
- CGI-Severity ≤ 2,
- Not meeting DSM-IV criteria for major depressive episode.

Response during the study at any point was also defined as the following:

- $\geq$ 50% decrease from baseline in the $HAMD_{17}$.

Theoretically, the time period that patients were considered responders up to the beginning of the placebo portion of the study is considered to be the "stabilization period." The difficulty in establishing this "stabilization period" is that the sponsor did not use this phrase in the protocol,

and also defined two types of response criteria (one response criteria based on the $HAMD_{17}$ at any point, and the other response criteria required to be randomized to the placebo controlled continuation phase).

The primary efficacy analysis for study HMBC compares the time to relapse during the placebo controlled portion of the study between treatment groups using the log rank test. Relapses associated with reemergence are also included as a relapse event. Survival curves are constructed using the Kaplan-Meir method. Time to relapse is assessed as the time from the beginning of the double blind portion of the study. During the placebo controlled portion of the study, patients were considered as relapse if they fulfilled the following criteria:

- An increase in the CGI-Severity score of at least 2 points relative to the rating at Visit 8 (just prior to randomization) for two consecutive visits, and

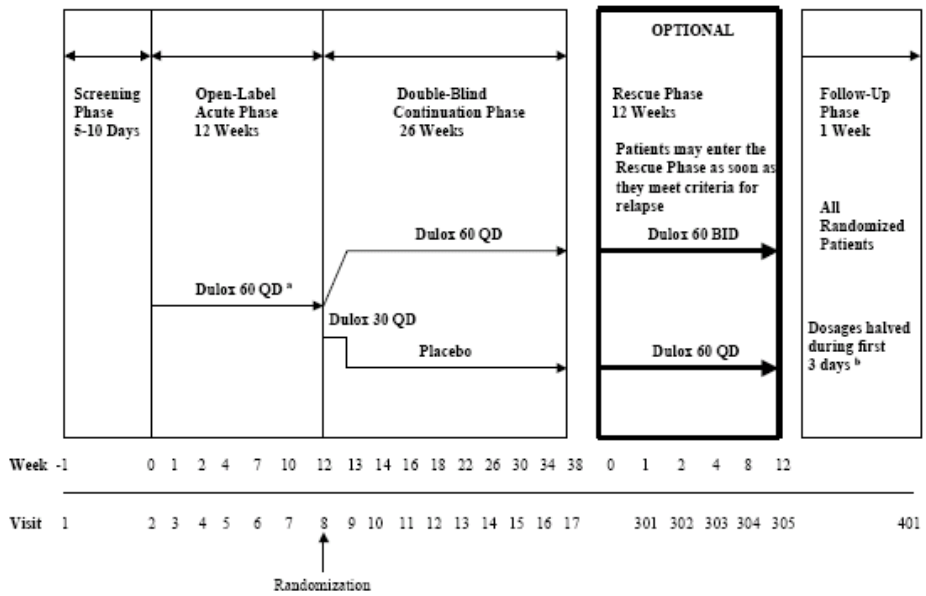
- Meeting the criteria for major depressive episode for two consecutive visits, as determined by the depression module of the MINI.

6.1.3 Study Design

HMBC begins with a 12 week open label treatment in which patients are treated with duloxetine 60 qd. Patients have to fulfill 3 criteria assessing efficacy (see section 6.1.2 above) prior to being randomized into the 26 week double blind placebo controlled portion of the study, in which time to relapse is assessed.

Below is the sponsor's schematic of the study design for HMBC.

Figure 6.1.3 Sponsor's study design for Study HMBC



6.1.4 Efficacy Findings

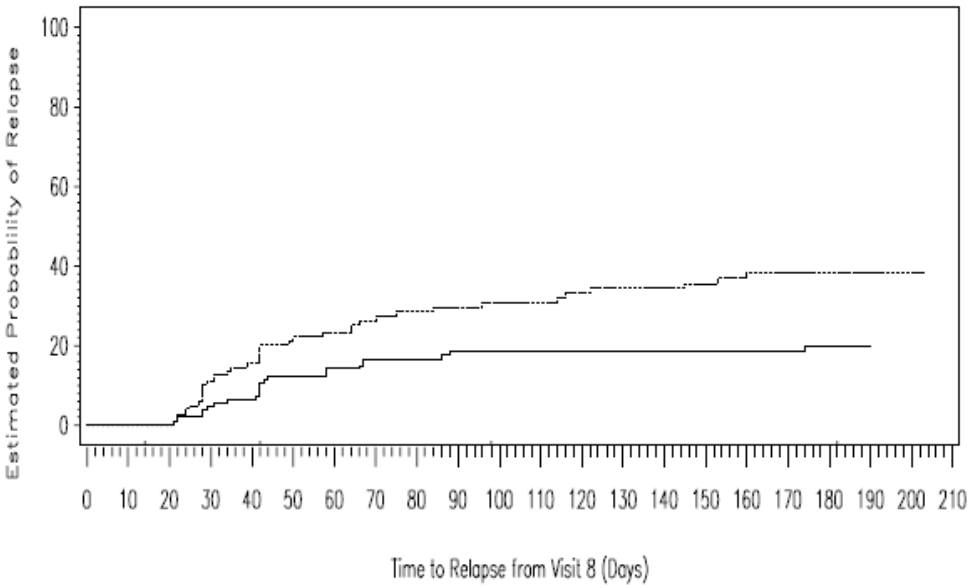
[For details, please refer to the Statistical Review and Evaluation by Yeh-Fong Chen, Ph.D., and the Appendix 10.1 describing Study HMBC]

To demonstrate the findings of estimated rate of relapse of the placebo controlled continuation phase of Study HMBC, the sponsor plotted their findings onto a Kaplan-Meier Plot of time to relapse (see Figure 6.1.4 below). As can be seen from Figure 6.1.4, the sponsor is able to demonstrate a **p-value=0.004** using a Log-Rank Test, and a **p=0.002** using a stratified (according to country) log-Rank Test. As described by Dr. Chen in her FDA statistical review, these results state that 23 out of 132 patients (17.4%) who were randomized to duloxetine 60 mg QD and 39 out of 137 patients (28.5%) who were randomized to placebo relapsed during the continuation therapy phase. These finding were confirmed by Dr. Chen, FDA statistical reviewer; (b) (4)

Figure 6.1.4 Kaplan-Meier Plot of Time to Relapse: All Randomized Patients in the placebo controlled randomized continuation portion of Study HMBC
(excerpt of sponsor's table in the study report for HMBC)

Percentage(SE,n at risk) at Selected Times(t) in DAYS

Therapy	#Pts.	#Evts.	t=14	t=42	t=98	t=182
1)PLACEBO	137	39	0.0(.00,122)	20.2(3.78, 85)	30.9(4.55,59)	38.3(4.97,22)
2)DLX60QD	132	23	0.0(.00,126)	10.8(2.82,106)	18.6(3.60,83)	19.7(3.71,31)



Log-Rank Test :p=0.004
Stratified Log-Rank Test :p=0.002

6.1.5 Efficacy Conclusions/Discussion

(b) (4)

(b) (4)

In her review, Dr. Chen explains that (b) (4) .

It is noted that the response criteria for randomization into the placebo controlled continuation phase occurred just 2 weeks prior to randomization and had the following criteria: (1) No longer meeting the diagnostic criteria for DSM-IV-defined MDD, (2) $HAMD_{17} \leq 9$ and (3) CGI-Severity ≤ 2. As Dr. Chen points out in her review, from the protocol design, it appears that patients were only required to have two weeks of stabilization before randomization.

In FDA team discussions, it was suggested that a period of stabilization could be defined using the protocol's response criterion of a ≥ 50 % decrease from the baseline in the $HAMD_{17}$ for each individual and then calculating an average time period of stabilization which would include approximately 50% of the population randomized to the placebo-controlled continuation phase. A major draw back to this method of describing the "average stabilization period" is that the $HAMD_{17}$ was not collected weekly---rather it was collected at visits that were two to three weeks apart, and the responder status in between these time intervals is unclear.

In her review, Dr. Chen offers an alternative analysis to describe a stabilization period achieved by at least 50% of the patients randomized to the placebo controlled continuous portion of the study. Using the response criteria of a ≥ 50 % decrease from the baseline in the $HAMD_{17}$, Dr. Chen summarizes the patients stabilization period in Tables 6.1.5a and 6.1.5b, below (note again, that the $HAMD_{17}$ scores were not observed weekly, and the responder status in between these 2-3 week time intervals is unclear) .

Table 6.1.5a Summary of percent of patients who have achieved stabilization (using criteria of ≥ 50 increase in $HAMD_{17}$ scores) at each time point assessed prior to randomization.
(**Modified** Table 6a from Dr. Yeh-Fong Chen's statistical review: draft)

Stabilization Period (**Weeks** prior to randomization)	2	5	8	10	11
Number of Patients stabilized at this time point (total randomized n=278)	278	246	184	107	40
Accumulative percent of patients achieving stabilization prior to randomization	(100%)	(88%)	(66%)	(38%)	(14%)

Table 6.1.5b Duration of Response and corresponding relapse rate using response criteria of $HAMD_{17}$(extracted from Dr. Yeh-Fong Chen's statistical review: draft)

Duration of Response (weeks)	>=5	>=8	>=10	>=11
Relapse rate Duloxetine placebo	 0.16(=19/116) 0.26(=32/122)	 0.17(=14/84) 0.25(=24/94)	 0.1=(5/50) 0.3(=16/53)	 0.11(=2/18) 0.33(=7/21)
p-value	0.0054	0.0163	0.0032	0.0852

In conclusion, it can be stated with certainty, that patients had a stabilization period of 2 weeks based on the criteria of randomization to the controlled portion of the study. As an alternative perspective, using alternative response criteria that were assessed infrequently, the data could suggest that approximately 66% of patients had a stabilization period of 8 weeks, while 88% achieved a stabilization period of 5 weeks prior to randomization.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths reported during the placebo controlled, continuous phase portion of the study.

7.1.2 Other Serious Adverse Events

Below is the sponsor's table summarizing the serious adverse events identified for all randomized patients in the continuation, or placebo controlled, phase of Study HMBC.

Table: 7.1.2 Serious adverse events in patients randomized to the placebo controlled (continuous) phase of Study HMBC.
(adapted from sponsor's table)

Preferred Term	PLACEBO (N=142) n	(%)	DLX60QD (N=136) n	(%)	Total (N=278) n	(%)
Arthralgia	1	(0.7)	0		1	(0.4)
Cholelithiasis	0		1	(0.7)	1	(0.4)
Gastrooesophageal reflux disease	0		1	(0.7)	1	(0.4)
Ovarian cyst	1	(0.7)	0		1	(0.4)
Suicidal ideation	0		1	(0.7)	1	(0.4)
Vaginal haemorrhage	0		1	(0.7)	1	(0.4)
Wrist fracture	0		1	(0.7)	1	(0.4)

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Adverse events associated with dropouts

In the placebo controlled phase of the study (a.k.a. the continuation phase), the dropout rates were comparable for both the placebo and the duloxetine group; this finding may occur, because patients who were unable to tolerate duloxetine had already withdrawn during the open label phase prior to the continuation phase. Below is the sponsor's table summarizing the withdrawals due to adverse events.

Table 7.1.3.1 Adverse events reported as reason for withdrawal in the randomized placebo controlled (continuous) treatment phase.

Event	PLACEBO (N=142) n(%)	DLX60QD (N=136) n(%)	Total (N=278) n(%)	Fishers Exact p-value
OVERALL	5(3.5%)	5(3.7%)	10(3.6%)	1.000
Anxiety	0(0.0%)	1(0.7%)	1(0.4%)	0.489
Back pain	1(0.7%)	0(0.0%)	1(0.4%)	1.000
Cholelithiasis	0(0.0%)	1(0.7%)	1(0.4%)	0.489
Colon spastic	0(0.0%)	1(0.7%)	1(0.4%)	0.489
Ejaculation failure	0(0.0%)	1(0.7%)	1(0.4%)	0.489
Gastrooesophageal reflux disease	0(0.0%)	1(0.7%)	1(0.4%)	0.489
Hypomania	1(0.7%)	0(0.0%)	1(0.4%)	1.000
Insomnia	1(0.7%)	0(0.0%)	1(0.4%)	1.000
Liver function test abnormal	1(0.7%)	0(0.0%)	1(0.4%)	1.000
Paraesthesia	1(0.7%)	0(0.0%)	1(0.4%)	1.000

7.1.4 Other Search Strategies

There were no other search strategies utilized in this review.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

It is unclear from the protocols if adverse events were specifically solicited or if adverse events were only recorded when a patient made specific complaints.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor grouped treatment-emergent adverse events by occurrence, using the Medical Dictionary for Regulatory Activities (MedDRA™) System Organ Class to classify events.

7.1.5.3 Incidence of common adverse events

The sponsor did not offer a table characterizing the common adverse events occurring at the end of the placebo controlled phase. Rather the sponsor provided two tables of treatment emergent adverse events at visits that were scheduled one and two weeks after randomization into the placebo controlled randomized portion of the study (sponsor refers to these weeks as: Weeks 9 and 10 of the full study). Therefore, it is difficult to characterize the incidence of common adverse events occurring during this phase.

When considering only the first and second week, the sponsor states that the adverse events occurring in ≥ 5% of patients in the duloxetine 60 mg QD treatment group (in decreasing frequency) were headache, dizziness, nausea, and arthralgia. For the placebo treatment group, the adverse events reported in ≥ 5% of patients in the placebo treatment group (in decreasing frequency) were headache, dizziness, anxiety, arthralgia, back pain, and insomnia.

Again, it must be kept in mind that the sponsor is only reporting the adverse events incidence for the first two week of the 26 week placebo-controlled portion of the study. No conclusions can be made regarding the common adverse events given the paucity of data provided.

7.1.5.4 Common adverse event tables

The sponsor only provided tables which described the first two weeks of common adverse events, and did not provide any data which would cover the 26 week period of this portion of the study.

7.1.5.5 Identifying common and drug-related adverse events

It is difficult to identify and comment on the common and drug-related adverse events, as the sponsor only provided data from the first two weeks of the 26 week randomized placebo-controlled portion of study HMBC.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory tests were conducted at baseline (at the beginning of the open label portion of the study), and at weeks 14 and 26 after randomization into the placebo controlled portion of the study.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This review will discuss the laboratory values for the randomized placebo controlled portion of the Study HMBC only.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Table 7.1.7.3.1 (below) lists the laboratory values that were determined by the sponsor to have a statistically significant difference in mean change from baseline when comparing the duloxetine treatment group with the placebo group.

Comparing incidents of endpoints laboratory abnormalities of the duloxetine and placebo groups, the sponsor found that statistical significance was seen in the mean change from baseline for following laboratory values:

- ALKPH: duloxetine Δ=0.6 > pbo Δ= -2.4 (p=.025)
- GGT: duloxetine Δ=0.3 < pbo Δ=1.4 (p=.035)
- CPK: duloxetine Δ=-34.8 < pbo Δ=81.1 (p=0.49)

Table 7.1.7.3.1 Laboratory values determined to have a significant difference in change from baseline comparing duloxetine and placebo groups in the 26 week randomized placebo controlled portion of Study HMDC
(adapted from sponsor table)

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy (Int*1)	p-Values Pair-wse*2
ALKPH	U/L	PLACEBO	93	73.8	22.6	-2.4	11.6	.025	
		DLX60QD	99	69.5	20.9	0.6	10.2	(.403)	.025
GGT	U/L	PLACEBO	93	35.7	57.4	1.4	24.1	.035	
		DLX60QD	99	26.9	22.8	0.3	17.2	(.398)	.035
AST	U/L	PLACEBO	93	22.8	9.9	3.6	35.3	.080	
		DLX60QD	99	23.7	12.6	-1.7	11.6	(.472)	.080
CPK	U/L	PLACEBO	93	115.2	101.0	81.1	878.0	.049	
		DLX60QD	99	165.8	589.6	-34.8	608.3	(.921)	.049

7.1.3.3.2 Marked outliers and dropouts for laboratory abnormalities

As can be seen from Table 7.1.3.3.2 below, there were no statistically significant differences observed in the ALT and AST levels when comparing the duloxetine group, and the placebo group in the placebo controlled portion of Study HMBC.

Table 7.1.3.3.2 Treatment emergent ALT and AST values ≥ 1,3,5,10, and 20x ULN
(adapted from sponsor Table HMBC.12.B.10)

Analyte	Multiples of Upper Limit	Therapy	N	n	(%)	Fisher's P-Value
ALT	1	PLACEBO	73	4	(5.48)	0.534
		DLX60QD	76	7	(9.21)	
	3	PLACEBO	92	2	(2.17)	0.231
		DLX60QD	99	0	(0.00)	
	5	PLACEBO	93	1	(1.08)	0.484
		DLX60QD	99	0	(0.00)	
	10	PLACEBO	93	0	(0.00)	.
		DLX60QD	99	0	(0.00)	
	20	PLACEBO	93	0	(0.00)	.
		DLX60QD	99	0	(0.00)	
AST	1	PLACEBO	76	3	(3.95)	1.000
		DLX60QD	86	4	(4.65)	
	3	PLACEBO	92	2	(2.17)	0.233
		DLX60QD	98	0	(0.00)	
	5	PLACEBO	92	1	(1.09)	0.482
		DLX60QD	99	0	(0.00)	
	10	PLACEBO	93	1	(1.08)	0.484
		DLX60QD	99	0	(0.00)	
	20	PLACEBO	93	0	(0.00)	.
		DLX60QD	99	0	(0.00)	

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital sign monitoring included heart rate and supine blood pressure at Weeks 1, 2, 4, 6, 10, 14, 18, 22 and 26/termination during the randomized placebo- controlled portion of the study (a.k.a. the continuation phase of the study). Height and weight were recorded at baseline, and weight was measured again at discontinuation.

Supine diastolic blood pressure in the duloxetine group demonstrated a statistically significant increase in supine diastolic blood pressure compared to placebo. Duloxetine also demonstrated a higher mean change from baseline for supine heart rate and systolic blood pressure, but these differences did not reach statistical significance (see Table 7.1.8.1 below). These findings are consistent with the most recently approved labeling (b) (4) .

The sponsor also assessed sustained elevation in blood pressure which they define as either a supine systolic or diastolic blood pressure > 140 mm Hg **and** an ↑ from baseline > 10 mm Hg at three consecutive visits. There was one (0.75%) patient in the duloxetine treated group who demonstrated a sustained elevation in blood pressure, compared to no placebo-treated patients.

Table 7.1.8.1 Vital Signs and Weight; mean change from baseline.
(adapted from sponsor table HMBC.12B.12)

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	Therapy (Int*1) p-Valu
CWGTENNO	PLACEBO	99	80.513	21.834	0.948	3.161	.964
	DLX60QD	97	81.451	22.716	1.030	3.264	(.008)
SUHRTRTE	PLACEBO	138	74.261	9.735	0.254	9.161	.207
	DLX60QD	133	73.444	10.120	1.624	10.187	(.622)
SUSYSTBP	PLACEBO	138	124.196	14.835	-0.609	14.356	.227
	DLX60QD	133	122.609	15.098	1.211	11.676	(.490)
SUDIASBP	PLACEBO	138	77.696	9.961	-1.007	9.133	.005
	DLX60QD	133	75.737	10.822	1.970	8.634	(.774)

Legend of Variable Abbreviations:

Abbrev.	Description
CWGTENNO	Weight - kg
SUDIASBP	Supine diastolic blood pressure
SUHRTRTE	Supine heart rate
SUSYSTBP	Supine systolic blood pressure

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

In the placebo portion of Study HMBC, ECGs were assessed at week 26/discontinuation of the placebo-controlled portion of the study (week 38 of exposure to duloxetine); readings were compared to baseline ECGs recording at the beginning of the open label acute phase of the study. There was no reference made to the timing of ECGs in relation to dosing or food intake.

7.1.9.2 Standard analyses and explorations of ECG data

The sponsor reports that there were no statistically significant differences between the duloxetine and the placebo group in assessing the incidence of treatment emergent abnormal ECGs. The sponsor states that there were 7 (15.9%) duloxetine patients compared to 4 (9.3%) placebo-treatment patients with treatment emergent abnormal ECGs (the sponsor does not provide data to determine what these abnormalities are). There was 1 (1.1%) patient in the duloxetine group who demonstrated a QTc prolongation (using Fredricia's calculations) during the placebo controlled portion of the study (no details located in this submission).

7.1.10 Immunogenicity

No immunogenicity studies were submitted in this application.

7.1.11 Human Carcinogenicity

No Carcinogenicity studies were submitted with this application

7.1.12 Special Safety Studies

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no studies on withdrawal phenomena and/or abuse potential submitted with this application.

7.1.14 Human Reproduction and Pregnancy Data

There were no studies regarding human reproduction and pregnancy data in this submission

7.1.15 Assessment of Effect on Growth

There were no studies submitted which specifically assess for growth changes with longer term use of duloxetine. There appears to be a very slight mean weight increase comparing mean change from baseline at the end of the 26 week placebo controlled portion (which correlates with 38 week of duloxetine use).

Table 7.1.15 Mean change in weight.
(excerpt from sponsor's table)

		-----Baseline------		-----Change to Endpoint-----		- p-Valu
Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)
PLACEBO	99	80.513	21.834	0.948	3.161	.964
DLX60QD	97	81.451	22.716	1.030	3.264	(.008)

7.1.16 Overdose Experience

As per Dr. Lourdes Villalba's safety review, the current labeling for the OVERDOSE section minimizes the risks now known and observed since this drug has been marketed. Dr. Villalba has requested further information from the sponsor regarding post marketing overdose events, and she will review the data when all requested information is received.

7.1.17 Postmarketing Experience

Duloxetine was approved for marketing in the United States in August, 2004, and is currently marketed for major depressive disorder (MDD)and diabetic peripheral neuropathy (DPNP). According to the sponsor, as of February 2006, duloxetine has been marketed as Cymbalta®/Xeristor® in 35 countries for MDD and 2 countries for DPNP, and as Yentreve®/Ariclam® in 14 countries for SUI (stress urinary incontinence).

Duloxetine was selected as a drug for the pilot New Molecular Entity (NME) project in which all post market safety information was evaluated in depth. Please refer to the final NME report for in depth results.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Study HMDC was the only study reviewed to support the sponsor's claim for maintenance of effect for the treatment of major depressive disorder. HMBC begins with a 12 week open label treatment in which patients are treated with duloxetine 60 qd. Patients have to fulfill 3 criteria assessing efficacy (see section 6.1.2 above) prior to being randomized into the 26 week double blind placebo controlled portion of the study, in which **time to relapse** is assessed.

Of the 618 patients screened, 533 were randomized into the 12 week open label portion (all taking duloxetine 60 mg qd). Of those enrolled, 278 (or 52%) patients completed this acute open label portion of the study, and 255 patients (or 48%) discontinued. Of the 278 patients entering the **26 week double blind placebo controlled (continuation phase) portion of the study**, 142 patients were randomized to placebo, while 136 patients were randomized to treatment with duloxetine 60 mg qd. The study was completed by 47 (or 33%) placebo patients, and 74 (or 54%) patients in the duloxetine 60 mg qd group. Patients discontinuing from the continuation phase due to relapse either discontinued completely (placebo: n=47 or 33%; duloxetine: n=33 or 24%) or entered the rescue phase of the study (placebo: n=58 41%; duloxetine: n=29 or 21%).

7.2.1.2 Demographics

For the 26 week placebo controlled portion of the study (a.k.a. the continuation phase), the majority of the patients were Caucasian females. There were 202 women (72.7%) and 76 men (27.3%) with a mean age of 45.22 years old (range 19 to 76 years). The population consisted of 260 (93.5 %) Caucasians, 13 (4.7 %) African Decent, 3 (1.1 %) Hispanic, 1 (0.4%) East/Southeast Asian, and 1 (0.4%) "other." The sponsor did not find a statistically significant difference in baseline demographics between the placebo and duloxetine groups.

7.2.1.3 Extent of exposure (dose/duration)

There are 136 patients diagnosed with major depressive disorder who were exposed to duloxetine in the placebo controlled portion of this study. The sponsor calculates that the mean days of exposure in this 26 week placebo controlled portion of the study was 125±69 days of exposure to duloxetine 60 mg daily. There were 32 (24%) patients had an exposure of ≥ 181 days, and 45 (33%) patients had an exposure of ≥ 182 days.

7.2.2 Literature

The sponsor submitted many general articles on subjects such as arrhythmias, generalized anxiety disorder, liver abnormalities, Steven Johnson's syndrome, urinary incontinence with few having direct discussion of duloxetine and its effect on these topics. There was no summary of how this search was conducted located in this submission.

7.2.3 Adequacy of Overall Clinical Experience

The majority of patients were Caucasians (93.5%) and women (72.7%). Non-Caucasians are underrepresented in the study population.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There were no special animal and/or in vitro testing accompanying this submission.

7.2.5 Adequacy of Routine Clinical Testing

The data presented was limited to the adult population.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

There were no special studies conducted for the maintenance use of duloxetine in patients suffering with major depressive disorder.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Duloxetine was selected as a drug for the CDER initiative pilot study to examine a New Molecular Entity two to three years post-market. The following were considered safety issues identified during this pilot study which require close follow up review and observation:

- Hepatotoxicity
- Effects on glucose control
- Serotonin syndrome
- Skin Reactions/hypersensitivity reactions [including erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)]
- Increased CPK
- Bleeding disorders

- Glaucoma
- Obstructive voiding symptoms/urinary retention
- Pancreatitis
- Sexual dysfunction
- Hallucinations
- EPS

The following were identified as safety concerns in class labeling:

- Suicidality
- Abnormal Bleeding (not yet labeled for duloxetine)
- Serotonin Syndrome
- Hyponatremia
- Activation of mania/hypomania
- Warnings of use in patients with bipolar disorder
- Concomitant use with MAOIs
- Discontinuation Syndrome

7.2.8 Assessment of Quality and Completeness of Data

The sponsor did not explain the rationale for their proposed labeling in any prominent way other than a note to the reviewer which was embedded within two tiers of folders in the electronic submission. The sponsor also did not define any stabilization period, and when asked during the review cycle to do this, merely stated that the protocol did use the phrase "stabilization" and it was unclear what FDA meant by this term. (Please note: this sponsor is actively in negotiation to have a similar extended efficacy claim for the use of atomoxetine in the treatment of ADHD).

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The safety concerns that arose with this supplement NDA data base have been discussed in the marketed labeling for duloxetine. However, the sponsor's presentation of the common adverse events was inadequate; this supplement only described the first two weeks of common adverse events in the 26 week placebo controlled portion of the study, and did not provide any data which would cover the remaining 24 weeks.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

In the 26 week, placebo controlled continuation phase of the study, the sponsor only used one dose (duloxetine 60 mg qd) compared to placebo. According to the labeling for major depressive disorder, there was no evidence that doses > 60 mg/day have shown any additional benefit.

8.2 Drug-Drug Interactions

There was no new information regarding drug-drug interactions in this supplement.
As stated in the marketed labeling, duloxetine has the potential to inhibit CYP1A2, thus increasing the concentration of drugs such as fluvoxamine and quinolone antibiotics. Because of duloxetine's inhibition of CYP2D6, it may result in higher concentration of drugs such as paroxetine, fluoxetine, quinidine, tricyclic antidepressnats (e.g.nortriptyline, amitryptline, and imiprmaine), phenothiazines and Type 1C antiarrhythmics (e.g. propafenone, flecainide).

8.3 Special Populations

There was no new information submitted in this supplement.

For **special populations**, the labeling states that duloxetine is not recommended for patients with end-stage renal disease, severe renal impairment, or hepatic insufficiency.

8.4 Pediatrics

There was no pediatric exposure submitted in this supplement. The sponsor states that they will be looking at safety exposure in their response to the pediatric written request.

8.5 Advisory Committee Meeting

There have been no advisory committee meetings held to discuss duloxetine.

8.6 Literature Review

In the brief literature review that the sponsor submitted, there was no mention of any unknown adverse events. However, the literature submitted primarily discussed general issues with little mention to duloxetine.

8.7 Postmarketing Risk Management Plan

There have been many postmarketing reports regarding safety issues with duloxetine. Duloxetine was the first drug assed in the CDER pilot study to assess the post marketing evaluation of new molecular entities. There were many safety issues identified that are actively being followed by the safety group of HFD-130, and the Office of Surveillance and Epidemiology (ODE). Please refer to Section 7.2.7 above for a listing of significant adverse events being followed.

9 OVERALL ASSESSMENT

9.1 Conclusions

The safety data submitted by the sponsor appeared to be consistent with the current approved labeling. However, it is difficult to comment on the common and drug-related adverse events observed, as the sponsor only provided data from the first two weeks of the 26 week randomized placebo-controlled portion of study HMBC. It would be helpful to have a table that would describe the incidents of the entire 26 weeks of the placebo controlled portion of the study, so that a better assessment of common adverse events could be characterized for this extended study.

The issue of efficacy labeling for the maintenance of effect for the treatment of major depressive disorder was complicated and difficult to sort out. The sponsor was not very helpful during the review process in helping to identify a stabilization period prior to the relapse prevention portion of the study. (b) (4) Dr. Yeh-Fong Chen, FDA statistician, was very instrumental in helping to clarify what the sponsor could (b) (4) appropriately claim as a stabilization period.

In conclusion, the sponsor has clearly demonstrated a stabilization period of 2 weeks.

> In her review, Dr. Chen offers an alternative analysis to describe a stabilization period achieved by at least 50% of the patients randomized to the placebo controlled continuous portion of the study. Using this alternative response criteria, the data could suggests that approximately 66% of patients had a stabilization period of 8 weeks, while 88% achieved a stabilization period of 5 weeks prior to randomization. Again, there is a major flaw in this method, as the alternative response criteria was not followed closely (i.e. at least weekly), making the responder status in between these 2-3 week time intervals unclear .

9.2 Recommendation on Regulatory Action

It is recommended that the sponsor claim with certainty that patients had a stabilization period of 2 weeks prior to randomization into the portion of the study assessing relapse.

If it is deemed acceptable that the sponsor had infrequent assessment of an alternative response criteria, the data suggests that approximately 66% of patients had a stabilization period of 8 weeks, while 88% achieved a stabilization period of 5 weeks prior to randomization into the portion of the study assessing relapse.

On the other hand, if using the infrequent assessment of an alternative response criteria is not acceptable, it is recommended that the sponsor conduct a study which has a well defined 12 week stabilization period. This recommendation is made in light of the fact that a two week stabilization period is not clinically significant in the treatment of major depressive disorder, and does not support a claim for long term treatment.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The HFD-130 safety group and the Office of Surveillance and Epidemiology (ODE) will be following the recommendations made during the CDER pilot New Molecular Entity initiative.

9.3.2 Required Phase 4 Commitments

In this submission, the sponsor states that they are preparing to assess duloxetine in the pediatric population in response to FDA's pediatric written request. It would be helpful if the sponsor also conducted a relapse prevention study in the pediatric population for the indication of major depressive disorder.

9.3.3 Other Phase 4 Requests

Because of the post marketing reports describing adverse events occurring as a result of patients opening the available capsules (See DMETS Memo), it is recommended that as the sponsor fulfills their response to the pediatric written request, the sponsor develop a formulation that would be safer and more palatable as part of their pediatric drug development program (e.g. sprinkles, oral solution).

9.3 Labeling Review

The following are recommendations regarding the sponsor's proposed labeling revision:

1. (b) (4)

2. (b) (4)

   (b) (4)
   .

   (b) (4)

3. (b) (4)

   (b) (4)

(b) (4)
.

4. The DMETS Medication Error Postmarketing Safety Review (Memo by Richard Abate, R.Ph., M.S.: 3/8/07) describes post marketing reports that patients are opening capsules despite the statement under Medication Adminsitration (Section 17.3) to not sprinkle, crush or chew the capsule. This report states that, as a result of altering the capsule, patients have experienced significant events including esophageal burning, GI symptoms, elevated blood pressure and serotonin syndrome.

   It is recommended that this warning not to alter the capsule be prominently displayed in the patient package insert. The memo recommends that this warning also be placed in the Dosage and Administration Section, but it is unclear which section in the new format would be appropriate. Another suggestion to emphasize these risks would be to add the possible consequence of altering the pill in the Medication Administration section (Section 17.3).

5. (b) (4)
.

6. It was suggested in the safety reviews during the CDER Pilot NME initiative of duloxetine, that the labeling for duloxetine did not include the class labeling for bleeding disorder, yet there appeared to be evidence of this event in the post-market analysis of duloxetine. Therefore, it is recommended that bleeding disorders be added to the class labeling aspect of the duloxetine labeling.

6. This labeling is in the new PLR (Physician Labeling Rule) format and will be reviewed by the entire team to ensure that the no information is omitted because of the conversion to a new labeling format.

10 APPENDICES

10.1 Review of Study HMBC

Study HMBC

Investigators/Location

This is a multicenter study including 29 principal investigators at 30 study sites located in four countries including France, Spain, Italy, and the United States. Please refer to the sponsor's amended study report of HMBC (submitted 1/8/2007) Appendix 16.1.4 for a full listing of all principal and subinvestigators.

Study Plan

Objective(s)/Rationale

The sponsor states that the primary objective of this study was to determine the comparison of time to relapse between duloxetine and placebo in adult patients diagnosed with major depressive disorder who have responded to 12 weeks of duloxetine open label treatment. Please note that the sponsor did not allow for a 12 week period of stabilization on drug during this open label treatment phase.

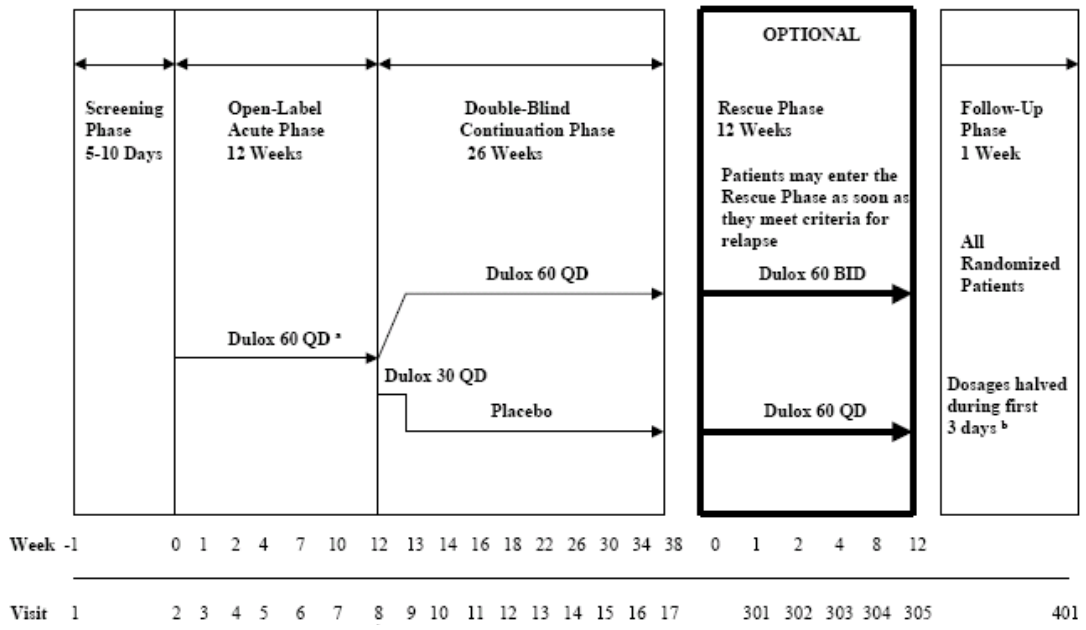
Population

Patients chosen for this study were physically healthy adults and diagnosed with major depressive disorder according to DSM-IV criteria; patients were required to have at lease one other prior episode of MDD. Required for participation was a $HAMD_{17}$ score ≥ 18 and a CGI-S score ≥ 4 at Visits 1 and 2.

Excluded from the study were patients with a co-morbid DSM-IV Axis I diagnosis, alcohol/drug/caffeine abuse, or uncontrolled narrow angle glaucoma. Also excluded were patients with a lack of response of current episode to two or more adequate courses of antidepressant therapies, treatment-resistant depression, previous enrollment in duloxetine studies, abnormal TSH concentrations, and treatment of investigational drug, fluoxetine, MAO-I, ECT within the past year. Sexually active females were required to use medically accepted forms of birth control. Psychotherapy was not allowed to be initiated or stopped with in 6 weeks prior to enrollment.

Design

The study begins with a 12 week open-label phase; responders proceed to the 26 week double blind placebo-controlled portion of the study in which time to relapse was assessed. The following is the schematic from the sponsor's protocol:



During the 12 week open label phase, all patients receive 60 mg qd duloxetine; patients may be reduced to 30 mg, but must be titrated up to a dose 60 mg qd by Week 5. Responders to duloxetine 60 mg qd must fill the following criteria by Weeks 10 and 12: 1) $HAMD_{17} \leq 9$, 2) CGI-Severity ≤ 2, and 3) not meeting DSM-IV criteria for major depressive episode. Patients who do not meet response criteria by Week 10 (at Visit 7) are discontinued.

Responders enter the 26 week double blind placebo controlled (continuation phase) portion of the study, and are randomized to receive either duloxetine 60 mg qd or placebo.
Patients randomized to placebo undergo a 1-week tapering, receiving duloxetine 30 mg for the first week of the study. **Reemergence** of depressive symptoms is defined as $HAMD_{17}$ score ≥ 12. **Relapse** is defined as fulfilling the following two criteria: 1) CGI-Severity score of ≥ 2 points for two consecutive visits, and 2) meeting criteria for major depressive episode for two consecutive visits as determined by the depression module of the MINI. Also, if a patient has a total more than 6 visits with a $HAMD_{17}$ score ≥ 12, they are considered to be relapsed (relapse associated with reemergence).

Relapsed patients may enter a continuation phase in which doses may be increased up to duloxetine 120 mg qd for up to 12 weeks. The study design concludes with a one week follow up phase in which patients taking duloxetine are giving titrated down to 30 mg qd for the first three days.

Vital signs (supine blood pressure), routine laboratory tests and ECGs are assessed at baseline and endpoint during each phase of the study.

Analysis Plan

The primary efficacy analysis compares the time to relapse during the continuation phase between treatment groups using the log rank test. Relapses associated with reemergence are also included as a relapse event. Survival curves are constructed using the Kaplan-Meir method. Time to relapse is assessed as the time from the beginning of the double blind portion of the study.

Other instruments used in this study are the Sheehan Disability Scale (SDS), Hamilton Depression Rating Scale ($HAMD_{17}$), Clinical Global Impression of Severity scale (CGI-S), Patient Global Impression of Improvement scale (PGI-I), Visual Analog Scales (VAS), and the Symptom Questionnaire, Somatic Subscale (SQ-SS).

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 618 patients screened, 533 were randomized into the 12 week open label portion (all taking duloxetine 60 mg qd). Of those enrolled, 278 (or 52%) patients completed this acute open label portion of the study, and 255 patients (or 48%) discontinued. Reasons given for discontinuation were the following: adverse events (n=60 or 24%), death (n=1 or 0.4%), lack of efficacy (n=10 or 4%), lost to follow up (n=43 or 17%), protocol violation (n=27 or 11%), protocol randomization/criteria not met (n=52 or 20%), and patient decision (n=62 or 24%).

Of the 278 patients entering the **26 week double blind placebo controlled (continuation phase) portion of the study**, 142 patients were randomized to placebo, while 136 patients were randomized to treatment with duloxetine 60 mg qd. The study was completed by 47 (or 33%) placebo patients, and 74 (or 54%) patients in the duloxetine 60 mg qd group. Patients discontinuing from the continuation phase due to relapse either discontinued completely (placebo: n=47 or 33%; duloxetine: n=33 or 24%) or entered the rescue phase of the study (placebo: n=58 41%; duloxetine: n=29 or 21%).

Table A10.1a Reasons for withdrawal during the 26 week placebo controlled continuation phase of Study HMBC

Reasons for Withdrawal	Duloxetine (60 mg qd) N= 136	Placebo N=142
Adverse events	5 (3.7)	5 (3.5%)
Lack of efficacy	1 (0.7)	3 (2.1)
Patient decision	11 (8.1)	15 (10.6)
Lost to follow up	6 (4.4)	7 (4.9)
Protocol violation	10 (7.4)	7 (4.9)
Total relapsed	62 (45.6)	95 (66.9)

Total completed	74 (54.4)	47 (33.1)

Demographics /Group Comparability

For the 26 week placebo controlled portion of the study (a.k.a. the continuation phase), the majority of the patients in this study were Caucasian females. There were 202 women (72.7%) and 76 men (27.3%) with a mean age of 45.22 years old (range 19 to 76 years). The population consisted of 260 (93.5 %) Caucasians, 13 (4.7 %) African Decent, 3 (1.1 %) Hispanic, 1 (0.4%) East/Southeast Asian, and 1 (0.4%) "other." The sponsor did not find a statistically significant difference in baseline demographics between the placebo and duloxetine groups.

Concomitant Medications

During the placebo portion of the study (continuation phase), concomitant medications used most frequently included Tylenol (59 patients or 21.2%), ibuprofen (57 patients or 20.5 %), multivitamin (738 or 13.7%), aspirin (20 or 7.2%), thyroxine (18 patients or 6.5%) and naproxen (18 patients or 6.5%). Table 10.1.3b below is a breakdown of select concomitant medications according to treatment group. It is noted that there is a statistically significant difference between the placebo and treatment group for the concomitant use of aspirin (p=0.019) and thyroxine (p=0.051); however, it is not possible to make any conclusions based on these findings as the actual numbers of patients using these medication is quite small.

Table A10.1b Concomitant medications used by at least 5% of patients in placebo-controlled portion of Study HMDC (adapted from sponsor's table HMBC.11B.2 from study report HMDC)

Drug Name	PLACEBO (N=142) n (%)	DLX60QD (N=136) n (%)	Total (N=278) n (%)	p-Value*
PATIENTS WITH >= 1 DRUG	120 (84.5)	110 (80.9)	230 (82.7)	.433
PATIENTS WITH NO DRUGS	22 (15.5)	26 (19.1)	48 (17.3)	.433
PARACETAMOL	30 (21.1)	29 (21.3)	59 (21.2)	1.00
IBUPROFEN	28 (19.7)	29 (21.3)	57 (20.5)	.768
ERGOCALCIFEROL/ASCORBIC ACID/FOLIC ACID/THIAM	15 (10.6)	23 (16.9)	38 (13.7)	.162
ACETYLSALICYLIC ACID	5 (3.5)	15 (11.0)	20 (7.2)	.019
LEVOTHYROXINE SODIUM	5 (3.5)	13 (9.6)	18 (6.5)	.051
NAPROXEN SODIUM	10 (7.0)	8 (5.9)	18 (6.5)	.809

Efficacy Results

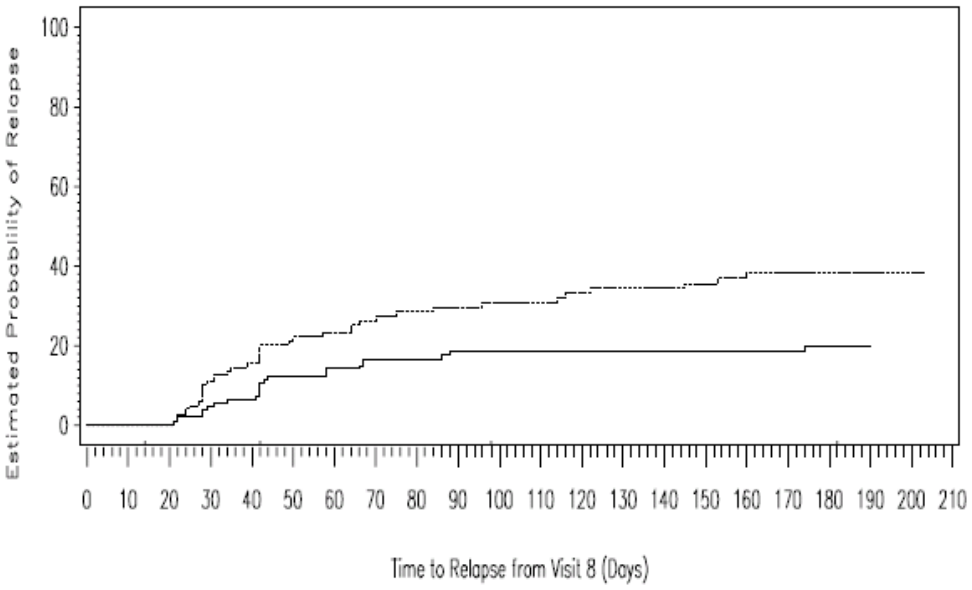
[For details, please refer to the Statistical Review and Evaluation by Yeh-Fong Chen, Ph.D]

To demonstrate the findings of estimated rate of relapse of the placebo controlled continuation phase of Study HMBC, the sponsor plotted their findings onto a Kaplan-Meier Plot of time to relapse (see Figure 6.1.4 below). As can be seen from Figure 6.1.4, the sponsor is able to demonstrate a **p-value=0.004** using a Log-Rank Test, and a **p=0.002** using a stratified (according to country) log-Rank Test. As described by Dr. Chen in her FDA statistical review, these results state that 23 out of 132 patients (17.4%) who were randomized to duloxetine 60 mg QD and 39 out of 137 patients (28.5%) who were randomized to placebo relapsed during the continuation therapy phase. These finding were confirmed by Dr. Chen, FDA statistical reviewer; (b) (4)

Figure A10.1c Kaplan-Meier Plot of Time to Relapse: All Randomized Patients in the placebo controlled randomized continuation portion of Study HMBC
(excerpt of sponsor's table in the study report for HMBC)

Percentage(SE,n at risk) at Selected Times(t) in DAYS

Therapy	#Pts.	#Evts.	t=14	t=42	t=98	t=182
1)PLACEBO	137	39	0.0(.00,122)	20.2(3.78, 85)	30.9(4.55,59)	38.3(4.97,22)
2)DLX60QD	132	23	0.0(.00,126)	10.8(2.82,106)	18.6(3.60,83)	19.7(3.71,31)



Log-Rank Test :p=0.004
Stratified Log-Rank Test :p=0.002

Table A10.1d Summary of percent of patients who have achieved stabilization (using criteria of ≥ 50 increase in $HAMD_{17}$ scores) at each time point assessed prior to randomization. (Modified Table 6a from Dr. Yeh-Fong Chen's statistical review: draft)

Stabilization Period (Weeks prior to randomization)	2	5	8	10	11
Number of Patients (total randomized n=278)	278	246	184	107	40
Accumulative percent of patients achieving stabilization prior to randomization	(100%)	(88%)	(66%)	(38%)	(14%)

Table A10.1e Duration of Response and corresponding relapse rate using response criteria of $HAMD_{17}$(extracted from Dr. Yeh-Fong Chen's statistical review: draft)

Duration of Response (weeks)	>=5	>=8	>=10	>=11
Relapse rate Duloxetine placebo	 0.16(=19/116) 0.26(=32/122)	 0.17(=14/84) 0.25(=24/94)	 0.1=(5/50) 0.3(=16/53)	 0.11(=2/18) 0.33(=7/21)
p-value	0.0054	0.0163	0.0032	0.0852

In conclusion, it can be stated with certainty, that patients had a stabilization period of 2 weeks based on the criteria of randomization to the controlled portion of the study. As an alternative perspective, using an alternative response criteria which was assessed infrequently, the data could suggest that approximately 66% of patients had a stabilization period of 8 weeks, while 88% achieved a stabilization period of 5 weeks prior to randomization.

Efficacy Conclusions/Discussion

(b) (4)

(b) (4)

It is noted that the response criteria for randomization into the placebo controlled continuation phase occurred just 2 weeks prior to randomization and had the following criteria: (1) No longer meeting the diagnostic criteria for DSM-IV-defined MDD, (2) $HAMD_{17} \leq 9$ and (3) CGI-Severity ≤ 2. As Dr. Chen points out in her review, from the protocol design, it appears that patients were only required to have two weeks of stabilization before randomization.

In FDA team discussions, it was suggested that a period of stabilization could be defined using the protocol's response criterion of a ≥ 50 % decrease from the baseline in the $HAMD_{17}$ for each individual and then calculating an average time period of stabilization which would include approximately 50% of the population randomized to the placebo-controlled continuation phase. A major draw back to this method of describing the "average stabilization period" is that the $HAMD_{17}$ was not collected weekly---rather it was collected at visits that were two to three weeks apart.

In her review, Dr. Chen offers an alternative analysis to describe a stabilization period achieved by at least 50% of the patients randomized to the placebo controlled continuous portion of the study. Using the response criteria of a ≥ 50 % decrease from the baseline in the $HAMD_{17}$, Dr. Chen summarizes the patients stabilization period in Tables 6.1.5a and 6.1.5b, below (note again, that the $HAMD_{17}$ scores were not observed weekly) .

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____ Draft Labeling (b5)

____ Deliberative Process (b5)

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See memo to file for additional comments and recommendation.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427/S-015, S-017

CHEMISTRY REVIEW(S)

Division of Post Approval Marketing Evaluation IV
Chemist Review of Supplement

1. Organization HFD-120
2. NDA Number: 21427
3. Supplement Numbers/Dates: SCM-015
   Letter Date: October31, 2006
   Stamp Date: November 2, 2006
4. Amendments/Reports/Dates:
5. Received by Chemist: December 1, 2006
6. Applicant Name and Address: Eli Lilly and Company
   Lilly Corporation Center
   Indianapolis, IN 46285
7. Name of the Drug: Cymbalta®
8. Nonproprietary name: Duloxetine Hydrochloride
9. Chemical Structure/ Chemical Name:
(+)-(S)-N-Methyl-©-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride
10. Dosage Forms: Delayed Release Capsules
11. Potency: 20, 30, 40, 60 mg
12. Pharmacological Category: Depression
13. How Dispensed: XXX (RX) _____(OTC)
14. Records and Reports current XXX (yes) _____(No)
15. Related IND/NDA/DMF: _____(yes) XXX (No)

16. Comments: This PA Efficacy Supplement provides for a new clinical indication. The CMC information has been cross-referenced to the original NDA and subsequent supplements. No new CMC information is provided in this submission. There are no labeling changes reported to the CMC related sections. However, the Applicant has reformatted the "How Supplied" Section into a tabular format from a list format. No additions or changes to the information are noted, other than the reformatting. An Environmental Assessment Report has been provided and based on the calculated assessment factors, the amount of duloxetine released into the environment does not appear to have a safety risk.

17. Conclusions and Recommendations: Based on the risk assessment data provided and the maximum exposure to humans as (b) (4) times less than the therapeutic dose, the increased amount of duloxetine in the environment does not appear to be a safety concern.

Recommendations: Recommend Approval of this PA Supplement.

18. Reviewer Name Julia C. Pinto, Ph.D., Chemist

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_✓__ Trade Secret / Confidential (b4)

____ Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427/S-015, S-017

ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT

and

FINDING OF NO SIGNIFICANT IMPACT

for

Cymbalta® (duloxetine hydrochloride) Capsules for maintenance of Efficacy in the Treatment of Major Depressive Disorder

NDA 21-427
S-015

Food and Drug Administration
Center for Drug Evaluation and Research

June 15, 2007

FINDING OF NO SIGNIFICANT IMPACT

for

NDA 21-427

Cymbalta® (duloxetine hydrochloride) Capsules

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and concluded that this action will not have a significant impact on the quality of the human environment. Therefore, an environmental impact statement will not be prepared.

In support of the supplement to this new drug application, Eli Lilly and Company prepared an environmental assessment (EA; attached) in accordance with 21 CFR 25 that evaluates potential environmental impacts due to use and disposal of this product. The application requests the approval of Cymbalta® (duloxetine hydrochloride) 20, 30, 40, and 60 mg gelatin capsules for maintenance of efficacy in the treatment of Major Depressive Disorder (MDD).

Duloxetine and its metabolites may enter the aquatic environment from patient drug use and disposal. The toxicity of duloxetine to environmental organisms (algae, Daphnia magna and rainbow trout) was characterized. An activated sludge respiration test was also conducted. Results indicate that the compound and its metabolites are not expected to be toxic to aquatic organisms or to inhibit sewage microorganisms at expected environmental introduction concentrations.

At U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital or clinic procedures. Empty or partially empty containers from home use will be disposed of through community solid waste management systems which typically include landfills, incineration, and recycling. Minimal quantities of unused drug are expected to be disposed of through sanitary sewer systems.

The Center for Drug Evaluation and Research has concluded that this product can be used and disposed of without expected adverse environmental impacts. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY:

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Attachment:

Environmental Assessment
Appended Electronic Signature Page

Environmental Assessment

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(b) (4)

Environmental Assessment for the Use of Duloxetine Hydrochloride

Description of the Proposed Action

Requested Approval

Eli Lilly and Company has filed a supplement to NDA for duloxetine hydrochloride pursuant to the Federal Food, Drug, and Cosmetic Act. Duloxetine hydrochloride will be marketed as gelatin capsules (20, 30, 40, and 60 mg) packaged in opaque, white HDPE bottles and in 2 mm thick Aclar® blister packs with aluminum foil backing. An Environmental Assessment has been submitted pursuant to 21 CFR part 25.

An environmental assessment of duloxetine hydrochloride was submitted with the original NDA 21-427. The current proposed supplement is not categorically excluded from assessment of environmental impact as dictated in the Federal Register (July 29, 1997, 21 CFR 25.31) due to the estimated concentration at the point of entry into the aquatic environment and due to the predicted increased use of duloxetine hydrochloride in the United States with the proposed changes. The use of duloxetine hydrochloride will result in one major pathway to the environment: sewage treatment facilities receiving influent from the general public. Wastes generated from production facilities are regulated by Federal, State and local environmental protection agencies and are not considered in this environmental assessment.

Need for Action

Duloxetine hydrochloride, a naphthyl ether amine, inhibits the uptake of serotonin and norepinephrine and lacks affinity for neurotransmitter receptors. In the current application, the following changes aer proposed: additional wording in the label to reflect maintenance of effect and an increase in the maximum dose from 60 to 100 mg for major depressive disorder.

Locations of Use

The location of the use of duloxetine hydrochloride will be primarily in the patient's home and workplace. There is no reason to expect use to be concentrated in a particular geographic region.

Disposal Sites

Empty or partially empty packages containing duloxetine hydrochloride will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling, although minimal quantities of unused drug could be disposed of in the sewer system.

Identification of the Chemical Substance

The identification of the chemical substance has not changed from that described in the original Environmental Assessment filed with NDA 21-427.

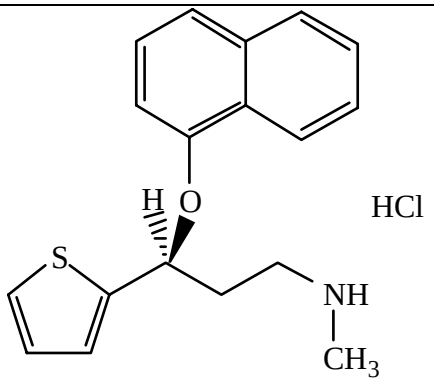
Nomenclature

Established Name (USAN):
(+)-N-methyl-γ-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride

Brand/Proprietary Name/Tradename
Cymbalta

Chemical Name (Uninverted)
(+)-(S)-N-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride

Chemical Abstracts Index Name (Inverted)
2-Thiophenepropanamine, N-methyl-γ-(1-naphthalenyloxy)-, hydrochloride, (S)-

Chemical Abstracts Service Number:	136434-34-9
Molecular Formula:	$C_{18}H_{19}NOS \bullet HCl$
Molecular Weight:	333.88
Structural Formula:	

Environmental Issues

Environmental Fate of Released Substances

The environmental fate of the released substance has not changed from that described in the original Environmental Assessment filed with NDA 21-427. Additionally, while the total use of duloxetine is expected to increase with the changes proposed in this application, it will still be below the maximum total amount estimated in the original Environmental Assessment. Thus the expected environmental concentrations will remain the same.

Physical and Chemical Characterization

Duloxetine is extensively metabolized by humans; less than 10% of the administered dose is excreted as parent compound (Confidential Appendix O). The water solubility of duloxetine hydrochloride was determined to be 21.6, 2.74, and 0.331 g/L at pH 4, 7, and 9, respectively (Appendix B). The dissociation constant (pK_a) of duloxetine hydrochloride was determined to be 9.34 (Appendix C). At pH 4, 7, and 9 the log of the n-octanol/water partition coefficient (log P_{ow}) of duloxetine hydrochloride was determined to be 0.781, 1.54, and 3.35, respectively (Appendix D). The K_d was measured in sewage sludge and ranged between 1166 to 1731 (Appendix E). The K_d can be normalized for the amount of organic carbon in the sludge to calculate a K_{oc} of 2893 to 4296 for duloxetine hydrochloride.

Characteristic	Duloxetine Hydrochloride		
pK_a		9.34	
K_{oc}		2893 to 4296	
K_d		1166 to 1731	
	pH 4	pH 7	pH 9
Solubility g/L	21.6	2.74	0.331
Log P_{ow}	0.781	1.54	3.35

The log P_{ow} at pH 9 is less than 3.5 indicating that the probability for bioaccumulation is low. However, it is greater than 3 suggesting that sorption to biosolids will occur. Indeed, the K_{oc} confirms that duloxetine hydrochloride will sorb to biosolids in wastewater treatment plants.

Vapor pressure of duloxetine hydrochloride was not determined because thermogravimetric analysis of duloxetine hydrochloride showed no weight loss below 160°C. Above this temperature, decomposition and melting occurs. Thus, in the environment, release to the atmosphere is not expected.

Environmental Depletion Mechanisms

Duloxetine hydrochloride hydrolyzes slowly at temperatures lower than or equal to 30°C, with a half-life ranging from approximately 1.5 to 3.5 months at 30°C (Appendix F). Based on its ultraviolet-visible absorption spectrum, the theoretical phototransformation of duloxetine hydrochloride is estimated to be 100% within one month (Appendix G). Duloxetine hydrochloride was not significantly biodegraded when incubated with activated sewage sludge for 8 days (Appendix E). However, the presence of a small non-duloxetine radioactive peak indicates that there is potential for transformation of duloxetine. Thus, the primary depletion mechanisms of duloxetine hydrochloride from the aqueous environment are sorption, hydrolysis, and photolysis.

It is not expected that duloxetine will persist in the environment. Its extensive metabolism in humans and the presence of a transformation product in the biodegradation study suggest that duloxetine will be subjected to biodegradation. In addition, duloxetine will slowly hydrolyze in the aqueous environment.

Environmental Concentrations

Expected Introduction Concentration (EIC) in water

Even with the increase in use expected with the proposed changes in the current supplemental application, the maximum amount used annually in the United States is still predicted to be less than 100,000 kg of duloxetine (free base). From this forecast, the expected introduction concentration (EIC) of duloxetine at the point of entry into the aquatic environment is calculated as follows:

$$EIC_{aquatic}\,(ppb) = \frac{100{,}000\text{kg} \times 1{,}000{,}000{,}000\mu\text{g/kg}}{1.214\text{x}10^{11}\,\text{L/day} \times 365\text{days}} = 2.3\mu\text{g/L}$$

where 1.214x10^{11} L/day is the volume of water entering publicly owned treatment works in the United States. This calculation assumes that all duloxetine produced in a year is used and enters the publicly owned treatment works system, drug product usage occurs throughout the United States in proportion to population and the amount of wastewater generated, and there is no human metabolism or microbial degradation.

This $EIC_{aquatic}$ can be adjusted for sorption to biosolids. The measured K_d for sorption to biosolids at 2.5 g/L was 1166. K_d is defined as:

$$K_d = \frac{\left(\dfrac{\text{Duloxetine}_{\text{biosolids}}}{\text{Mass}_{\text{biosolids}}}\right)}{\left(\dfrac{\text{Duloxetine}_{\text{water}}}{\text{Mass}_{\text{water}}}\right)}$$

where $\text{Duloxetine}_{water}$ and $\text{Duloxetine}_{biosolids}$ are the amounts of duloxetine in water and biosolids, respectively. If the total amount of duloxetine in the water and the sludge is $\text{Duloxetine}_{total}$, then the above equation can be rearranged to give:

$$\text{Duloxetine}_{\text{water}} = \frac{\text{Duloxetine}_{\text{total}} \times \text{Mass}_{\text{water}}}{\text{Mass}_{\text{biosolids}} \times \left(K_d + \dfrac{\text{Mass}_{\text{water}}}{\text{Mass}_{\text{biosolids}}}\right)}$$

A typical water treatment facility has a biosolids concentration in the aerator basin of 3 to 6 g/L (Metcalf & Eddy, 1991). Using the more conservative number, in one liter of water, $\text{Duloxetine}_{total}$ is 2.3 µg, Mass_{water} is 1000 g (or 1000 mL) and $\text{Mass}_{biosolids}$ is 3 g. Solving for $\text{Duloxetine}_{water}$, the expected introduction concentration (EIC) in the aqueous phase adjusted for sorption to solids is:

$$\text{EIC}_{aquatic} = 0.5\mu g / L$$

Expected Environmental Concentration (EEC) in water

The Expected Environmental Concentration, EEC, can be calculated for the aquatic environment after consideration of dilution of treatment facility effluent by receiving waters. Based on dilution factors for treatment facilities available from the EPA, a dilution factor of 10 is appropriate. This concentration is considered for long-term exposure scenarios.

$$\text{EEC}_{aquatic\,(afterdilution)} = 0.05\mu g / L$$

Expected Introduction Concentration (EIC) in solids

It is also possible to determine the amount of duloxetine bound to the biosolids in a wastewater facility. The total duloxetine in one liter is 2.3 µg so in this case, the amount that must be sorbed to 3 g of biosolids is 1.8 µg. Thus:

$$\text{EIC}_{biosolids} = 600\mu g / kg$$

The residence time for sludge in wastewater facilities is 5 to 10 days. Appendix E describes a biodegradation study with duloxetine hydrochloride in which it was observed that after 8 days in contact with sludge, at least one degradation product of duloxetine was detected. The lag time to detection of a degradation product may indicate that microorganisms must become adapted in order to use duloxetine as a food source. In a wastewater treatment plant, it is assumed that the duloxetine concentration will be constant and thus the microorganisms will be continually exposed to duloxetine. This could result in greater biodegradation than observed in the study described in

Appendix E. Therefore, it is not unreasonable to assume that, in a wastewater facility, some degradation of duloxetine will occur.

Biosolids from treatment facilities are often applied to land as fertilizer and the majority of the application is to cropland. The rate of application is limited by the quantity of pollutants in the biosolids and by the nitrogen concentration. The total amount of nitrogen in biosolids ranges from 3 to 8% on a dry weight basis (Sullivan, 1998). The total nitrogen includes ammonium nitrogen and organic nitrogen. Ammonium nitrogen is immediately available for crop use but is also susceptible to loss through volatilization upon application. The organic nitrogen is available following mineralization by soil microbes. For this assessment it is assumed that all of the nitrogen is essentially available to the crops. Therefore, the least amount of nitrogen in biosolids would be 3% on a dry weight basis. Corn silage utilizes a maximum rate of nitrogen at 480 pounds/acre (539 kg/ha, Hammond et al., 1994). Using this application rate of nitrogen, a maximum rate of application of biosolids to agricultural land can be calculated.

$$\frac{539\text{kg}_{\text{Nitrogen}}}{\text{ha}} \times \frac{100\text{kg}_{\text{biosolids}}}{3\text{kg}_{\text{Nitrogen}}} = 17{,}967\text{kg}_{\text{biosolids}} / \text{ha} = 18\text{metrictons}_{\text{biosolids}} / \text{ha}$$

An incorporation depth of 15 cm into the top layer is typical in land application of biosolids (EPA, 1993). Assuming that the mass of soil is 1500 kg/m^3, the concentration of duloxetine in the soil after application of biosolids with 600 µg duloxetine/kg concentration is estimated to be:

$$\frac{18{,}000\text{kg}_{\text{biosolids}} \times 600\mu\text{g}_{\text{duloxetine}} / \text{kg}_{\text{biosolids}}}{10{,}000\text{m}^2 \times 0.15\text{m} \times 1500\text{kg}_{\text{soil}} / \text{m}^3} = 4.8\mu\text{g}_{\text{duloxetine}} / \text{kg}_{\text{soil}}$$

Summary

Duloxetine hydrochloride will enter the environment through its use by the general population. While human metabolism of duloxetine is extensive, estimations of concentrations of duloxetine in the environment were calculated based on total elimination as the parent compound. The Expected Introduction Concentration in the aqueous environment ($EIC_{aquatic}$) could be as high as 2.3 µg/L. The primary depletion mechanism of duloxetine from the aqueous environment is sorption to biosolids at water treatment facilities. Consideration of this depletion mechanism is used to calculate an adjusted $EIC_{aquatic}$ of 0.5 µg/L. The concentration in biosolids could be as high as 600 µg/kg. If biosolids are applied to land, then duloxetine may enter the terrestrial environment at a concentration in the soil ($EIC_{terrestrial}$) of 4.8 µg/kg. Duloxetine is not expected to volatilize and therefore will not enter the atmospheric environment. Duloxetine is not expected to be persistent in the environment due to its potential for degradation.

Environmental Effects of Released Substances

The environmental effects of duloxetine hydrochloride in aquatic organisms were investigated in a battery of toxicity studies conducted according to OECD guidelines. Since the original Environmental Assessment was submitted with NDA 21-427, an additional toxicity study has been conducted in earthworms. The earthworms study was included in the sNDA submitted in April 2006 for the use of duloxetine in the treatment of generalized anxiety disorder. The results of all the toxicity studies are summarized below.

Microbial Inhibition (Tier One)

The effect of duloxetine hydrochloride on sewage microorganisms was tested by incubating activated sludge with duloxetine for 3 hours (Appendix H). The endpoint measured was respiration rate. The no-observed-effect concentration (NOEC) was 2 mg/L and the EC50 was determined to be 36.5 mg/L (expressed as duloxetine free base).

Fish Acute Toxicity (Tier Two)

The acute toxicity of duloxetine hydrochloride to rainbow trout was determined in juvenile fish following exposure to the compound for 96 hours (Appendix I). The endpoint measured was mortality. The NOEC was 0.45 mg/L and the 96-hour LC50 was estimated to be 1.3 mg/L (expressed as duloxetine free base).

Invertebrate Acute Toxicity (Tier Two)

The acute toxicity of duloxetine hydrochloride to *Daphnia magna* was determined following exposure to the compound for 48 hours (Appendix J). The endpoint measured was immobilization. The NOEC was determined to be 1.1 mg/L and the 48-hour EC50 was estimated to be 2.4 mg/L (expressed as duloxetine free base).

Algal Toxicity (Tier Two)

The acute toxicity of duloxetine hydrochloride to green algae was determined using the species *Psuedokirchneriella subcapitata* (Appendix K). The algal cells were exposed for 72 hours and the endpoints measured were inhibition of biomass and average growth rate. Biomass, the area under the growth curve, was sensitive to duloxetine with a 72-hour EC50 of 0.064 mg/L and a NOEC of 0.011 mg/L (expressed as duloxetine free base).

Earthworm Toxicity (Tier Two)

The acute toxicity of duloxetine hydrochloride to *Eisenia fetida* was determined following exposure to the compound incorporated in an artificial soil for 14 days (Appendix L). The endpoints measured were mortality and growth (weight change). The NOEC was determined to be 1000 mg/kg (the highest concentration tested) and the 14-day LC50 was > 1000 mg/kg (expressed as duloxetine free base).

Chronic Toxicity (Tier Three)

The chronic toxicity of duloxetine hydrochloride was determined using *Daphnia magna* in a full life-cycle test with endpoints of size, survival, and reproduction (Appendix M). Along with body length, the most sensitive endpoint in the study was reproduction. The EC50 and NOEC values of 0.28 mg/L and 0.011 mg/L (expressed as duloxetine free base), respectively, were determined.

Risk Assessment

To assess the environmental risk of duloxetine in the environment, the median effect concentration was compared to the Maximum Expected Environmental Concentration, or MEEC. To protect all species, the quotient of the two numbers (the Assessment Factor) must be above 1000 for Tier One screening, above 100 for Tier Two, and above 10 for Tier Three screening as suggested by guidance from the FDA.

Effects Concentrations compared to expected environmental concentrations.

Aquatic Environment					
Species	NOEC (µg/L free base)	LC50 or EC50 (µg/L free base)	MEEC (µg/L free base)	LC50 or EC50 ÷ MEEC	Required Assessment Factor
Sewage microorganisms (3 hours)	2000	36,500	0.5	73,000	≥1000
Rainbow trout (96 hours)	450	1300	0.5	2600	≥100
Daphnia magna (48 hours)	1100	2400	0.5	4800	≥100
Pseudokirchneriella subcapitata (72 hours)	11	64	0.5	128	≥100
Daphnia magna (21 days)	11	280	0.05*	5600	≥10
Terrestrial Environment					
Species	NOEC (µg/kg free base)	LC50 (µg/kg free base)	MEEC (µg/kg free base)	LC50 ÷ MEEC	Required Assessment Factor
Eisenia fetida (14 days)	1000000	>1000000	4.8	>208333	≥100

*Note: for chronic exposure a dilution factor of 10 was utilized.

The calculated assessment factors in all cases are greater than the required factors and in no case were sublethal effects observed at concentrations equal to the MEEC. These results indicate that duloxetine release to sewage treatment plants and the environment does not pose an environmental risk.

Other Issues

Effects of Serotonin Reuptake Inhibitors on Aquatic Organisms

There is evidence in the literature that serotonin reuptake inhibitors can have sublethal effects on fish. Many studies have used selective serotonin reuptake inhibitors (SSRIs) as tools to probe the normal physiological role of serotonin in aquatic organisms. For example, Khan and Thomas (1992) demonstrated that fluoxetine (a potent SSRI) itself had no effect on the release of gonadotropin or on gonadotropin releasing hormone's stimulation of gonadotropin in Atlantic croaker (10 mg/kg by injection). With co-administration of serotonin by injection, 10 mg/kg fluoxetine did potentiate serotonin's increase of gonadotropin releasing hormone's stimulation of gonadotropin. In goldfish, as well, injected fluoxetine had no effect on gonadotropin levels itself, but did potentiate the effect of serotonin (Somoza et al., 1988). Foran et al. (2004) reported, however, that exposure to low levels of fluoxetine in water (nominally 0.1 to 5 µg/L) had no effect on reproductive endpoints (fecundity, fertilization, hatching response) in medaka (*Oryzias latipes*).

SSRIs can also have sublethal effects on aquatic invertebrate species. Fluoxetine has been shown to increase gonadal development in crustaceans with injections of 15 mg/kg in crayfish (Kulkarni et al., 1992) and about 18 mg/kg in crabs (Sarojini, 1993). Bivalves appear to be very sensitive to the effects of fluoxetine and other SSRIs on physiological endpoints. Ram et al. (1993) showed that serotonin (in water or by injection) induces zebra mussels to spawn within hours. Fong (1998) demonstrated that 5 µM (1.5 mg/L) fluoxetine in water caused spawning in 100% of male mussels while 0.05 µM (0.015 mg/L) was the lowest effective concentration and induced 20% of male mussels to spawn. Fluoxetine has been reported to have reproductive effects in cladocerans. Flaherty and Dodson (2005) reported increased fecundity in *Daphnia magna* following chronic exposure to 0.036 mg/L fluoxetine. Fecundity was slightly (<10% compared to control) increased at 0.056 mg/L fluoxetine and decreased at concentrations of 0.11 mg/L and greater in *Ceriodaphnia dubia* (Brooks et al. 2003). Henry et al. (2004) reported that concentrations of fluoxetine greater than 0.089 mg/L decreased *C. dubia* fecundity.

Like fluoxetine, duloxetine also has serotonin reuptake inhibitory activity. In a chronic toxicity study with *D. magna*, both body length and reproduction were affected by duloxetine exposure as summarized in this assessment. The NOEC for both body length and reproduction was 0.011 mg/L; fecundity was reduced at higher concentrations. This NOEC concentration for duloxetine in *D. magna* is more than 20 times greater than the maximum concentration of duloxetine expected to be discharged into surface water.

Potential Effects on Humans

If a human were to drink two liters of surface water at the maximum EEC of 0.05 µg/L duloxetine, the dose would be 0.1 µg. This dose would be at least 200,000 times less than the therapeutic dose of duloxetine. Thus, it is not expected that humans will be adversely affected by environmental concentrations of duloxetine.

Summary

Duloxetine and related metabolites in the environment originate from wastewater facilities. In wastewater facilities, duloxetine is expected to partition to the solids resulting in a reduction of the aqueous concentration. The expected duloxetine environmental concentration in water is not expected to affect aquatic organisms based on the toxicity of duloxetine to fish, invertebrates and algae. Duloxetine is not expected to persist in the aquatic environment because it is subject to degradation, hydrolysis, and photolysis. The maximum concentration of duloxetine expected in soil resulting from agricultural land application of biosolids is not expected to affect terrestrial organisms based on the lack of toxicity of duloxetine to earthworms. The amount of duloxetine that humans could be exposed to by drinking surface water with the maximum expected environmental concentration of duloxetine would be substantially less than the therapeutic dose range. In summary, no adverse environmental effects have been identified from the use of duloxetine in the treatment of human populations.

Mitigation Measures

As no adverse environmental effects have been identified in this environmental assessment from the use of duloxetine in the treatment of major depressive disorder and generalized anxiety disorder, no mitigation measures are needed. This action has no known effects on endangered or threatened species or historic properties.

Alternatives to the Proposed Action

As no adverse environmental effects have been identified from the use of duloxetine in the treatment of major depressive disorder and generalized anxiety disorder, there is no need for alternatives to the proposed action.

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See Appendix N for curriculum vitae

Consulting Agencies

See Confidential Appendix P for contract testing laboratories

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Nonconfidential Appendices

Appendix A: Duloxetine Data Summary Table

DULOXETINE DATA SUMMARY TABLE	
PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility	At pH 4 21.6 g/L At pH 7 2.74 g/L At pH 9 0.331 g/L
Dissociation Constant	$pK_a = 9.34$
Log Octanol/Water Partition Coefficient	Log P_{ow} At pH 4 0.781 At pH 7 1.54 At pH 9 3.35
Vapor Pressure or Henry's Law Constant	Not determined, assumed to be nonvolatile. Thermogravimetric analysis indicates decomposition and melting do not occur until 160°C.
Sorption/Desorption (K_{oc})	2893 to 4296

DEPLETION MECHANISMS	
Hydrolysis	Half life at temperatures equal to or lower than 30°C is 1.5 to 3.5 months
Aerobic Biodegradation	No significant degradation in 8 days. Small radioactive degradation product indicates eventual degradation.
Soil Biodegradation	Not determined
Photolysis	Theoretical phototransformation is 100% loss within one month in pH 4, 7 and 9 aqueous buffers.
Metabolism	Human metabolism is extensive, <10% excreted as parent compound.

ENVIRONMENTAL EFFECTS	
Microbial Inhibition	EC50 36.5 ppm NOEC 2 ppm
Acute Toxicity	*Daphnia magna* (48 hr) EC50: 2.4 ppm NOEC: 1.1 ppm *Oncorhynchus mykiss* (96 hr) EC50: 1.3 ppm NOEC: 0.45 ppm *Pseudokirchneriella subcapitata* (72 hr) $EC_{biomass}50$: 0.064 ppm $NOEC_{biomass}$: 0.011 ppm $EC_{growthrate}50$: 0.20 ppm $NOEC_{growthrate}$: 0.029 ppm *Eisenia fetida* (14 days) LC50: >1000 mg/kg NOEC: 1000 mg/kg
Chronic Toxicity	Full Life-Cycle Toxicity Test with *Daphnia magna* (21 days) LOEC: 0.037 ppm NOEC: 0.011 ppm MATC: 0.020 ppm $EC_{survival}50$: 0.45 ppm $EC_{reproduction}50$: 0.28 ppm

*Appendix B: Report Summary - S*tudy #: 1982.6114

Report Title: Duloxetine Hydrochloride - Determination of the Water Solubility of a Test Substance Following OECD Guideline 105

Study #: 1982.6114

Study date: June 2001

Methods:

The aqueous solubility of duloxetine hydrochloride was determined in pH 4, 7, and 9 aqueous buffers. Duloxetine hydochloride was added to 250 mL round bottomed flasks containing 100 mL of the buffer solutions. Test samples were agitated on a shaker table in a 30°C environmental chamber for equilibration periods of 24, 48 or 72 hours. After the equilibration period, the flasks were moved to an environmental chamber at 20°C for 24 hours with continued shaking. Duplicate samples were taken from the flasks and centrifuged at 25,848 g for 20 minutes. The supernatants were analyzed for duloxetine by HPLC.

Results:

The length of the equilibration time at 30°C did not affect the water solubility. Solubility decreased with increasing pH.

	Mean water solubility of duloxetine hydrochloride at 20°C (g/L)
pH 4	21.6
pH 7	2.74
pH 9	0.331

*Appendix C: Report Summary - S*tudy #: 1982.6115

Report Title: Duloxetine Hydrochloride - Determination of the Dissociation Constant for a Test Substance Following OECD Guideline 112

Study #: 1982.6115

Study date: June 2001

Methods:

The dissociation constant of duloxetine was determined at 20°C by a titration method using a Brinkman Titrino Workcell Version 4.0, Metrohm titrator. Two concentrations of duloxetine hydrochloride were prepared in CO_2-free water: 2.98 mM and 0.596 mM. The 2.98 mM solution was titrated with 0.150 mL aliquots of 0.1 M hydrochloric acid. The 0.596 mM solution was titrated with 0.020 mL aliquots of 0.1 M sodium hydroxide. The software program recorded the cumulative milliliters added and the resulting pH after each addition.

Results:

The dissociation constant (pK_a) was determined from the titration curve with 0.1 M sodium hydroxide. Titration with 0.1 M hydrochloric acid did not result in a titration curve. The mean pK_a for duloxetine hydrochloride was determined to be 9.34 at 20°C.

*Appendix D: Report Summary - S*tudy #: 1982.6127

Report Title: Duloxetine Hydrochloride – Determining the Partitioning Coefficient (n-Octanol/Water) of a Test Substance by the Flask-Shaking Method Following OECD Guideline 107

Study #: 1982.6127

Study date: June 2001

Methods:

The octanol/water partition coefficient (P_{ow}) of duloxetine hydrochloride was determined at pH 4, 7, and 9. A stock concentration of 201 mg/L duloxetine hydrochloride was prepared in buffer-saturated n-octanol. Solutions were prepared in duplicate for each pH using the volume ratios of 1:16, 1:8, and 1:4 of n-octanol-saturated buffer to duloxetine n-octanol stock. The mixtures were placed in centrifuge tubes with Teflon®-lined caps and rotated for five minutes at 20°C, centrifuged and re-equilibrated. Each phase was then analyzed by HPLC.

Results:

The partition coefficients were dependent on pH but independent of concentration.

	Mean P_{ow} (range)	Log P_{ow}
pH 4	6.05 (5.76 to 6.39)	0.781
pH 7	34.7 (33.2 to 36.3)	1.54
pH 9	2250 (2110 to 2320)	3.35

Appendix E: Report Summary - Study #: 1982.6123

Report Title: Duloxetine hydrochloride - Determination of the Inherent Biodegradability and Adsorption of a Test Substance by the SCAS Test, Modified from OECD Guideline 302A

Study #: 1982.6123

Study date: June 2001

Methods:

[^{14}C]Duloxetine hydrochloride was used to determine the kinetics of adsorption to sewage sludge and the aerobic biodegradability of duloxetine in activated sludge.

For adsorption determination, duplicate 500 mL flasks containing 200 mL 0.01 M $CaCl_2$ and 2500, 1250, 625, or 313 mg/L sludge solids were incubated with 1.01 mg/L [^{14}C]duloxetine hydrochloride. The flasks were stirred in an environmental chamber at 22 ± 3°C for four hours. At timepoints 0, 1, 2, and 4 hours, 30 mL homogenous samples were taken from each flask. Samples were split with one portion being extracted and analyzed for parent material by HPLC/RAM and LSC and the other portion centrifuged to isolate the supernatant for assay of parent material. The organic carbon content of the sludge was also determined.

For assessment of biodegradation potential, duplicate 500 mL flasks containing 250 mL of sewage sludge with 2500 mg/L solids were incubated with 1.00 mg/L of [^{14}C]duloxetine hydrochloride. The flasks were stirred in an environmental chamber at 22 ± 3°C. The flasks were stoppered and connected to a volatiles trapping system. Samples (20 mL) were taken from the flasks at 0, 8, 24, 72, 96, 120, 144, and 192 hours. The volatiles traps were sampled at 96 and 192 hours. Sludge samples were analyzed by HPLC/RAM following extraction of the whole sample. Volatile trap samples were assayed by LSC.

Results:

Adsorption of duloxetine hydrochloride to solids reached a plateau by 2 hours incubation with the sewage sludge. The adsorption coefficients ($K_{d(sludge)}$) at 4 hours were calculated to be 1166, 1269, 1197, and 1731 for 2500, 1250, 625, and 313 mg solids/L, respectively. The adsorption coefficients expressed as a function of the organic carbon content ($K_{oc(sludge)}$) of the activated sludge were calculated to be 2893, 3150, 2970, and 4296.

During the biodegradation study, duloxetine concentrations dropped from 91.3% at 0 hour to 62.1% by 8 hours. There was no further decline in duloxetine concentration over the remaining 8 days. Therefore, this initial decline is most likely attributable to extraction inefficiency as duloxetine becomes more tightly bound to the sludge solids. After 8 days, a small degradation peak was observed accounting for approximately 1.5% of the total radioactivity. The presence of this degradation product indicates the eventual biodegradability of duloxetine.

*Appendix F: Report Summary - S*tudy #: 1982.6120

Report Title: Duloxetine Hydrochloride – Determination of the Abiotic Degradation of the Test Substance by Hydrolysis at Three Different pH Values Following OECD Guideline 111

Study #: 1982.6120

Study date: June 2001

Methods:

Preliminary Test:

A hydrolysis study with duloxetine was conducted in three aqueous buffers, pH 4, 7, and 9. Duloxetine hydrochloride was added to the buffers for a final concentration of 10 mg/L (expressed as duloxetine free base). Aliquots of each solution were incubated in 50 mL volumetric flasks in a 50°C water bath for 5 days. All flasks were wrapped in foil. Analysis for duloxetine concentration was performed on days 0 and 5.

Definitive Test:

A hydrolysis study with duloxetine was conducted in the same three aqueous buffers above. Two 200 mL aliquots of each solution containing 10 mg/L duloxetine were incubated in volumetric flasks for 28 days in a 40°C water bath. A third 200 mL aliquot was incubated for 35 days at 30°C. All flasks were wrapped in foil. At days 0, 3, 7, 10, 12, 14, 17, 20 and 28 samples were removed from the 40°C incubation for analysis. Samples were taken from the 30°C incubation at days 0, 3, 7, 10, 12, 17, 28, and 35.

Results:

Preliminary Test:

The percent duloxetine remaining after 5 days at pH 4, 7, and 9 was 56.4%, 75.9%, and 60.7%, respectively.

Definitive Test:

The following first order hydrolysis rate characteristics for duloxetine were calculated.

pH	°C	Initial [Duloxetine] on Day 0 (mg/L)	[Duloxetine] at end of test (mg/L)	Hydrolysis Rate Constant (Day^{-1})	Half Life (Days)
4	30	10.4	6.07	0.0165	41.88
7	30	10.0	8.05	0.0069	100.62
9	30	10.0	7.43	0.0096	72.48
4	40	9.98	2.92	0.0440	15.73
7	40	10.2	5.67	0.0219	31.69
9	40	9.84	4.21	0.0306	22.64

Appendix G: Report Summary - Study #: 1982.6130

Report Title: Duloxetine Hydrochloride - Determination of the Ultraviolet-Visible Absorption Spectrum in Aqueous Solution Following OECD Proposed Guideline for Phototransformation of Chemicals in Water

Study #: 1982.6130

Study date: June 2001

Methods:

Solutions of 0.0015 M duloxetine hydrochloride were prepared in pH 4 and pH 7 buffers and in unbuffered pure reagent water. A solution of 0.0003 M duloxetine hydrochloride was prepared in pH 9 buffer. The absorption spectra of the test solutions were measured using a Hewlett-Packard Model 8453 UV-Vis spectrophotometer. Absorbance peaks recorded in the wavelength range for natural sunlight (i.e. 295 to 800 nm) were used to calculate the propensity for phototransformation of duloxetine.

Results:

Absorbance peaks were observed in the range of 295 to 325 nm. The molar absorption coefficient was determined for each peak and using these values it was calculated that within 30 days, 100% of duloxetine would be phototransformed at pH 4, 7, and 9 and in pure reagent water.

*Appendix H: Report Summary - S*tudy #: 1982.6126

Report Title: Duloxetine Hydrochloride - Activated Sludge Respiration Inhibition Following OECD Guideline 209

Study #: 1982.6126

Study date: June 2001

Methods:

Duloxetine hydrochloride was incubated with synthetic sewage feed and activated sludge (1.5 g/L solids concentration) in a volume of 500 mL in 1000 mL beakers. There were five treatment levels consisting of one replicate each. Four treatment levels of 3,5-dichlorophenol were incubated as above as a reference control for the study. There were two controls consisting of synthetic sewage feed and activated sludge only and an abiotic control with synthetic sewage feed only. The nominal concentrations of duloxetine (expressed as free base) were 2, 6, 18, 54, and 162 mg/L. The stock solution (500 mg/L) used to make the test concentrations was analyzed by HPLC and determined to be 498 mg/L duloxetine (free base). The nominal concentrations of 3,5-dichlorophenol were 3.0, 10, 30 and 100 mg/L. After 3 hours and 25 minutes of incubation during which the test systems were aerated, homogenous samples from each replicate and control were collected. The pH was measured and the dissolved oxygen was monitored over 10 minutes in a Strathkelvin Instruments oxygen system while the samples were continuously stirred in a water bath. From these measurements, the oxygen consumption rate was calculated for each treatment level and control.

Results:

The temperature of the test solutions was maintained between 18.5 and 21.9°C during the incubation and the water bath used during the oxygen measurements was maintained at approximately 21°C. The pH in all treatments was between 7.27 and 7.59. The respiration rates for the control vessels were 29.3 and 31.1 mg O_2/L/hr. The abiotic control respiration rate was -1.8 mg O_2/L/hr. The respiration rates for the reference compound were 26.9, 15.4, 3.5 and 0.6 mg O_2/L/hr for 3.0, 10, 30, and 100 mg/L, respectively. The EC50 of 3,5-dichlorophenol was calculated to be 11.1 mg/L which is within the acceptable limits (5.0 to 30 mg/L) as specified in the OECD 209 Guideline. Respiration rates for the treatment levels were 30.7, 21.8, 26.0, 7.7 and -0.8 mg O_2/L/hr for 2, 6, 18, 54, and 162 mg/L duloxetine, respectively. The no-observed effect concentration for duloxetine was 2 mg/L and the EC50 was calculated to be 36.5 mg/L.

*Appendix I: Report Summary - S*tudy #: 1982.6125

Report Title: Duloxetine Hydrochloride - Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static-Renewal Conditions

Study #: 1982.6125

Study date: June 2001

Methods:

The acute toxicity of duloxetine to rainbow trout was assessed according to OECD guideline 203. Juvenile trout (mean weight 0.75 g, mean length 42 mm) were exposed to mean measured concentrations of duloxetine of 0 (control), 0.45, 0.89, 1.9, 3.8, 8.6, and 17 mg/L (here and below expressed as duloxetine free base) for 96 hours. A total of 10 fish were exposed to each treatment level in a volume of 15 L. At 48 hours, the fish were transferred to fresh exposure solutions. Daily mortality and behavioral changes were recorded.

Results:

Temperature in the test system was maintained between 13 and 14°C. The pH and dissolved oxygen ranged from 6.7 to 7.4 and 6.2 to 10.2 mg/L, respectively. At 96 hours the cumulative mortality at concentrations ≥1.9 mg/L was 100%. There was no mortality in lower treatment levels or the control. Lethargic swimming behavior was observed in the 0.89 mg/L. The 96 hour LC50 was determined to be 1.3 mg/L duloxetine with 95% confidence intervals of 0.89 to 1.9. The 96 hour no-observed-effect concentration was 0.45 mg/L duloxetine.

*Appendix J: Report Summary - S*tudy #: 1982.6116

Report Title: Duloxetine Hydrochloride - Acute Toxicity to Daphnids (*Daphnia magna*) Under Static Conditions

Study #: 1982.6116

Study date: June 2001

Methods:

The acute toxicity of duloxetine to daphnids was assessed according to OECD guideline 202. Daphnids (≤24 hours old) were exposed to mean measured concentrations of duloxetine of 0 (control), 0.10, 0.52, 1.1, 2.1, 4.2 and 8.5 mg/L (expressed as duloxetine free base) for 48 hours. Four replicates were included at each treatment level. Each replicate contained five animals in 200 mL of test solution. The test solutions were prepared with fortified well water (initially pH 8.0, conductance 550 µmhos/cm, total hardness as $CaCO_3$ 180 mg/L, and total alkalinity as $CaCO_3$ 120 mg/L). At 24 and 48 hours, water quality measurements were made and the number of immobilized daphnids in each replicate was recorded.

Results:

During the testing period the temperature ranged from 19 to 21°C, the pH from 7.9 to 8.2 and the dissolved oxygen from 8.6 to 10.3. No immobilization or other adverse effects (e.g. lethargy) were observed in treatment levels ≤1.1 mg/L duloxetine and the control. Immobilization occurred in 35, 100 and 100% of daphnids exposed to 2.1, 4.2 and 8.5 mg/L duloxetine, respectively. The surviving daphnids in the 2.1 mg/L group were observed to be lethargic. The 48-hour EC50 and 95% confidence limits were calculated to be 2.4 mg/L and 1.1 to 4.2 mg/L duloxetine, respectively. The no-observed-effect concentration was 1.1 mg/L duloxetine.

*Appendix K: Report Summary - S*tudy #: 1982.6118

Report Title: Duloxetine hydrochloride - Acute Toxicity to the Freshwater Green Alga *Pseudokirchneriella subcapitata*, Following OECD Guideline #201

Study #: 1982.6118

Study date: June 2001

Methods:

A static toxicity test was conducted to evaluate the effects of duloxetine hydrochloride on the green alga, *Pseudokirchneriella subcapitata*. There were six treatment levels containing duloxetine hydrochloride and three replicates at each treatment. The initial measured concentrations in the treatments were 0.0053, 0.011, 0.029, 0.070, 0.20 and 0.47 mg/L duloxetine (concentrations and all results below are expressed as the free base). There were six replicates for the control. To each replicate, approximately one million algal cells were added to 100 mL of appropriately treated Algal Assay Procedure medium in sterile 250 mL flasks to give an initial cell concentration of 10,000 cells/mL. The cells were cultured under continuous illumination at 400 to 490 footcandles and continuous shaking for 72 hours. The pH and conductivity during the test ranged from 7.4 to 8.2 and 80 to 90, respectively. The temperature was 24°C. At 24, 48, and 72 hours, a sample was removed from each flask and the cells were counted using a hemocytometer. These measurements were used to calculate the growth rate and biomass for each replicate.

Results:

After 72 hours, the concentration of duloxetine in all treatments was <10% of the nominal concentration. An additional replicate in the 0.029 mg/L treatment in which no cells were added also contained less than 10% of the initial concentration after 72 hours. Thus the disappearance of duloxetine was probably due in large part to photolysis. There is no established method to maintain constant exposure concentrations in algal toxicity studies if test material declines over the study. After 72 hours the control growth rate was 1.61 $days^{-1}$ (standard deviation = 0.020) and for treatment concentrations ≥0.070 mg/L the rate was significantly reduced (≤1.51 $days^{-1}$). Thus, the no-observed-effect concentration (NOEC) for growth rate was 0.029 mg/L. The median effective duloxetine concentration on reduction of growth rate (EC50) was 0.20 mg/L with 95% confidence limits of 0.088 to 0.31 mg/L. After 72 hours, the biomass (the area under the growth curve) of the control cells was 10,500 cells·days/mL. At 0.47 mg/L duloxetine biomass was significantly reduced. Based on these results, the NOEC for biomass would be 0.20 mg/L. However, duloxetine concentrations ≥0.029 mg/L duloxetine caused >10% reduction of biomass. Thus, the NOEC for biomass was considered to be 0.011 mg/L rather than 0.20 mg/L. The EC50 at 72 hours was calculated to be 0.064 mg/L with 95% confidence limits of 0.019 to 0.23 mg/L. Biomass was the most sensitive endpoint and, therefore, the most conservative EC50 and NOEC for this study were initial duloxetine concentrations of 0.064 and 0.011 mg/L, respectively.

*Appendix L: Report Summary - S*tudy #: 1982.6133

Report Title: Duloxetine Hydrochloride - Acute Toxicity to Earthworms (*Eisenia fetida*) following OECD Guideline #207

Study #: 1982.6133

Study date: February 2002

Methods:

The acute toxicity of duloxetine to earthworms was assessed according to OECD guideline 207. Adult earthworms (300-600 mg) were exposed to 63, 130, 250, 500 and 1000 mg/kg duloxetine (as free base) in artificial soil for 14 days. Four replicates of ten earthworms each were exposed to each concentration and a blank control in 750 g (wet weight) of amended artificial soil. Mortality and observations of surviving earthworms were recorded on days 7 and 14. On day 14 the surviving earthworms were collectively weighed on a per replicate basis after being rinsed with deionized water and blotted dry.

Results:

Temperature, pH and moisture content in the test system ranged from 19 to 21°C, 5.8 to 6.5, and 21 to 39%, respectively. There was 100% survival in all treatment levels and controls. The 14-day NOEC was 1000 mg/kg and the LC50 was >1000 mg/kg. After 14 days, the mean change in body weight of earthworms exposed to 63, 130, 250, 500 and 1000 mg/kg duloxetine was -16.0%, -16.0%, -16.3%, 17.2%, and 26.8%, respectively. The mean weight change in the control group was -14.2%.

*Appendix M: Report Summary - S*tudy #: 1982.6129

Report Title: Duloxetine Hydrochloride - Full Life-Cycle Toxicity Test with Water Fleas, *Daphnia magna* Under Flow-Through Conditions, Following FIFRA Guideline 72-4, OECD Guideline #211, and OPPTS Draft Guideline 850.1300.

Study #: 1982.6129

Study date: June 2001

Methods:

Daphnia magna, ≤24 hours old, were exposed to duloxetine hydrochloride for 21 days in a flow-through exposure system. There were six treatment levels and a control with four replicate vessels in each treatment. Each replicate vessel held 10 daphnids in a volume of 1.4 L. Test solutions were delivered to the vessels at a rate of six vessel volumes per 24-hour period to provide a 90% solution replacement rate of approximately 9 hours. The mean measured concentrations in the treatments were 0 (control), 0.011, 0.037, 0.080, 0.14, 0.26 and 0.50 mg/L duloxetine (expressed here and below as the free base) prepared in fortified well water. Conditions during the exposure were 19 to 22°C and a light:dark cycle of 16:8 hours at 30 to 70 footcandles. The number of immobilized adult daphnids and observations of abnormal behavior were recorded daily. Assessments of offspring released were determined beginning on day 7 and three times per week through day 21.

Results:

Water quality parameters monitored during the test included pH (7.9 to 8.2), conductivity (500 µmhos/cm), total hardness (180 mg/L as $CaCO_3$), and total alkalinity (110 to 120 mg/L as $CaCO_3$). After 21 days mean percent survival in the treatments was 95, 100, 93, 93, 100, 100, and 38% in the control, 0.011, 0.037, 0.080, 0.14, 0.26 and 0.50 mg/L duloxetine, respectively. The EC50 for survival was calculated to be 0.45 mg/L. After 21 days, the mean body length of daphnids exposed to ≥0.037 mg/L duloxetine was significantly reduced from the control average of 5.1 mm. The mean dry weight of daphnids exposed to ≥0.14 mg/L was significantly reduced compared to the control average of 1.1 mg. After 21 days the mean cumulative number of offspring released per female daphnid in the treatments was 161, 166, 140, 131, 113, and 72 for control, 0.011, 0.037, 0.080, 0.014, and 0.26 mg/L duloxetine, respectively. The reproduction for the 0.50 treatment was not analyzed in the statistics because of the significant survival effect. Offspring numbers in treatment levels ≥0.037 were significantly different from the control. The no-observed-effect concentration and the EC50 for reproduction were calculated to be 0.011 and 0.28 mg/L duloxetine, respectively.

Appendix N: Curriculum Vitae of Preparers

Alison Nimrod Perkins

Lilly Research Laboratories, Indianapolis, IN

Ph.D.	Pharmacology/Toxicology, University of Mississippi	1996
B.S.	Chemistry, Tulane University	1988

Previous Experience: Research Scientist, University of Mississippi in the National Center for Natural Products Research (1997 to 1999). Supervised technical staff of the Biological Core. This group was responsible for screening extracts and pure compounds from natural products for various biological activities. Primary effort included development of new assays. Author on several publications and abstracts in the natural products arena as well as environmental toxicology. Guest lecturer for undergraduate and graduate level courses in pharmacology and toxicology.

Current Responsibility: Research Scientist, Health, Safety and Environmental. Prepares environmental risk assessments for animal and pharmaceutical products for submission to the FDA and Europe. Prepares guidelines for production facilities for containment of active products.

Professional Activities:

Editorial Board: Environmental Toxicology and Chemistry
Member: Society of Environmental Toxicology and Chemistry
Reviewer: ETC, Journal of Natural Products, Journal of Biomolecular Screening

Roger D. Meyerhoff

Lilly Research Laboratories, Greenfield, IN

Ph.D.	Fisheries/Pharmacology & Toxicology, Oregon St. Univ.	1980
M.S.	Fisheries/Limnology & Water Pollution, Oregon St. Univ.	1976
B.S.	Fisheries and Wildlife Biology, Univ. Calif. at Davis	1974

Previous Experience: Senior Toxicologist up to Research Advisor and Head of Environmental Science and Hazard Communications (1980 to 2004). Conducted acute and chronic environmental toxicology studies with over 20 aquatic and terrestrial species and coordinated aquatic and terrestrial field studies. Author of a number of abstracts, papers, and chapters on the results of these studies and lecturer on environmental risk assessment to undergraduates and graduate students at several universities. Has prepared risk assessments for pesticides, animal products, and pharmaceutical products to support submissions to the EPA, FDA, Europe, Australia and Japan since 1982. As Head of Environmental Science and Hazard Communications, was responsible for personnel and operations supporting environmental safey at production facilities, registration of new products (conduct of inhalation, aquatic, wildlife, microbial, and environmental chemistry studies), and workplace safety (material safety data sheets, caution statements, and risk assessments for human exposure).

Current Responsibility: Senior Research Advisor for Health, Safety and Environmental in Lilly Research Laboratories. Responsible for human and environmental risk assessments to support product registrations, workplace safety, product safety, and environmental safety at production facilities.

Professional Activities:
Chairman (1993-1995), SETAC Foundation for Environmental Education
President (1991-1992), Society of Environmental Toxicology & Chemistry (SETAC)
Board of Directors (1987-1993), SETAC
Member (1991-Present), PhRMA Environmental Working Group
Member (1987 - Present), An. Health Inst. Sci. Com., Env. Working Group
Member (1985-1987), National Agricultural Chemical Association
Subcommittee on Environmental Toxicology and Chemistry

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/s/

Jon E. Clark
6/15/2007 01:49:32 PM

Moheb Nasr
6/20/2007 10:53:14 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: June 15, 2007

From: Raanan A. Bloom, Ph.D.
OPS/PARS

To: Teshara G. Bouie
OPS/ONDQA/DPMA

Through: Jon Clark, M.S.
OPS/PARS

Subject: Cymbalta® (Duloxetine hydrochloride) - 20, 30, 40, and 60 mg gelatin capsules for maintenance of efficacy in the treatment of Major Depressive Disorder (MDD): Environmental Assessment Review

NDA # 021-427 S-015
Submission Date: December 18, 2006

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Background

The submitted environmental assessment (EA), undated (submission cover letter 12/18/2006), supports an efficacy supplement to new drug application NDA 021-427 for Cymbalta® (duloxetine hydrochloride) - 20, 30, 40, and 60 mg gelatin capsules for maintenance of efficacy in the treatment of Major Depressive Disorder (MDD).

Review of the Current Submission

The EA was prepared in accordance with 21 CFR 25 by Eli Lilly and Company The EA is basically identical to the April 27, 2006, EA previously submitted and approved for the use of Cymbalta® as a treatment for generalized anxiety disorder (S-011). A FONSI was issued for S-011 on January 16, 2007.

No new information is provided in this EA. The sponsor claims that the total amount of duloxetine free base required in the peak market with the addition of a claim for MDD is not more than 100,000 kg/year. Environmental exposures are calculated using this value (b) (4)

Using this information and the algorithm described in the FDA EA Guidance for Industry document, the Expected Introduction Concentration (EIC) of duloxetine in the aquatic environment is (b) (4) (ppb). The EIC in the aqueous phase adjusted for sorption to solids is estimated to be (b) (4). The Expected Environmental Concentration, EEC, calculated after consideration of dilution of treatment facility effluent by receiving waters ((b) (4) dilution) is estimated to be (b) (4)

The following toxicity effects data were generated on aquatic species. (b) (4) conducted testing according to OECD Guidelines and in compliance with Good Laboratory Practices (GLPs). An activated sludge respiration test was also conducted.

(b) (4)

Results indicate that duloxetine does not inhibit sewage microorganisms at concentrations expected in wastewater treatment plants and therefore duloxetine residues are not expected to disrupt wastewater treatment process.

The applicant performed acute toxicity testing in algae, Daphnia magna and rainbow trout. The EC_{50} or LC_{50} to MEEC (maximum expected environmental concentration) ratio was

greater than 100 and the NOEC was greater than the MEEC for each study indicating that no effects would be expected.

As discussed in the review for the EA submitted under S-011, typical testing would end after the acute testing phase. However, there is some evidence in the literature that selective serotonin re-uptake inhibitors (SSRI) have sub-lethal reproductive effects on aquatic organisms. Duloxetine is an SSRI. Therefore, the chronic toxicity study described above was conducted with the invertebrate D. magna to probe for effects that would not be noticed easily in other test systems. Based on test results, the EC_{50} to MEEC ratio is greater than 10 and the NOEC is greater than the MEEC indicating that no effects would be expected.

Sludge from publicly owned treatment works (POTW) may be applied to soil. If the maximum rate for applying sludge (biosolids containing approximately (b) (4)) to soil is (b) (4) the concentration of duloxetine in the top 15 cm of the soil compartment is (b) (4) . This concentration is below the 100 ppb level stated in the 2000 VICH Guideline that triggers the need for terrestrial ecotoxicity testing for veterinary medicinal products. The applicant's focus on testing of aquatic species is appropriate.

Comments and Conclusions

Based on an evaluation of the information provided in this and previous EAs for Cymbalta® and in FDA guidance, no further testing is required and no adverse effects are expected from the introduction of duloxetine into the environment due to the use of Cymbalta®

A Finding of No Significant Impact (FONSI) is recommended.

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/s/

Raanan Bloom
6/15/2007 10:42:47 AM
ENV ASSESSMENT

Jon E. Clark
6/15/2007 01:48:58 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427/S-015, S-017

PHARMACOLOGY REVIEW(S)

Supplemental New Drug Application
Complete Response to Efficacy Supplement – OCP Review

NDA:	21-427
Serial Number:	015
Type of Submission:	SE-1 AL Complete Response to Maintenance of Effect Claim Labeling for Efficacy Supplement
Generic Name:	Duloxetine HCl Enteric Coated - Delayed Release Capsules
Brand Name:	Cymbalta Capsules
Formulation(s); **Strength(s);** **Route(s)**	Modified Release Capsule 20 mg, 30 mg, 60 mg PO
Sponsor:	Lilly Indianapolis, IN
Letter Date:	September 28, 2007
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Team Leader	Raman Baweja, Ph.D.

1 BACKGROUND AND REGULATORY HISTORY

The following in the regulatory history per the sponsor:

"On October 31, 2006, Lilly submitted a sNDA for a Maintenance of Effect indication for the treatment of Major Depressive Disorder. This sNDA, which is S-015, also contained revised labeling in the new PLR format. In the Action Letter to Lilly from the Division of Psychiatry Products (DPP), dated August 27, 2007, the Division stated that the sNDA was approvable, pending agreement on final labeling. This submission contains Lilly's Complete Response to the approvable letter."

In addition Lilly states: *"that the currently implemented labeling for Cymbalta contains* (b) (4) *"Changes Being Effected" (CBE) sNDA submission* (b) (4) *that the FDA has not yet taken action on"*. Specifically

(b) (4)

S-017, CBE submitted May 17, 2007

2 REVIEW

This reviewer was not previously assigned to any of the aforementioned supplemen (b) (4) and did not work on any of the FDA proposed labeling changes in the present submission. Consequently, this review was limited to those sections of the labeling that contain proposed changes to clinical pharmacology information, and the review focused exclusively on whether the sponsor accepted proposed labeling changes from the clinical division as outlined in the August 27th, 2007 approvable letter. Thus except where noted this review should not be taken to indicate this reviewer either agrees with or disagrees with the labeling proposed by the medical division or the sponsor, except where specifically noted.

The following sections of the submitted labeling were reviewed:

2.3 Dosing in Special Populations

5.9 Clinically Important Drug Interactions

8 USE IN SPECIFIC POPULATIONS

12 CLINICAL PHARMACOLOGY

N.B. Section Numbering is per the sponsor's present submission.

3 COMMENTS TO MEDICAL DIVISION

The sponsor accepted all FDA labeling recommendations in sections 2.3, 5.9, and 8.

With regards to (b) (4) added additional language on observed adverse reactions. These changes are acceptable to this reviewer.

4 SIGNATURES

Ronald E. Kavanagh, BS Pharm, Pharm.D., Ph.D., OCP/DCP-1	**Date**
Andre Jackson, Ph.D. Secondary Reviewer for Raman Baweja, Ph.D., Team Leader, OCP/DCP-1	**Date**

CC:

DFS	NDA 21-427 SE1-015 AL
DPP	(GlassR, KhinN, MathisM, LaughrenT, BenderB, HardemannS, DavidP)
OCP/DPE1	(JacksonA, BawejaR, KavanaghR, UppoorR, MehtaM)

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/s/

Ron Kavanagh
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BIOPHARMACEUTICS

Andre Jackson
10/23/2007 11:05:30 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427/S-015, S-017

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	21-427 (SE1_015)
Drug Name:	CYMBALTA® (LY248686, duloxetine hydrochloride)
Indication:	Major Depressive Disorder
Applicant:	Eli Lilly and Company
Dates:	Date of Document: 10/31/2006
	PDUFA Due Date: 9/1/2007
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.
	James Hung, Ph.D.
Medical Division:	Division of Psychiatry Drug Products, HFD-130
Clinical Team:	Clinical Reviewer: Roberta Glass, M.D.
	Clinical Team Leader: Ni Aye Khin, M.D.
Project Manager:	William Bender, LCDR, USPHS

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1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Study F1J-MC-HMBC is a positive study. Based on the study design, it demonstrated only two weeks of maintenance effect for duloxetine 60 mg QD in treating patients with major depressive depression. Nevertheless, most patients appeared to be stabilized longer than two weeks before randomization according to the other response criterion by 50% reduction of $HAMD_{17}$ total score. This length of period that patients responded continuously to the drug before randomization was on average 7.55 weeks (b) (4)

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this submission, the sponsor submitted one efficacy study (F1J-MC-HMBC) to support the use of Cymbalta (duloxetine hydrochloride) for maintenance of efficacy in the treatment of major depressive disorder (MDD). The acute efficacy of duloxetine as a treatment for depression was already established in four randomized, double-blind, placebo controlled, fixed-dose studies in adult outpatients meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

In Study F1J-MC-HMBC, the maintenance of efficacy of duloxetine 60 mg QD compared with placebo was evaluated by the time to relapse among patients with MDD, without psychotic features, who responded to open-label duloxetine 60 mg QD treatment after 12 weeks. Relapse during the randomization phase was defined as an increase in Clinical Global Impressions of Severity (CGI-Severity) score of at least two points relative to randomization baseline for two consecutive visits and meeting the criteria for MDD for two consecutive visits, as determined by the depression module of the Mini Inernational Neuropsychiatric Interview (MINI).

Based on the sponsor's analysis results, the sponsor concluded that in all randomly assigned patients, those treated with duloxetine were shown to have significantly longer time to relapse compared with placebo-treated patients. (b) (4)

1.3 STATISTICAL ISSUES AND FINDINGS

The data of Study F1J-MC-HMBC supported the maintenance of effect of duloxetine 60 mg QD in treating patients with major depressive disorder. However, the length of maintenance effect of duloxetine 60 mg QD that the data actually supported is not clear. The length of maintenance effect of a drug is generally claimed based on the fixed period of patients who were stabilized in the study before they are randomized into the continuation therapy phase. According to the protocol of this study, patients only need to meet the response criterion at two weeks prior to randomization. Since patients could have been stabilized much earlier and longer than two weeks prior to randomization, we asked the sponsor to provide further information regarding patients' lengths of stabilization period. The average period of all randomized patients' continuous response to duloxetine 60 mg QD by 50% reduction of $HAMD_{17}$ total score prior to two weeks before randomization appears to be 5.55 weeks long. So, patients seemed to be stabilized for 7.55 weeks on average before randomization. (b) (4)

2. INTRODUCTION

2.1 OVERVIEW

The acute efficacy of duloxetine as a treatment for depression was established in four randomized, double-blind, placebo-controlled, fixed-dose studies in adult outpatients (ages 18 to 83) meeting Diagnostic and Statistical Manual of mental Disorders, Fourth Edition (DSM-IV) criteria for major depressive disorder (MDD). In addition to the aforementioned four acute treatment studies, duloxetine was also studied in one large (n=1279) open-label 1-year study in MDD, two additional 8-week acute MDD studies and one standard relapse prevention, or say randomized withdrawal trial (Study F1J-MC-HMBC) for duloxetine 60 mg QD's maintenance of efficacy in the treatment of MDD. This NDA application was submitted mainly for that (b) (4) F1J-MC-HMBC.

In Study F1J-MC-HMBC, the maintenance of efficacy of duloxetine 60 mg QD compared with placebo was evaluated by the time to relapse among patients with MDD. The difference between duloxetine 60 mg QD and placebo was evaluated by the Log-rank test. Based on the sponsor's analysis results for all ITT randomized patients, those treated with duloxetine were shown to have significantly longer time to relapse compared with placebo-treated patients (p=0.004). (b) (4)

(b) (4)

2.2 DATA SOURCES

The electronic submission of this NDA was stored in the CDER's electronic document room (EDR) by the following link: \\CDSESUB1\N21427\S_015\2006-10-31. The sponsor's analysis results and data per the FDA's request regarding stabilization criterion was stored by the following link: \\CDSESUB1\N21427\S_015\207-05-15.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

The following description is based on the sponsor's clinical study report. Any discrepancy between the study report and study protocol will be discussed in the section of statistical reviewer's comments.

3.1.1 Description of Study F1J-MC-HMBC

3.1.1.1 Study Objectives

The primary objective of this study was:

- To assess the maintenance efficacy of duloxetine 60 mg once daily (QD) compared with placebo by a comparison of the time to relapse among patients with Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV)-defined major depressive disorder (MDD), without psychotic features, who responded to open-label duloxetine treatment after 12 weeks. Patients were assessed during 26 weeks of the continuation therapy phase.

The secondary objectives of the study were as follows:

- To assess the impact of treatment with duloxetine and placebo during the continuation therapy phase on quality of life as measured by Sheehan Disability Scale (SDS) and Quality of Life in Depression Scale (QLDS).

- To compare the efficacy of treatment with duloxetine and placebo during the continuation therapy phase on physical symptoms, as measured by Visual Analog Scale for pain (VAS) and Symptom Questionnaire, Somatic Subscale (SQ-SS).

- To evaluate the efficacy of treatment with duloxetine as compared with placebo during the continuation therapy phase as measured by (1) 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) total score (2) Clinical Global Impression of Severity Scale (CGI-Severity) (3) Patient Global Impression of Improvement Scale (PGI-Improvement) and (4) HAMD subscales.

- To assess the impact of treatment with duloxetine and placebo during the continuation therapy phase on safety and tolerability, as measured by treatment-emergent adverse events, vital signs, laboratory measurements, and the Patient Global Impression of Sexual Function (PGI-SF).

- To evaluate whether an increase in the dose of duloxetine from 60 mg QD to 60 mg twice daily (BID) during the rescue therapy phase restores response among patients who relapsed.

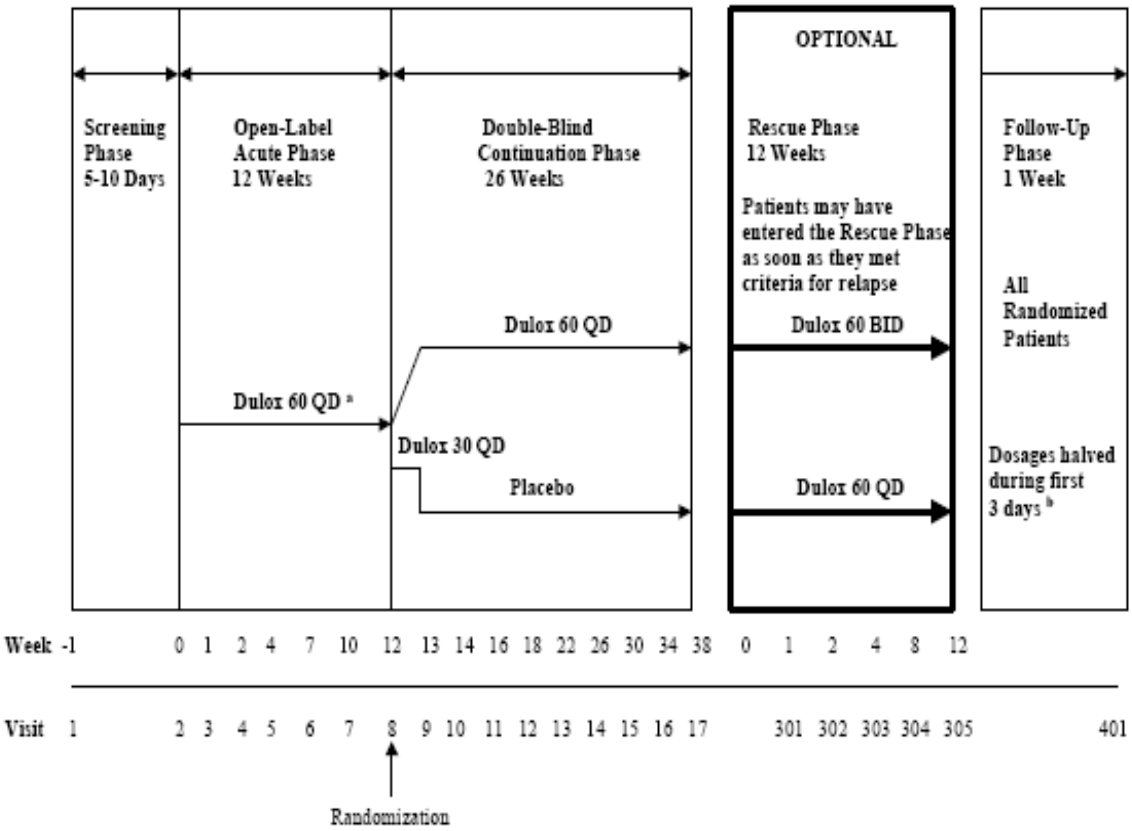
- To evaluate whether reintroduction of duloxetine 60 mg QD during the rescue phase restores response among placebo-treated patients who relapsed.

- To assess the efficacy and safety of duloxetine during the 12-week, open-label, acute therapy phase, using the above measures.

3.1.1.2 Study Design

This was a randomized, double blind, placebo-controlled, parallel group study of 278 randomized patients who had previously met the Diagnostic and Statistical Manual of Mental Disorder Fourth Edition (DSM-IV) diagnostic criteria for major depressive disorder (MDD), without psychotic features prior to entering the acute therapy phase, and responded to duloxetine 60 mg once daily (QD) at the end of the 12-week, open-label acute phase. The study consisted of the following phases: Screening Phase, Acute Therapy Phase, Continuation Therapy Phase, Rescue Therapy Phase (Optional) and Follow-Up Phase. The duration of the acute therapy phase was 12 weeks and of the continuation therapy phase was 26 weeks. Figure 1 illustrates the study design.

Figure 1 Illustration of Study Design for Study F1J-MC-HMBC



[a] Patients who had difficulty tolerating duloxetine 60 mg QD (two capsules) had, at the investigator's discretion, the number of capsules reduced to 30 mg QD (one capsule) at any time up to Visit 5. The dose was returned to 60 mg QD no later than Visit 5 or the patient was discontinued.
[b] The specific dosage reductions were shown in the study protocol.
Source: Sponsor's Figure HMBC.9.1.

3.1.1.3 Efficacy Variables and Analyses

Efficacy Variables

The primary efficacy variable was time to relapse during the continuation phase. The 'Response' for determining eligibility for randomization in the continuation therapy phase was defined as, at Visit 7 and Visit 8:

- No longer meeting the diagnostic criteria for DSM-IV-defined MDD, and
- $HAMD_{17} \leq 9$, and
- CGI-Severity ≤ 2.

The 'Relapse' during the continuation therapy phase was defined as:

- An increase in the CGI-Severity score of at least two points relative to the rating at Visit 8 for two consecutive visits; and
- Meeting the criteria for major depressive episode for two consecutive visits, as determined by the depression module of the MINI. However, the temporal criterion (2 weeks) had to be met at only the second visit.

The 'Relapse associated with reemergence' was defined as:

- Six visits of any kind (weekly or regularly scheduled, consecutive or nonconsecutive) during the continuation phase with a HAMD score ≥ 12.

Efficacy Analyses

The primary efficacy analysis compared the time to relapse during the continuation phase between treatment groups using the log rank test. The log rank test measured the discrepancy accumulated across the entire duration of continuation treatment. For this analysis, relapses associated with reemergence were also included as relapse events. Survival curves were constructed using the Kaplan-Meier method. Time to relapse was the time from Visit 8 to the first visit during the continuation therapy phase at which the patient satisfied the relapse criteria. For patients who did not relapse during the continuation phase, the time to censoring was the time from Visit 8 to the patient's endpoint visit during the continuation therapy phase.

The sponsor stated in the clinical study report that for labeling purposes, (b) (4)

Reviewer's Note: (b) (4) Therefore, only the primary efficacy analysis for the primary endpoint would be evaluated and reported in this review.

3.1.2 Efficacy Results of Study F1J-MC-HMBC

3.1.2.1 Disposition of Patients and Baseline Characteristics

Disposition of Patients

Table 1 shows a summary of patient disposition during the screening and acute therapy phases of the study. A total of 681 patients entered the screening phase. Of

these 681 patients, 148 failed to met entry criteria or declined to participate in the study. The remaining 533 patients were enrolled into the acute therapy phase and received duloxetine 60 mg once daily (QD) at Visit 2.

Table 1. Patient Disposition During Acute Therapy Phase for Study F1J-MC-HMBC

Patient Population	Total Number of Patients
Screened	681
Enrolled (Duloxetine 60 mg QD)	533
Completed (and Randomized)	278
Discontinued	255
Adverse event	60
Death	1
Lost to Follow-up	43
Protocol Violation	27
Protocol Randomization Criteria not met	52
Patient Decision	62
Lack of Efficacy	10

Source: Sponsor's Figure HMBC.10.1 of CSR.

Table 2 shows a summary of patient disposition during the continuation therapy phase of the study. A total of 278 patients continued in the study at the end of the acute therapy phase and were randomized to receive either duloxetine 60 mg AD or placebo at Visit 8.

Table 2. Patient Disposition during Continuation Therapy Phase for Study F1J-MC- HMBC

Patient Population	Duloxetine 60 mg QD	Placebo
Randomized	136	142
Completed	74	47
Entered Rescue Phase	29	58
Discontinued	33	37
Adverse Event	5	5
Lost to Follow-Up	6	7
Lack of Efficacy	1	3
Patient Decision	11	15
Protocol Violation	10	7

Source: Sponsor's Figure HMCB.10.2 of CSR.

Baseline Demographic Characteristics

Table 3 summarizes patient characteristics at baseline during the acute phase. As shown in the table, patients had a mean age of 43.39 years, with the majority being Caucasian and female.

Table 3. Patient Characteristics at Baseline during Acute Therapy Phase for Study F1J-MC-HMBC

Variable	DLX60QD (N=533)
Origin: No. (%)	
African Descent	34 (6.4)
Western Asian	1 (0.2)
Caucasian	479 (89.9)
East/Southeast A	2 (0.4)
Hispanic	14 (2.6)
Other	3 (0.6)
Gender: No. (%)	
Female	383 (71.9)
Male	150 (28.1)
Age: yrs	
Mean (SD)	43.39 (12.72)
Height: cm (Visit 2)	
Mean (SD)	167.60 (9.72)
Weight: kg (Visit 2)	
Mean (SD)	82.13 (22.32)

Source: Sponsor's Table HMBC.11A.1 of CSR.

Table 4 summarizes patient characteristics at baseline during the continuation therapy phase. As shown in the table, a statistically significant difference between treatment groups was observed for height, and no statistically significant differences in age, gender, origin or weight were observed. Patients had a mean age of 45.22 years.

Table 4. Patient Characteristics at Baseline during Continuation Therapy Phase for Study F1J-MC-HMBC

Variable	Placebo (N=142)	DLX60QD (N=136)	Total (N=278)	P-Value*
Origin: No. (%)				
African Descent	8 (5.6)	5 (3.7)	13 (4.7)	0.565
Caucasian	132 (93.0)	128 (94.1)	260 (93.5)	
East/Southeast A	0	1 (0.7)	1 (0.4)	
Hispanic	1 (0.7)	2 (1.5)	3 (1.1)	
Other	1 (0.7)	0	1 (0.4)	
Gender: No. (%)				
Female	110 (77.5)	92 (67.6)	202 (72.7)	0.066
Male	32 (22.5)	44 (32.4)	76 (27.3)	
Age: yrs				
Mean (SD)	44.76 (11.85)	45.71 (12.69)	45.22 (12.26)	0.47
Height: cm (Visit 8)				
Mean (SD)	165.80 (9.87)	168.51 (10.01)	167.13 (10.01)	0.017
Weight: kg (Visit 8)				
Mean (SD)	80.87 (22.18)	83.34 (22.13)	82.07 (22.15)	0.427

* Frequencies are analyzed using a Chi-Square test. Source: Sponsor's Table HMBC.11B.1 of CSR.

Baseline Psychiatric Evaluation

Table 5 summarizes baseline mean scores for $HAMD_{17}$ total score, CGI-Severity, PGI-Improvement, and VAS overall pain. As shown in the table, mean baseline scores were similar across all treatment groups for each of the baseline measurements.

Table 5. Baseline Psychiatric Evaluation during Continuation Therapy Phase (Visit 8) for Study F1J-MC-HMBC

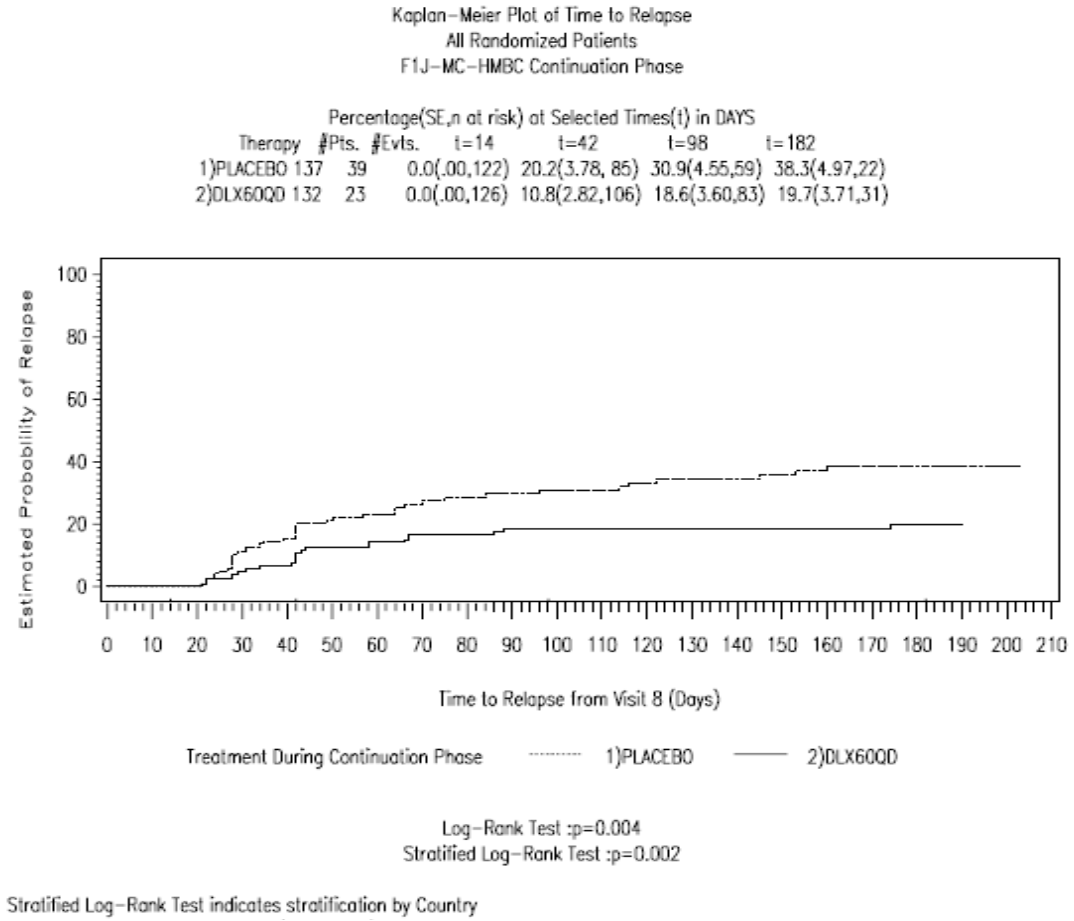
Variable	Placebo	DLX60QD	Total	P-Value*
$HAMD_{17}$ Total Mean (SD)	4.60 (2.44)	4.86 (2.44)	4.73 (2.44)	0.370
CGI-Severity Mean (SD)	1.37 (0.48)	1.36 (0.48)	1.36 (0.48)	0.677
PGI Improvement Mean (SD)	1.81 (0.70)	1.90 (0.74)	1.86 (0.72)	0.404
VAS-Overall Mean (SD)	16.69 (22.51)	16.18 (19.46)	16.44 (21.04)	0.775

* Means are analyzed using a Type III Sum of Squares analysis of variance
Source: Sponsor's Table HMBC.11B.4 of CSR.

3.1.2.2 Sponsor's Efficacy Analysis Results

The following figure 2 shows the Kaplan-Meier estimate of time to relapse and the p-values from the log-rank test by the sponsor.

Figure 2. Sponsor's Results of Kaplan-Meier Estimate of Time to Relapse for All Randomized Patients in Continuation Therapy Phase for Study F1J-MC-HMBC



Source: Figure HMBC.11B.1 of Clinical Study Report

According to the results, 23 out of 132 patients (17.4%) who were randomized to duloxetine 60 mg QD and 39 out of 137 patients (28.5%) who were randomized to placebo relapsed during the continuation therapy phase. Both the unstratified and country-stratified analyses (p=0.004 and p=0.002, respectively) demonstrated that the differences between duloxetine 60 mg QD and placebo were statistically significant. Patients in duloxetine 60 mg QD groups had longer time to relapse than patients in placebo.

Reviewer's Note: This reviewer found that the above primary analysis results were based on a total of 269 patients but the study actually randomized 278 patients to the continuation phase of this study. The sponsor clarified that there were 9 patients who were randomized at the beginning of the continuation phase (Visit 8) but who discontinued at Visit 9. Since these patients did not have any CGI-Severity information after randomization, the relapse status could not be determined and these patients were not included in any analyses of time to relapse. To follow the ITT principle, this reviewer performed the analysis by treating these 9 patients as censored observations and also a sensitivity analysis by treating these 9 patients as relapsed. It was found that both analysis results were similar comparing to the sponsor's analysis results by removing these 9 patients.

3.1.2.3 Statistical Reviewer's Comments

1. This reviewer confirmed the sponsor's analysis results for the primary endpoint. Based on the results for all patients (total 269), patients on duloxetine 60 mg QD showed statistically significantly longer time to relapse than patients on placebo.

2. The length of a drug's long term maintenance effect in a randomized withdrawal trial is generally determined by patients' stabilization period before they are randomized into the continuation therapy phase. In this study, although the design of the study included a 12 weeks of open label acute therapy phase before randomization, no clear definition of stabilization period was prospectively defined. One RESPONSE criteria defined in the protocol for determining patients' eligibility for randomization in the continuation therapy phase was "at Visit 7 and Visit 8, patients who had (1) No longer meeting the diagnostic criteria for DSM-IV-defined MDD, (2) $HAMD_{17} \leq 9$ and (3) CGI-Severity ≤ 2. It seems that patients were only required to have two weeks of stabilization before randomization. (b) (4)

During the review of this NDA, we asked the sponsor to clarify the definition of patients' stabilization period. The sponsor responded to us that they were uncertain to what is meant by the term 'stabilization' as it was not defined or used in the original submission. They further stated that although there were two response criteria used in the acute phase, they were used for very different purposes.

After discussing with the medical reviewer, Dr. Roberta Glass and her team leader, Dr. Ni Khin, we asked the sponsor to provide more information regarding patients' duration of continuous response and also compute the average of time that patients have response (defined by ≥50% decrease from baseline in the $HAMD_{17}$ before 2 weeks prior to randomization). This average was found to be 5.55 weeks. So, on average patients had continuous response for 7.55 weeks before randomization. This reviewer confirmed the sponsor's provided information and calculations. However, whether this average is acceptable to be claimed in the labeling as the length of maintenance effect of the drug needs to be carefully considered. It is not clear whether the positive study results based on all patients still support this type of interpretation.

(b) (4)

(b) (4)

To help the medical division to make decision regarding the length of maintenance effect for duloxetine 60 mg QD, this reviewer calculated the standard deviation (SD) , summarized patients' period of stabilization (Table 6a) and also performed the subgroup analysis by patients' duration of response based on ≥50% reduction in HAMD17 total scores (Table 6b). The SD was found to be 2.87 weeks.

Based on Table 6a, only 24% and 14% of patients were stabilized for 10 and 11 weeks, respectively. So, only 38% (=24%+14%) of patients were stabilized for at least 10 weeks. (b) (4) Note that this study was only designed to observe patients' response at certain weeks (Weeks 1, 2, 4, 7, 10 and 12) during the open-label acute phase. Whether patients were observed frequently to be determined to have continuous response may be another concern.

Table 6a: Reviewer's Summary of Patients' Stabilization Period

Stabilization Period (Weeks)	2	5	8	10	11
Number of Patients (Percentage)	32 (12%)	62 (22%)	77 (28%)	67 (24%)	40 (14%)

Table 6b:

Duration of Response	≥5	≥8	≥10	≥11
Relapse rate Duloxetine placebo	 0.16(=19/116) 0.26(=32/122)	 0.17(=14/84) 0.25(=24/94)	 0.1=(5/50) 0.3(=16/53)	 0.11(=2/18) 0.33(=7/21)
p-value	0.0054	0.0163	0.0032	0.0852

3.2 EVALUATION OF SAFETY

The evaluation of safety was not performed in this review. Please see the clinical review for this evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

For the primary efficacy variable, time to relapse during the continuation phase, the sponsor performed the subgroup analysis for the following factors: age, gender, race, baseline $HAMD_{17}$ total scores, HAMD anxiety, HAMD insomnia, number of previous episodes of depression, and number of previous drugs received for depression. In addition to the log-rank test for testing the treatments' differences in each subgroup, the sponsor also conducted a proportional hazards regression with treatment, subgroup and treatment-by-subgroup interaction effects in the model. The Wald chi-square test p-value of the interaction was reported. This reviewer confirmed the sponsor's analysis results.

4.1 GENDER, RACE AND AGE

Table 7 shows the sponsor's subgroup analysis results for gender, race and age. Based on the results, no statistically significant treatment-by-subgroup interactions were observed. The sponsor then concluded that the efficacy of duloxetine 60 mg QD in

increasing time to relapse was not inconsistent between younger and older patient subsets, between male and female patient subsets, and between patients of Caucasian and other racial subset.

Table 7 Sponsor's Subgroup Analysis for Gender, Race and Age for Study F1J-MC-HMBC

Sub-group	Therapy by Subgroup p-value*	Subgroup p-value*	strata	N	Placebo n (%)	DLX60QD n (%)	p-value**
Age	.630	.896	<55	211	31 (28.4)	19 (18.6)	0.019
			>=55	58	8 (28.6)	4 (13.3)	0.071
Gender	.844	.321	Male	72	6 (20)	6 (14.3)	0.315
			Female	197	33 (30.8)	17 (18.9)	0.011
Race	.862	.648	Caucasian	252	37 (28.9)	22 (17.7)	0.004
			Other	17	2 (22.2)	1 (12.5)	0.651

*P-values are from the proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as covariates. **P-values are from log-rank test.
Source: Table HMBC.11B.14 of Clinical Study Report

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

Table 8 shows the sponsor's subgroup analysis results for baseline $HAMD_{17}$ total scores (by two different cut-offs), baseline HAMD anxiety, baseline HAMD insomnia, the number of previous episodes and whether patients used any drug for depression previously. Based on the analysis results, no statistically significant treatment-by-subgroup interactions were observed. So, the sponsor concluded that the presence of anxiety or insomnia did not statistically significantly affect the analysis of time to relapse, and also that there was no evidence showing that the efficacy of duloxetine 60 mg QD in increasing time to relapse was inconsistent between different baseline severity groups of patients, between patients with an incidence of previous depressed episodes greater than or equal to the median and patients with an incidence of previous depressed episodes less than median, and between patients who have not received previous drugs for depression and patients who have received ≥ 1 previous drugs for depression.

Table 8 Sponsor's Subgroup Analysis by Baseline $HAMD_{17}$ total score, Baseline HAMD Anxiety, Baseline HAMD Insomnia, Number of Previous Episodes and Whether Patients Used Any Drug for depression Previously for Study F1J-MC-HMBC

Subgroup	Therapy by Subgroup p-value*	Subgroup p-value*	strata	N	Placebo n (%)	DLX60QD n (%)	p-value**
Baseline $HAMD_{17}$	0.986	0.810	<19	16	3 (33.3)	0 (0)	0.072
			≥19	253	36 (28.1)	23 (18.4)	0.011
Baseline $HAMD_{17}$	0.915	0.828	<25	168	23 (28.8)	15 (17.0)	0.025
			≥25	101	16 (28.1)	8 (18.2)	0.075
Baseline HAMD Anxiety	0.961	0.527	Yes	195	33 (30.3)	16 (18.6)	0.017
			No	74	6 (21.4)	7 (15.2)	0.250
Baseline HAMD Insomnia	0.210	0.035	Yes	154	15 (19.2)	13 (17.1)	0.277
			No	115	24 (40.7)	10 (17.9)	0.004
Previous Episodes	0.195	0.081	<Median	122	15 (23.8)	4 (6.8)	0.005
			≥Median	147	24 (32.4)	19 (26)	0.063
Previous Drug for Depression	0.107	0.142	=0	68	7 (21.2)	7 (20.0)	0.976
			≥1	201	32 (30.8)	16 (16.5)	<0.001

*P-values are from the proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as covariates. **P-values are from log-rank test.
Source: Table HMBC.11B.14 of Clinical Study Report

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The data of Study F1J-MC-HMBC supported the maintenance of effect of duloxetine 60 mg QD in treating patients with major depressive disorder. However, the length of maintenance effect of duloxetine 60 mg QD that the data actually supported is not clear. The length of maintenance effect of a drug is generally claimed based on the fixed period of patients who were stabilized in the study before they are randomized into the continuation therapy phase. According to the protocol of this study, patients only need to meet the response criterion at two weeks prior to randomization. Since patients could have been stabilized much earlier and longer than two weeks prior to randomization, we asked the sponsor to provide further information regarding patients' lengths of stabilization period. The average period of all randomized patients' continuous response to duloxetine 60 mg QD by 50% reduction of $HAMD_{17}$ total score

prior to two weeks before randomization appears to be 5.55 weeks long. So, patients seemed to be stabilized for 7.55 weeks on average before randomization. (b) (4)

5.2 CONCLUSIONS AND RECOMMENDATIONS

Study F1J-MC-HMBC is a positive study. Based on the study design, it demonstrated only two weeks of maintenance effect for duloxetine 60 mg QD in treating patients with major depressive depression. Nevertheless, most patients appeared to be stabilized longer than two weeks before randomization according to the other response criterion by 50% reduction of $HAMD_{17}$ total score. This length of period that patients responded continuously to the drug before randomization was on average 7.55 weeks (b) (4)

Yeh-Fong Chen, Ph.D.
Mathematical Statistician

cc: NDA 21-427
HFD-130/Dr. Laughren
HFD-130/Dr. Khin
HFD-130/Dr. Glass
HFD-130/Mr. Bender
HFD-700/Dr. Nevius
HFD-700/Ms. Patrician
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/Dr. Yang

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/s/

Yeh-Fong Chen
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7/5/2007 09:18:09 AM
BIOMETRICS

James Hung
7/5/2007 09:44:27 AM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-427/S-015, S-017

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-427 SUPPL # 015 HFD # 130

Trade Name Cymbalta

Generic Name Duloxetine Hydrochloride

Applicant Name Eli Lilly

Approval Date, If Known November 28, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

three years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21427 Cymbalta (duloxetine hydrochloride) for Major Depressive Disorder, Generalized Anxiety Disorder, and Diabetic

Peripheral Neuropathic Pain

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

F1J-MC-HMBC

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

21-427

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

F1J-MC-HMBC

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ! !

IND # YES ☐ ! NO ☐
! Explain:
Was not carried out under an IND.

Investigation #2 ! !

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 ! !

YES ☐ ! NO ☐

Explain:	! Explain: Not Applicable.
Investigation #2	! !
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: CDR William H. Bender
Title: Senior Regulatory Project Manager
Date: 11/30/2007

Name of Office/Division Director signing form: ODE1/DPP/Thomas Laughren, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Thomas Laughren
11/30/2007 12:40:53 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # :_____21-427_____ Supplement Type (e.g. SE5): _SE1_____ Supplement Number: _____015____

Stamp Date:____October 1, 2007_____ PDUFA Goal Date: _____December 1, 2007_____

HFD-130____ Trade and generic names/dosage form:_____Cymbalta (duloxetine hydrochloride) 20mg, 30m g, and 60mg capsules_____

Applicant: ____Eli Lilly_____ Therapeutic Class: _____Maintenance treatment in Major Depressive Disorder_____

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

XYes. Please proceed to the next question.

- ❑ **No. PREA does not apply. Skip to signature block.**

**** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.***

Indication(s) *previously approved* (please complete this section for supplements only):_____Major Depressive Disorder, Diabetic Neuropathy, and Generalized Anxiety Disorder_____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s):___one____

Indication #1: _____Maintenance Treatment of Major Depressive Disorder_____

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**

XNo. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

XYes: Please proceed to Section A.

No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**

XOther:_____The sponsor is currently studying this drug in acute pediatric studies and this is considered sufficient. Therefore, the Sponsor is not required to perform maintenance studies in the pediatric population since it is often difficult to perform long-term studies within this age group.

._____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
_____*William H. Bender*_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- ❑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

William Bender
11/28/2007 12:22:46 PM

David, Paul A

From: David, Paul A
Sent: Tuesday, November 20, 2007 10:58 AM
To: 'Bryan E Boggs'
Cc: Bender, William
Subject: Cymbalta NDA 21-427/S-015

Good Morning Bryan,
Bill is out of the office this morning. Therefore, I'm covering his Cymbalta - MDD maintenance project which has a due date of 12-1-07.

The Agency has the following questions, below, in regards to sexual dysfunction.

Regarding Sexual dysfunction, we ask that you respond to the following issue on why the gender reversals for the Delgado paper that Lilly provided and labeling:
1) The data in the Delgado paper seems to provide support for the language in labeling, but there are some discrepancies. The paper shows that overall, both drugs are worse than placebo, but paroxetine is also clearly worse than duloxetine (Fig 1). Broken down by gender (Fig 2), these differences persist for females, but not for males (for males, the only statistical finding is paroxetine worse than pbo).
2) Labeling gives the overall results ok for duloxetine, but then gives different results by gender. Why?

Given the UF due date of a week from this Friday, we would appreciate a response to these questions by close of business today if at all possible.

If you have any questions, feel free to contact me.
Regards,
Paul

CAPT Paul A. David, R.Ph.
Chief, Project Management Staff
Division of Psychiatry Products/HFD-130
Food and Drug Administration

10903 New Hampshire Avenue, Building 22, Room 4100
Silver Spring, Maryland 20993-0002

Phone: 301-796-1058
Fax: 301-796-9838
paul.david@fda.hhs.gov

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/s/

Paul David
11/20/2007 11:01:14 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **HFD- 860/Biopharm / Ray Baweja for Ron Kavanagh**

FROM: **HFD-130 (Division of Psychiatry Products); Bill Bender**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/05/07		21-427 s-015	**Complete Response to our 8/28/07 AE letter**	**09/28/07**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cymbalta (Duloxetine)		Maintenance tx of depression	Complete response and initial label review meeting on 10/18/07 and a final label meeting on 11/15/07

NAME OF FIRM: **Lilly**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW

OTHER *(SPECIFY BELOW)*:

PRE IND teleconference

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

COMMENTS/SPECIAL INSTRUCTIONS:

The sponsor's complete response can be found at the following link: :
\\CDSESUB1\NONECTD\N21427\S_015\2007-09-28
Our 8/28/07 AE letter is attached to this consult.

Thank you,
Bill

SIGNATURE OF REQUESTER

Bill Bender
Regulatory Project Manager
301-796-2145
William.bender@fda.hhs.gov

METHOD OF DELIVERY (Check one)

☐ MAIL **X** HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Monday, June 18, 2007 9:02 AM
To: 'bboggs@lilly.com'
Cc: Bender, William
Subject: NDA 21-427/ 015 stat request

Dear Bryan,

For Study F1J-MC-HMBC, you described findings for the subset of patients who had continuously responded for the 10 weeks before randomization. However, this analysis results do not seem to be included in the clinical study report. Please locate the results if they are in your NDA submission. Otherwise, please provide the results as soon as possible.

Thanks,
Rimmy

Renmeet Grewal, Pharm.D., LCDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

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/s/

Renmeet Grewal
6/18/2007 09:07:40 AM
CSO

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Wednesday, June 13, 2007 2:39 PM
To: 'bboggs@lilly.com'
Cc: Bender, William
Subject: NDA 21-427 S015

Good Afternoon Brian,
I am covering for Bill this week, and the statistics reviewer has the following request:

For Study F1J-MC-HMBC, you stated in the clinical study report that there were 278 patients randomized to the continuation phase. However, your analysis results for the primary endpoint were obtained only based on total 269 patients (Figure HMBC.11B.1). Where are those 9 randomized patients? It was found that some patients based on your analysis data sets (HMBCWKLY and HMBCDRUG) had values recorded for the variable DOTC but not for the variable RELCRIT. Please clarify the discrepancy and provide the status of relapse for those 9 randomized patients. If there is a mistake in your date set, please provide the correct one.

Thanks,
Rimmy

Renmeet Grewal, Pharm.D., LCDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

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/s/

Renmeet Grewal
6/13/2007 04:06:26 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **HFD- 860/Biopharm / Ray Baweja**

FROM: **HFD-130 (Division of Psychiatry Products); Bill Bender**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 9, 2007		21-427	**Labeling meeting for the maintenance tx of depression**	**June 9, 2007**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cymbalta (duloxetine)		MDD	**Meeting is on 8-7-07.**

NAME OF FIRM: **Lilly**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW

OTHER *(SPECIFY BELOW)*:

PRE IND teleconference

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This meeting is scheduled to discuss Lilly's labeling for their s-NDA (015), maintenance treatment of depression. Attached to this consult is the most recently approved labeling for Cymbalta and their proposed labeling.

Thank you,
Bill

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Bill Bender **Regulatory Project Manager** **301-796-2145** **William.bender@fda.hhs.gov**	☐ MAIL **X** HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Bender, William

From: Bender, William
Sent: Thursday, May 31, 2007 9:48 AM
To: 'Bryan E Boggs'
Subject: NDA 21-427 Cymbalta S-015 maintenance of effect

Good Morning Bryan,

Regarding your subgroup analysis results for Study HMBC, we can not find any variable in any data sets to identify the patient's status of having previous drug for depression. Could you please tell us where this variable is located if it has been included in the submitted data sets? Otherwise, could you please send it in with the variable of patient ID in the same file as soon as possible.

Thank you,
William H. Bender
LCDR, USPHS
Regulatory Health Project Manager, FDA/CDER/DPP
Phone: 301-796-2145
william.bender@fda.hhs.gov

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/s/

William Bender
6/1/2007 08:21:47 AM
CSO

Bender, William

From: Bender, William
Sent: Thursday, March 15, 2007 8:18 AM
To: 'Bryan E Boggs'; 'Ann Robbins Sakai'
Subject: NDA 21-427 maintenance of effect

Good Morning Bryan,

Please provide a new proposed labeling in PLR (physician labeling rule) format (both clean and marked-up, word version) which incorporates the following proposed changes:

- S-015 (maintenance treatment of MDD)

(b) (4)

Additionally, please use the last approved labeling (Agency approval letter dated 2/23/07) as the base document. For the marked-up version, different highlight colors may be used for (b) (4) S-015.

Additionally, our Study Endpoints and Label Development (SEALD) Team have created (attached) a list of the most frequently encountered PLR format/content deficiencies. We are asking you to verify that none of these deficiencies are in your PLR labeling. If you find, at the conclusion of your PLR review, that there are deficiencies in your submitted PLR labeling, please amend your application to correct these deficiencies. Please note that this is not an exhaustive list and you are also encouraged to review our PLR guidance documents located at the following internet address: http://www.fda.gov/cder/regulatory/physLabel/default.htm

We request that you complete this review and respond to this e-mail within 30 days.

Thank you,

William H. Bender
LCDR, USPHS
Regulatory Health Project Manager, FDA/CDER/DPP
Phone: 301-796-2145
william.bender@fda.hhs.gov

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/s/

William Bender
3/15/2007 10:10:04 AM
CSO

Bender, William

From: Bender, William
Sent: Thursday, February 08, 2007 3:46 PM
To: 'Bryan E Boggs'
Subject: FW: N21427 SE1- 015

Hi Bryan,
Regarding this efficacy supplement for treatment of Maintence MDD, please provide either an environmental assessment document or a waiver based on revised calculations.

Thanks,
William H. Bender
LCDR, USPHS
Regulatory Health Project Manager, FDA/CDER/DPP
Phone: 301-796-2145
william.bender@fda.hhs.gov

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/s/

William Bender
2/9/2007 09:54:16 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OPS, Staff (HFD-354)
Attn: Bai Nguyen (301-796-1531)
WO21 RM3523

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Teshara G. Bouie, ONDQA, Division of Post-Marketing Assessment, 301-796-1649

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2/5/2007		21-427	SE8-015	December 18, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cymbalta			May 23, 2007

NAME OF FIRM: Lilly

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This efficacy supplement is located in the EDR. Please evaluate the environmental assessment. This supplement is due September 1, 2007.

SIGNATURE OF REQUESTOR
Teshara G. Bouie

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Teshara Bouie
2/5/2007 03:29:44 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-427

Eli Lilly Company
Attention: Bryan Boggs, Manager
U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285-2643

Dear Dr. Boggs:

Please refer to your 10-31-06 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cymbalta (Duloxetine Hydrochloride) delayed-release capsules 20mg, 30mg, and 60mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on December 29, 2006 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Bill Bender, Regulatory Project Manager, at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
1/9/2007 02:51:03 PM

Bender, William

From: Bryan E Boggs [BOGGS_BRYAN_E@LILLY.COM]
Sent: Tuesday, January 02, 2007 8:05 AM
To: Bender, William
Subject: RE: NDA 21-427 MOE indication
Attachments: emfalert.txt

Bill,

I wish you a Happy New Year. I have some numbers you had asked for prior to the holidays. Lilly was closed between Christmas and the New Year, so I did not this breakdown for you until today.

Investigator site 603, with satelite site 903.

main site 603: 36 enrolled (25 screen failed)/randomized 11 (7 d/c'd)/4 completed
satelite site 903: 8 enrolled (3 screen failed)/randomized 5 (0 d/c'd)/ 5 completed

investigator 603 total: 44 enrolled (28 screen failed)/randomized 16 (7 d/c'd)/ 9 completed

Kind regards,
Bryan

Bryan E Boggs/AM/LLY

12/22/2006 12:56 AM

To william.bender2@fda.hhs.gov
cc
Subject RE: NDA 21-427 MOE indication Link

Hi Bill,

As an update. I have a correction to the post-hoc analysis patient numbers (the question I anticipated you would ask). Site 304 had 17 patients and site 603 had 6 patients included in this analysis.

I am told that I'll get the breakdown by location for patients enrolled at investigator site 603 for HMBC by tomorrow morning.

Kind regards,
Bryan

Bryan E Boggs/AM/LLY

To "Bender, William" <William.Bender2@fda.hhs.gov>
cc

12/19/2006 04:27 PM

Subject RE: NDA 21-427 MOE indication Link

Bill,

I do not have the split for site 603. Patient numbers are assigned by investigator, so I'll have to get back to you on this. I will need to get a study research associate involved to look that up.

Regarding overall enrollment, site 304 had 30 patients assigned to treatment and 603 had 32 patients assigned to treatment (page 2176 of study report).

I'll anticipate your next question will be how many of these subjects were included into the ad-hoc efficacy analyses. I know that investigator 304 had 13 patients included in this analysis, but I do not know how many 603 had. I am still looking into that, and will hopefully have this tomorrow.

Kind regards,
Bryan

"Bender, William" <William.Bender2@fda.hhs.gov>

12/19/2006 03:12 PM

To Bryan E Boggs <BOGGS_BRYAN_E@LILLY.COM>

cc

Subject RE: NDA 21-427 MOE indication

Hi Bryan,

How many subjects were enrolled at each location for site 603?

How many subjects were enrolled for site 304?

Thanks,
Bill

From: Bryan E Boggs [mailto:BOGGS_BRYAN_E@LILLY.COM]
Sent: Tuesday, December 19, 2006 2:39 PM
To: Bender, William
Subject: Re: NDA 21-427 MOE indication

Hello Bill,

An update to your investigator question:

Site 603 (Dr. Louise Beckett) had a satelite site. Both sites for this investigator are listed here:

IPS Research Company
1111 North Lee, Suite 407
Oklahoma City, OK 73103

IPS Research Company - Satelite Site 903
708 24th Avenue Northwest
Norman, OK 73069

Regards,
Bryan

Bryan E Boggs/AM/LLY

12/19/2006 12:35 PM

To "Bender, William" <William.Bender2@fda.hhs.gov>
cc
Subject Re: NDA 21-427 MOE indication Link

Hello Bill,

Investigator 304 is Odile Bourgeois-Adragna, MD:

Cabinet Du Dr. O. Bourgeois-Adragna
44 Avenue De Gameville
Saint Orens 31650
France

Investigator 603 is Dr. Louise Beckett, MD,

Louise Beckett, MD
IPS Research Company
Suite 400
1111 North Lee
Oklahoma City, OK 73103

It appears that our investigator listing page in the CSR (page 2141) stops after the 500 series. We do in fact have 10 investigators in the 600 series (600-609) and 7 investigators in the 700 series (700-706) not included within the CSR. Attached is the complete investigator listing for study HMBC.

[attachment "Draft Investigator Listings HMBC.doc" deleted by Bryan E Boggs/AM/LLY]

Kind regards,
Bryan

"Bender, William" <William.Bender2@fda.hhs.gov>

12/19/2006 10:43 AM

To Bryan E Boggs <BOGGS_BRYAN_E@LILLY.COM>
cc
Subject NDA 21-427 MOE indication

Good Morning Bryan,

Could you please let me know who the investigators and site locations are for the following study sites 304 and 603.

Thanks,
Bill

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

/s/

Thomas Laughren
1/4/2007 09:43:23 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-427/S-015 **PRIOR APPROVAL SUPPLEMENT**

Eli Lilly Company
Attention: Bryan Boggs, Pharm.D.
Manager, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Boggs:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Cymbalta (duloxetine hydrochloride) Capsules, 20mg, 30mg, and 60mg

NDA Number: 21-427

Supplement number: 015

Review Priority Classification: Standard (S)

Date of supplement: October 31, 2006

Date of receipt: November 1, 2006

This "Prior Approval" supplemental application proposes the use of Cymbalta for maintenance of effect in the treatment of Major Depressive Disorder (MDD).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 29, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 1, 2007.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call me at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

Bill Bender, R.Ph.
Senior Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

William Bender
12/20/2006 02:36:56 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
HFD- 710/Stat	HFD-130/ Division of Psychiatry Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/08/2006		21,427	SNDA for maintenance tx of depression	10/31/2006

Cymbalta	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
			12/19/06 45 day filing meeting

NAME OF FIRM: LILLY

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Attached is the electronic submission from Lilly regarding the maintenance treatment of major depression.

\\CDSESUB1\N21427\S_015\2006-10-31

Thank you.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Bill Bender, R.Ph. Regulatory Project Manager 301-796-2145 william.bender@fda.hhs.gov	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

William Bender
11/13/2006 09:21:51 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-427 Supplement # 015 Efficacy Supplement Type SE-

Proprietary Name: Cymbalta
Established Name: Duloxetine
Strengths: 20mg, 30mg, and 60mg

Applicant: Eli Lilly
Agent for Applicant (if applicable): Bryan Boggs

Date of Application: October 31, 2006
Date of Receipt: November 1, 2006
Date clock started after UN:
Date of Filing Meeting: December 19, 2006
Filing Date: January 12, 2007
Action Goal Date (optional): User Fee Goal Date: September 1, 2007

Indication(s) requested: Maintenance of efficacy in the treatment of Major Depressive Disorder.

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) X (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S X P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO ☐

User Fee Status: Paid X Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☐
  If yes, explain: N/A

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO X
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES X NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES X NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES X NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic Combined paper + eNDA ☐
   This application is in: NDA format CTD format ☐
   Combined NDA and CTD formats X

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES X NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments: N/A

3. This application is an eCTD NDA. YES ☐
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments: N/A

- Patent information submitted on form FDA 3542a? YES X NO ☐

- Exclusivity requested? YES, _____ Years NO X
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES X NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES X NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO X

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ N/A ☐

- PDUFA and Action Goal dates correct in tracking system? YES X NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: N/A

- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) October 5, 2005 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO X
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES X NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO X

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO X

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A X YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A X YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO X

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ N/A ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ N/A ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☐ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ N/A ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 19, 2006

NDA #: 21-427

DRUG NAMES: Cymbalta (duloxetine capsules)

APPLICANT: Eli Lilly and Company

BACKGROUND: Lilly is submitting this supplement (015) for the maintenance of effect in patients with major depressive disorder (MDD). Lilly has submitted one positive Phase 3, placebo-controlled study in patients with MDD (study F1J-MC-HMBC). In addition, this submission includes extensive safety information on duloxetine form other approved indications.

ATTENDEES: Thomas Laughren, M.D., Division Director
Mitchell Mathis, M.D., Deputy Division Director
Ni Khin, M.D., Clinical Team Leader
Peiling Yang, Ph.D., Statistician Team Leader
Roberta Glass, M.D., Medical Reviewer
Janice Brown, Ph.D., Chemistry Reviewer
Yeh-Fong Chen, Ph.D., Statistician Reviewer
Antoine El Hage, Pharmacologist, Site Reviewer
Bill Bender, R.Ph., Senior Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Robert Glass
Secondary Medical:	
Statistical:	Yeh-Fong Chen
Pharmacology:	
Statistical Pharmacology:	
Chemistry:	Janice Brown
Environmental Assessment (if needed):	
Biopharmaceutical:	
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Antoine El Hage
OPS:	
Regulatory Project Management:	Bill Bender
Other Consults:	

Per reviewers, are all parts in English or English translation? YES X NO ☐
If no, explain:

CLINICAL FILE X REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES X NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO X

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A X YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A X FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE X REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☐ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO X
  YES

PHARMACOLOGY/TOX N/A X FILE ☐ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO X

CHEMISTRY FILE X REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☐ NO X
  If yes, was microbiology consulted for validation of sterilization?
  YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

X No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Bill Bender
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☐

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(*b*) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)?
YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply <u>and</u> identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

  YES ☐ NO ☐

  *If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
  Was this listed drug product(s) referenced by the applicant? (see question # 2)

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

  N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

William Bender
1/10/2007 11:57:40 AM
CSO