CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-427

Medical Review #3

CLINICAL REVIEW

NDA 21-427 Cymbalta (duloxetine)

Application Information

NDA #:	21-427
Sponsor:	Eli Lilly and Company
Clock Date:	November 13, 2001

Drug Name

Generic Name:	Duloxetine HCl
Trade Name:	Cymbalta

Drug Categorization

Pharmacological Class:	Serotonin and norepinephrine re-uptake inhibitor
Proposed Indication:	Treatment for Major Depressive Disorders
NDA Classification:	6 S
Dosage Forms:	20, 30, 50-mg capsules
Route:	Oral

Reviewer Information

Clinical Reviewer:	Paul J. Andreason, M.D.
Completion Date:	August 16, 2002

Table of Contents

Clinical Review for NDA 21-427

Executive Summary

I. Recommendations

A. Recommendation on Approvability

I recommend that the Division take an approvable action on NDA 21-427 from a clinical point of view. NDA 21-427 presents adequate data to support the claim that duloxetine is safe and effective in the treatment of Major Depressive Disorder. Several changes need to occur in labeling before duloxetine can be approved for marketing. These are outlined in section X of this review (Review of Labeling).

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Risks of duloxetine treatment are minimal. One potential risk that effected a significant minority of patients was hypertension. Patients taking duloxetine should be monitored regularly for hypertension. There is evidence for a dose dependent increase in the incidence of elevated blood pressure with duloxetine treatment. These increases do not appear to pose an acute risk; however, given that the treatment of Major Depressive Disorder (MDD) is chronic in nature, patients' blood pressures could easily drift into ranges that are associated with increased risk of heart disease and stroke. 24% of patients taking duloxetine 120-mg/day experienced elevated blood pressures versus 9% of placebo patients.

Phase IV studies should include appropriate studies in the pediatric population of depressed patients.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

There were 755 patients who received duloxetine in the 6 double blind, placebo and active controlled studies of MDD. A total of 2314 duloxetine patients were included in the primary safety database. 1032 of these patients were randomized to duloxetine in placebo-controlled trials in the primary safety database (MDD plus studies of urinary incontinence), and 1282 patients were enrolled in the open-label (uncontrolled) Study HMAU of patients with MDD. 704 patients have received duloxetine for at least 180-days. 520 patients were exposed to duloxetine in study HMAU for 1 year or more. The 2314 patients in the primary safety database represent approximately 754 patient-years exposure to duloxetine.

In the combined primary and secondary databases 3490 patients were exposed to duloxetine therapy. The bulk of the long-term exposure at relevant doses was obtained in study HMAU. The HMAU final report was submitted with the 120-day safety update.

B. Efficacy

The effectiveness of duloxetine in the treatment of DSM-IV–defined major depressive disorder (measured by reduction in HAMD17 total score) has been established in three positive studies: HMATb, HMBHa, and HMBHb. Two of these studies employed a single fixed dose of 60-mg/day. HMATb employed 20-mg BID and 40-mg BID dosing that was effective. The minimum effective dose therefore appears to be 20-mg BID. The forced titration studies (HMAQ a and b) that allowed for doses up to 60-mg BID failed. There were not distinguishable differences in treatment response between the 20-mg and 40-mg BID groups. There is no data to suggest that doses above 40-mg BID will be of any added value though one can not say that they might not be beneficial to some patients.

C. Safety

The safety testing of duloxetine in human subjects is adequate. The sponsor has exposed enough patients to surpass the ICH guidelines for the safety testing of new drugs. Appropriate clinical monitoring was done to account for what was learned about the drug from the preclinical toxicology data.

Duloxetine is adequately safe to use in the treatment of MDD. As with almost any drug, there are some adverse events that will not be tolerable for some patients. The adverse event profile for duloxetine appears to be similar to that of other SNRI drugs with some exceptions.

There were no deaths in the duloxetine development program that were likely to be drug related.

There were three serious adverse events that I felt were possibly related to duloxetine treatment. Two were cases of orthostatic hypotension and one was a case of elevated liver function tests after an overdose of multiple drugs. The two cases of hypotension were both elderly patients who were hospitalized. Orthostasis resolved in both cases after drug discontinuation.

The serious event that was coded as "elevated LFT" was reported as serious due to the circumstance of the overdose. There was no evidence of liver necrosis and the patient was not jaundiced. In the analysis of treatment-emergent abnormal values for hepatic analytes at anytime during the study, there was a significant difference for ALT. 19/941 (2%) duloxetine treated patients versus 4/664 (0.6%) placebo patients developed values that were high. Another way of examining this is via abnormal increases, even within the normal range. An abnormal change was defined as an increase >26U/L. 48/950 (5.1%) duloxetine treated patients versus 17/668 (2.5%) placebo treated patients met this threshold (Fishers Exact p=0.01). It is difficult to ascribe clinical significance to these observations. There are no cases of jaundice, or hyperbilirubinemia associated with increases in hepatic analytes. It appears that duloxetine like many drugs may cause seemingly benign increases in LFTs that do not correlate with serious liver toxicity. One can not, however, rule out serious problems that might occur at a rate of less than 1/1000 at this point.

Duloxetine is associated with a dose dependent increase in the rate of developing elevated blood pressure during treatment. Though none of the elevations were acutely serious, chronically

elevated blood pressure is associated with long-term health risks. Therefore patients taking duloxetine should have their vital signs regularly monitored.

Duloxetine does not seem to lead to urinary retention in a large group of patients as was the case with reboxetine; however, there is a small signal for urinary in the primary safety database. This is somewhat surprising since duloxetine is under review for the treatment of urinary incontinence. The sponsor administered duloxetine to men with BPH. In Study F1J-MC-SAAI: Duloxetine Hydrochloride Versus Placebo in Patients with Irritative Symptoms of Benign Prostatic Hyperplasia (BPH), there was only one dropout due to urinary retention in 69 males treated with duloxetine for 4-weeks. Treatment-emergent adverse events occurring in at least 5% of duloxetine-treated patients were abnormal ejaculation, diarrhea, dizziness, and somnolence. There is no evidence for dose dependence. Generally speaking, patients with BPH tolerated the drug fairly well. This was a small but pertinent study because this group is at a high risk for urinary retention.

Treatment with duloxetine is associated with symptoms of sexual dysfunction. Results of the ASEX seem to suggest that male sexual function is more effected than female. Total ASEX score increased by a mean of 1.5 (SD 4.4, p=0.02) in men taking duloxetine versus –0.04 in men taking placebo. There was no difference in the placebo versus duloxetine treated female patients mean total ASEX score. Analysis by item shows a significant difference on item 4 (achieving orgasm) for men - (duloxetine treated men had an increase of 0.7 versus 0.0 for placebo treated men [SD1.3, p=<0.001]). A more useful analysis to estimate the numbers of patients with changes in sexual function might be the percentage of patients (sub-divided by sex) who experienced a 2 point increase in score on any item of the ASEX from baseline to end of treatment. This could be done with the present data sets and I suggest that that the results of this type of analysis be mentioned in labeling.

The following table enumerates what I consider to be common and drug related adverse events with duloxetine treatment (defined as events reported by >5% of patients and at a rate that is at least twice as often as placebo).

Common and Drug Related Adverse Events in the Primary Placebo Controlled Pooled Database (occurrence rate of ≥5% and at least twice placebo)				
Adverse Events	**Placebo**		**Duloxetine**	
	(N=723)		**(N=1032)**	
	n	**(%)**	**n**	**(%)**
Nausea	50	(6.9)	225	(21.8)
Dry mouth	47	(6.5)	166	(16.1)
Fatigue	33	(4.6)	114	(11.0)
Dizziness (excluding vertigo)	38	(5.3)	110	(10.7)
Constipation	27	(3.7)	109	(10.6)
Somnolence	21	(2.9)	80	(7.8)
Appetite decreased NOS	15	(2.1)	67	(6.5)
Sweating increased	11	(1.5)	56	(5.4)

Discontinuing treatment with duloxetine is associated with symptoms that are qualitatively similar to other antidepressants such as SSRIs (dizziness, nausea, headache, paraesthesia, insomnia, diarrhea, nightmares, and at times vomiting). Though no real comparative statements can be made about the intensity of withdrawal to SSRIs, it appears that the symptoms are relatively mild and reliably predictable for a significant minority of patients. Tapering duloxetine at discontinuation appears to be advisable (and it is suggested by the sponsor in labeling) for optimal patient comfort, but abrupt withdrawal of treatment does not appear to pose any serious risk of toxic withdrawal.

D. Dosing

The sponsor proposes a starting dose of 60-mg per day in a single dose. Patients in clinical trials tolerated starting with single doses of 60-mg daily generally well. In clinical trials, target doses higher than 60-mg/day were started at 20-mg BID. It is therefore reasonable to suggest starting at 20-mg BID or single doses of up to 60-mg/day. Doses were increased by 10-20-mg BID on a weekly basis in the forced titration studies. Doses greater than 60-mg/day should be divided BID because of a lack of safety data on single dosing greater than this. Doses higher than 120-mg/day (60-mg BID) are not recommended.

Duloxetine may be taken with or without food. Bedtime dosing for single dose administration would be reasonable since somnolence was both common and drug related.

Tapering duloxetine on discontinuation is recommended. During the development program, patients were discontinued abruptly from treatment and experienced, dizziness, nausea, headache, paraesthesia, insomnia, diarrhea, nightmares, and at times vomiting. Tapering will more than likely decrease both the severity and incidence of discontinuation associated adverse events; however, no particular tapering regimen was tested.

E. Special Populations

Age, Sex, Ethnicity-There is no evidence that the dose or choice of duloxetine for treatment be modified based on age in adulthood, sex, or racial origin. Studies in the pediatric population have yet to be performed.

Pregnancy, Labor, Delivery and Nursing-The effect of duloxetine on pregnancy, labor and delivery in humans is unknown. I recommend that duloxetine be placed in pregnancy category C. Because duloxetine and its metabolites cross the placenta in rats and because of the possibility that duloxetine and its metabolites may have adverse effects on the newborn, duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Duloxetine and its metabolites are excreted into the milk of lactating rats. Excretion of duloxetine and its metabolites into human milk is unknown, but nursing while on duloxetine is not recommended

Smoking Status—Duloxetine bioavailability appears to be about 34% lower in smokers than in nonsmokers. Dosage modifications are not necessary.

Renal Insufficiency—Duloxetine Cmax and AUC values were approximately 2-fold higher in patients with end stage renal disease (ESRD) receiving chronic intermittent hemodialysis, compared with subjects with normal renal function. In contrast, the elimination half-life was similar in both groups. Studies have not been conducted in patients with a moderate degree of renal dysfunction. Population PK analyses suggest that mild renal dysfunction has no significant effect on duloxetine apparent clearance. A lower dose should be considered for patients with ESRD .

Hepatic Insufficiency—Six cirrhotic patients had a mean duloxetine apparent plasma clearance that was approximately 15% that of age- and gender-matched healthy subjects after receiving a 20 mg dose of duloxetine. The Cmax was similar in the cirrhotic patients, but the half-life was 34 hours longer. A lower starting dose should be considered for patients with clinically significant liver impairment .

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Duloxetine (Cymbalta®) is an orally administered serotonin and norepinephrine reuptake inhibitor (SNRI). It is recommended for the treatment of Major Depression at a single daily dose of 60-mg. The safety and efficacy of duloxetine has not been established in the pediatric population. [redacted]. There is no recommended dose adjustment for elderly patients. The maximum recommended daily dose is 60-mg BID.

B. State of Armamentarium for Depression

The pharmacological armamentarium for the treatment of depression is now vast; however, no one class of drugs offers broad ranged superiority. Each class possesses unique and useful clinical qualities but also has characteristic drawbacks. Clinicians' initial choice of antidepressant is often based on the adverse event profile and patients' ease of compliance since there is no clear winner with respect to antidepressant efficacy.

There are five major pharmacologic classes of drugs that are approved for the treatment of depression in the US: selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), and "others" (where there is neither a clear mechanism or class distinction). Though not a pharmacological intervention electro-convulsive therapy (ECT) is a very effective treatment for Major Depression, but it is reserved for the most serious and treatment refractory cases.

Venlafaxine (Effexor and Effexor XR®) is the only approved SNRI. It is characteristically associated with hypertension.

Four of the five SSRIs are approved for depression. Fluoxetine, citalopram, sertraline, and paroxetine are approved for the treatment of depression. Fluvoxamine is approved for the treatment of Obsessive Compulsive Disorder (OCD) and is often used off-label for the treatment of depression. Adverse events that are characteristically associated with these drugs include sexual dysfunction and an SSRI discontinuation syndrome.

Other or atypical first line antidepressant drugs include nefazadone, trazadone, and bupropion. Nefazadone and trazadone are quite sedating. Bupropion, unlike many of the antidepressants, does not adversely effect sexual functioning.

TCA (amitriptyline, imipramine, desipramine, nortriptyline, as well as other heterocyclic drugs) are effective treatments yet are out of favor in the clinical community as first line agents because of associated anticholinergic and antihistaminic side effects such as sexual dysfunction, somnolence, dry mouth, constipation, blurred vision, weight gain, orthostasis, fatality in

overdose and sometimes cardiac arrhythmias. They are now considered an important yet second line drug treatment because of their characteristic adverse events.

Monoamine oxidase inhibitors (MAOI) are effective antidepressants but are associated with malignant hypertension in combination with certain foods and other antidepressants, serotonin syndrome associated with combination use with SSRI, and orthostatic hypotension. This class of drugs restricts patients to a narrower choice of foods and both prescription and over-the-counter medications. They are considered useful and effective but third line drugs in the treatment of depression.

C. Important Milestones in Product Development

5 March 1992: IND #38,838 opened for duloxetine enteric-coated pellet formulation
16 December 1999: Depression End of Phase II Meeting
15 August 2001: Pre-NDA Meeting

Duloxetine has not been marketed in any country at this time.

D. Important Issues with Pharmacologically Related Agents

Venlafaxine is the only other SNRI marketed in the US. Venlafaxine is associated with dose dependent increases in blood pressure, and routine monitoring of blood pressure is recommended in labeling.

Reboxetine, an SNRI marketed in Europe but not in the US, is associated with urinary retention especially in males.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The Division of Biometrics consultant concurs with the sponsors statistical analysis of the three positive pivotal studies.

OCPB review recommends an approvable action for NDA 21-427. Duloxetine is extensively metabolized with over 80% of the dose recovered as metabolites. Approximately 70% of the dose is recovered in the urine almost exclusively as metabolites. The major primary metabolites include, hydroxy-duloxetine, N-desmethyl-duloxetine, and dihydrodiol-duloxetine. The various hydroxy metabolites are formed by CYP1A2 and CYP2D6 and account for around 2/3's – 4/5's of duloxetine's elimination. N-demethylation probably occurs via CYP2C11.

Clinical Pharmacology and Chemistry reviews are not available for comment at the writing of this review; however, the executive CAC minutes were available. These minutes indicated that there was no evidence for mutagenicity or genotoxicity in a standard battery.

CD-1 mice exhibited increased incidence of tumors but they were limited to benign endometrial stromal tumors in the uteruses and hepatocellular adenomas and carcinomas in the livers of HD females, only. In Fisher 344 rats there was an increased incidence of tumors was limited to a slight increase in the incidence of benign interstitial cell tumor in testes of male rats, a common, benign tumor. The Committee agreed with the Sponsor and the Reviewer that the mouse study was adequate and that the positive carcinogenicity findings were hepatocellular adenomas and carcinomas in livers of high-dose females. The Committee agreed that the rat study was negative for carcinogenicity findings.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Tmax for duloxetine is approximately 6-hours. Steady state concentrations are achieved after three days of dosing. The elimination half-life of duloxetine ranges from 8.1 to 17.4 hours (5th to 95th percentile, mean of 12.1 hours) and the apparent plasma clearance ranges from 33 to 261 L/hr (5th to 95th percentile, mean of 101 L/hr).

In a ^{14}C ADME study (SAAZ), duloxetine was well absorbed (72% of total radioactivity excreted in urine) and extensively metabolized (about 3% of plasma radioactivity accounted for by duloxetine). Numerous metabolites (>11) were formed and excreted primarily in urine.

Total radioactivity half-life ($t_{½}$) was substantially longer than the duloxetine $t_{½}$ (120 hours versus 10.3 hours). Major biotransformation pathways involved oxidation of the naphthyl ring at the 4-, 5-and 6- positions followed by further oxidation, methylation, and conjugation. The major metabolites in plasma and urine were glucuronide conjugate of 4-hydroxy duloxetine, and the sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine. Other metabolites in plasma were a glucuronide conjugate of dihydroxy/catechol duloxetine and a glucuronide conjugate of 6-hydroxy, 5-methoxy duloxetine. Urine contained additional metabolites beyond those found in plasma.

In study SBAA, food did not affect the maximum plasma concentration (Cmax); marginally decreased AUC (11%); and delayed Tmax by about 4 hours. Bedtime administration decreased Cmax (26%) and AUC (17%); and delayed Tmax 4-hours. Nonetheless, the changes were not regarded as clinically important. Proposed product labeling provides information about these changes but recommends dosing without regard to meals.

Specific drug-drug interaction studies were performed with duloxetine and desipramine (a CYP2D6 substrate), theophylline (a CYP1A2 substrate), and paroxetine (a CYP2D6 inhibitor). Based on the extent of the increase in desipramine AUC, duloxetine was considered a moderate inhibitor of CYP2D6 compared to paroxetine and fluoxetine. When duloxetine was administered at the maximum therapeutic dose (60 mg BID) with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. Therefore, caution should be used if duloxetine is co-administered with medications that are predominately metabolized by the CYP2D6 system and which have a narrow therapeutic index.

Paroxetine co-administration increased duloxetine Cmax and AUC values. Paroxetine (20 mg QD) decreased the apparent plasma clearance of duloxetine about 37%. Duloxetine did not have significant effects on the pharmacokinetics of theophylline and therefore was not considered an important CYP1A2 inhibitor.

Increased gastric pH by the co-administration of famotidine (a H2 -antagonist) and Mylanta® (an antacid) did not change duloxetine pharmacokinetics. In contrast, activated charcoal significantly decreased duloxetine plasma concentrations and t½ , indicating its potential use in the management of duloxetine overdose.

Duloxetine did not alter the amnestic effects of lorazepam, yet the lorazepam and duloxetine combination was associated with an increased sedation on both subjective and objective tests. There were no significant pharmacokinetic interactions between duloxetine and lorazepam.

Study HMBA explored the effects of ethanol administration with and without duloxetine and duloxetine alone on a performance test battery. 16 healthy volunteers (10 women and 6 men) were given the Automated Performance Test System (APTS) at 0.5 and 1.5 hours after a treatment. Ethanol + duloxetine resulted in numerically worse performance, compared to ethanol alone or to duloxetine + ethanol placebo, on all tests except grammatical reasoning and pattern comparison; however, in no case was the difference between ethanol alone and ethanol + duloxetine significant. Duloxetine alone (+ ethanol placebo) did not result in a worsening of performance on any test.

Studies in special populations revealed pharmacokinetic differences between elderly and younger subjects, men and women, smokers and nonsmokers, healthy subjects and those with hepatic or renal impairment; however, because of the broad inter-subject variability, these differences appear to be only clinically relevant for patients with impaired hepatic or renal function.

There are no significant differences in duloxetine pharmacokinetics between Caucasian and non-Caucasian healthy subjects. A population analysis performed for MDD patients suggests that Caucasian (~56%) and Hispanic (~39%) populations have similar pharmacokinetic characteristics of duloxetine. Because patients of either African or Asian descent only constituted a small portion of the study population, no meaningful assessment of pharmacokinetic differences could be performed for these ethnic subgroups.

Duloxetine undergoes extensive metabolism to numerous metabolites. The major metabolic pathways involve oxidation of the naphthyl ring followed by further oxidation, methylation and conjugation. The two major circulating metabolites of duloxetine are the glucuronide conjugate of 4-hydroxy duloxetine and the sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine. In vitro studies indicate that neither of these metabolites contributes to the pharmacologic activity of duloxetine. Both CYP2D6 and CYP1A2 are involved in the initial oxidation to 4-hydroxy, 5-hydroxy, and 6-hydroxy duloxetine. Duloxetine does not inhibit CYP3A, CYP1A2, or CYP2C9 in vitro and does not cause induction of CYP3A or CYP1A2 in vitro in human hepatocytes.

B. Pharmacodynamics

Dose tolerability was evaluated in studies HMAP and HMAR. Doses up to 40-mg BID (80-mg/day total dose) were generally well tolerated. Study HMAP evaluated the safety, adverse event profile, pharmacokinetics, and effect on urinary flow. Eight subjects received duloxetine. Duloxetine administration was associated with a small increase in recumbent systolic and diastolic blood pressure, and a small decrease in recumbent heart rate. Duloxetine had no clinically important effects on electrocardiograms or on cardiac intervals. No major effects of duloxetine on urine flow were observed. Mild withdrawal symptoms (e.g., insomnia and abnormal dreams) and a small increase in recumbent heart rate occurred in several subjects when duloxetine was abruptly discontinued at the end of the study.

Study HMAR evaluated daily duloxetine doses of up to 160-mg/day for 6-days. Insomnia was the most frequent adverse event, particularly at the highest dose. An increase in standing heart rate was observed and was possibly related to the drug plasma concentration (Emax 19.6 bpm; EC50 71.8 ng/mL).

IV. Description of Clinical Data and Sources

A. Overall Data

The sponsor presents 6 well designed, appropriately controlled clinical trials- 3 of which support the sponsors claim. All safety, efficacy, and pharmacokinetic data is generated by the sponsor. No literature reports are presented as support for the drug's approval.

B. Tables Listing the Clinical Trials

Table IV.B.1 lists the controlled clinical trials in the sponsor's development program for duloxetine. A more detailed list may be found in the appendix.

Table IV.B.1 Principal Controlled Clinical Trials in NDA 21-427

Study/ No. of Sites/ Location	Study Title	Study Design	No. of Patients/ By Gender/ Mean Age/ Age Range	Treatment (mg/ day)
F1J- MC- HMAQa 8 sites US	Duloxetine Versus Placebo in the Treatment of Major Depression	Multicenter, parallel, double- blind, randomized placebo- controlled, forced titration; double- blind placebo lead- in and lead- out	N= 173 (F= 111; M= 62) Mean age= 41. 4 Age range= 18.7- 65.0	Duloxetine 20- 60 mg PO BID Fluoxetine 20 mg PO QD

Table IV.B.1 Principal Controlled Clinical Trials in NDA 21-427

F1J-MC-HMAQb 11 sites US	Duloxetine Versus Placebo in the Treatment of Major Depression	Multicenter, parallel, double-blind, randomized, placebo-controlled, forced titration; double-blind placebo lead-in and lead-out	N= 194 (F= 129; M= 65) Mean age= 40. 4 Age range= 18.9-64.4	Duloxetine 20-60 mg PO BID Fluoxetine 20 mg PO QD
F1J-MC-HMATa 22 sites US	Duloxetine Versus Placebo and Paroxetine in the Acute Treatment of Major Depression	Multicenter, parallel, double-blind, randomized, placebo- and active comparator-controlled, fixed dose; double-blind placebo lead-in and lead-out	N= 354 (F= 218; M= 136) Mean age= 43. 7 Age range= 18.0-82.2	Duloxetine 20 mg or 40 mg PO BID Paroxetine 20 mg PO QD
F1J-MC-HMATb 22 sites US	Duloxetine Versus Placebo and Paroxetine in the Acute Treatment of Major Depression	Multicenter, parallel, double-blind, randomized, placebo- and active comparator-controlled, fixed dose; double-blind placebo lead-in and lead-out	N= 353 (F= 217; M= 136) Mean age= 40. 5 Age range= 18.2-78.2	Duloxetine 20 mg or 40 mg PO BID Paroxetine 20 mg PO QD
F1J-MC-HMBHa 18 sites US	Duloxetine Once-Daily Dosing Versus Placebo in the Acute Treatment of Major Depression	Multicenter, parallel, double-blind, placebo-controlled, fixed dose; blinded placebo lead-out	N= 245 (F= 163; M= 82) Mean age= 42. 4 Age range= 18.6-77.7	Duloxetine 60 mg PO QD
F1J-MC-HMBHb 23 sites US	Duloxetine Once-Daily Dosing Versus Placebo in the Acute Treatment of Major Depression	Multicenter, parallel, double-blind, placebo-controlled, fixed dose; blinded placebo lead-out	N= 267 (F= 184; M= 83) Mean age= 40. 9 Age range= 19.2-82.9	Duloxetine 60 mg PO QD

C. Postmarketing Experience

Duloxetine is not marketed in any country.

D. Literature Review

Duloxetine is not marketed in any country and the sponsor is the sole source of drug product for research. Hence there are only a few published articles that address clinical use of duloxetine in humans. These articles were reviewed by the sponsor and this reviewer. These articles were based on data that is included in the submission.

V. Clinical Review Methods

A. How the Review was Conducted

The clinical review was divided into two general sections-efficacy review and safety review. The review of efficacy focused on the individual pivotal studies. There was no examination of pooled efficacy data. Safety data was examined starting from the integrated summary of safety (ISS). Deaths, serious adverse events, and adverse dropouts were reviewed for all studies and indications performed in all countries. Data from controlled clinical trials of Major Depressive Disorder were pooled, when appropriate, to explore common and drug related adverse event, treatment related changes in laboratory analytes, changes in ECG and vital signs, and other specific searches.

B. Overview of Materials Consulted in Review

The electronic version of this submission was used for the entire clinical review process. The NDA application was generally complete. For the most part, the clinical review drew only from materials included in the NDA submission and the 120-day safety update.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The submission was check for internal consistency. Case report forms (CRF) for deaths and serious adverse events were reviewed and cross checked with patient summaries. The Division of Scientific Investigations (DSI) was consulted and site visits were made.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Trials were conducted in accordance with Good Clinical Practice Guidelines (GCP).

E. Evaluation of Financial Disclosure

There was no evidence that the integrity of the studies was adversely influenced because of financial conflicts.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Duloxetine is effective in the treatment of Major Depressive Disorder. Three of six pivotal studies of the treatment of Major Depressive Disorder with duloxetine demonstrated that duloxetine was effective. The three studies that did not support duloxetine as effective were

failed studies in that the effectiveness a proven drug for the treatment of Major Depressive Disorder could not be distinguished from placebo.

B. General Approach to Review of the Efficacy of the Drug

The review of clinical efficacy focused on the 6 placebo controlled trials of patients with Major Depressive Disorder on an individual basis. Pooled data from multiple studies was not considered in the review of efficacy. These follow in section C.

C. Detailed Review of Trials Supporting the Use of Duloxetine for the Treatment of Depression

C-1 F1J-MC-HMAT(b)

Duloxetine Versus Placebo and Paroxetine in the Acute Treatment of Major Depression.

The HMAT protocol consisted of two identical studies conducted in parallel (groups a and b). Investigators were divided into two separate study groups prior to study start-up. Group (a) failed to reach a priori levels of significance and is not described in detail. The sponsor submits study group (b) as a supportive pivotal study.

C-1.A Investigators and sites for HMAT(b)

There were 20 individual investigators who provided data for study HMAT(b). Two of the investigators had two separate sites so that there were 22 sites. Names of investigators and numbers of patients for each site may be found in the appendix.

C-1.B Objectives

The primary objective of study HMAT(b) was to assess the efficacy of duloxetine 40 mg BID is versus placebo in the acute treatment of patients with DSM-IV–defined major depressive disorder.

C-1.C Study Population

The study population of HMAT was to include outpatients aged at least 18 years with a primary diagnosis of major depression as defined by the DSM-IV, and confirmed by use of the Mini International Neuropsychiatric Interview (MINI). Patients were required to have a 17-Item Hamilton Depression Rating Scale (HAMD17) total score $\geq$15 and a Clinical Global Impressions of Severity Scale (CGI-Severity) total score $\geq$4 at both screening and baseline (Visits 1 and 2).

The baseline visit occurred after 1-week of single blind placebo treatment. At the baseline visit, placebo responders (i.e. patients whose HAM-D and CGI-S dropped below 15 and 4 respectively) were discontinued from the study. Detailed inclusion and exclusion criteria may be found in the appendix.

C-1.D Design

This was a multicenter, parallel, double-blind, randomized, placebo-controlled, 8-week clinical trial comparing duloxetine 40-mg BID and 20-mg BID with paroxetine 20-mg QD and placebo in the acute treatment of patients with DSM-IV– defined Major Depressive Disorder. After enrollment and screening patients entered a 1-week single blind placebo run-in phase. If they

continued to have HAM-D and CGI-S scores that were above the pre-defined threshold, then they advanced to randomization and an 8-week double blind treatment phase. All patients started on the target dose of drug except for the duloxetine 40-mg BID group. This group started at duloxetine 20-mg BID for 2-weeks the advanced to 40-mg BID. The duloxetine 40-mg BID group was thus only exposed to this dose for 6-weeks.

After the acute 8-week double-blind treatment phase, patients were discontinued from treatment in a single blind fashion and observed for discontinuation associated events for 2-weeks.

C-1.E Assessments

The primary efficacy variable was the HAM-D_{17} change from baseline to endpoint versus placebo in the ITT patient population. A schedule of events in the appendix (table C-1.E) gives a detailed listing of assessments and when they were performed.

C-1.F Patient Disposition

Patients were approximately 40 years old (mean 40.5 min 18.2 max 78.2 years), with the majority being Caucasian (81%) and female (62%). Marginally statistically significant treatment-group differences in weight were observed at baseline, with the patients in the paroxetine treatment group showing the highest weight at baseline. There were no between treatment group differences with respect to age, sex, or ethnicity.

Table C-1.F.1 lists reasons that patients dropped out of the study in order of decreasing frequency.

Table C-1.F.1 Reasons for Discontinuation in Study HMAT(b)

	PLACEBO	DLX 20 BID	DLX 40 BID	PRX 20 QD	Total
Enrollment	N=89	N=86	N=91	N=87	N=353
Reason	n(%)	n(%)	n(%)	n(%)	n(%)
Any reason	37(42%)	31(36%)	38(42%)	38(44%)	144(41%)
Lack of efficacy, patient/MD perception	23(26%)	10(12%)	6(6.6%)	11(13%)	50(14%)
Adverse event	8(9.0%)	10(12%)	14(15%)	8(9.2%)	40(11%)
Personal conflict or other patient decision	3(3.4%)	5(5.8%)	9(9.9%)	6(6.9%)	23(6.5%)
Unable to contact patient(lost to followup)	2(2.2%)	3(3.5%)	3(3.3%)	7(8.0%)	15(4.2%)
Protocol violation	0(.00%)	3(3.5%)	5(5.5%)	5(5.7%)	13(3.7%)
Physician decision	1(1.1%)	0(.00%)	1(1.1%)	1(1.1%)	3(.85%)

	p-Values*					
	Overall	**1vs2**	**1vs3**	**1vs4**	**2vs3**	**2vs4**	**3vs4**
Any reason	.763	.535	1.00	.879	.446	.353	.880
Lack of efficacy, patient/MD perception	.003	.020	<.001	.035	.299	1.00	.207
Adverse event	.524	.625	.256	1.00	.515	.628	.258
Personal conflict or other patient decision	.352	.491	.133	.327	.407	1.00	.592
Unable to contact patient(lost to followup)	.304	.679	1.00	.098	1.00	.329	.205
Protocol violation	.093		.059	.028	.721	.720	1.00

(1) = PLACEBO, (2) = DLX 20 BID, (3) = DLX 40 BID, (4) = PRX 20 QD

***P- values obtained from Fisher's exact test**

The placebo group had significantly greater dropout rates than any of the treatment groups due to lack of efficacy by the Fisher's Exact Test. The paroxetine group had a trend toward greater rates of loss to follow-up. Other than these exceptions, there were no differences between placebo and the treatment groups with respect to drop out rates.

C-1.G Baseline Demographics/Severity of Illness

The paroxetine group patients had a slightly greater mean weight at baseline than the other treatment groups (approximately 89-kg versus 82-kg as the next lower mean weight). There were not any other significant differences in demographic characteristics between groups such as age, sex, ethnicity, or height. Patients had a mean age of 40-year and the majority were white (81%) and female (62%). There were no between group differences in severity of illness. A detailed table of patient demographics may be found in the appendix (Table C-1.G.1).

C-1.H Concomitant Medications During Double Blind Treatment

The use of concomitant psychotropic medication was generally not allowed. There were no differences in the types of concomitant medication or the rates at which they were used between treatment groups except for calcium. 15% of placebo patients versus 0-3% of the patients in the other groups used calcium. These differences are unlikely to be clinically relevant.

C-1.I Efficacy Results

The primary efficacy evaluation was a comparison between the duloxetine 40 mg BID and placebo treatment groups at Visit 8, using repeated measures analysis of the change from baseline in the 17-Item Hamilton Depression Rating Scale (HAMD17) total score. Primary efficacy conclusions were based on an analysis of all randomized patients.

The following table (C-1.I.1) displays the results of the sponsors primary efficacy analysis at visit 8 (8 weeks of double blind treatment-also referred to as week-9 of the study). Duloxetine 40-mg BID and 20-mg BID dose groups had significantly greater changes in the HAM-D 17 total score at visit 8. Paroxetine did not separate from placebo at the study endpoint but did separate after 4 and 6 weeks of double blind treatment.

Table C-1.I.1 Repeated Measures Analysis of All Randomized Patients HAM-D_{17} Total Score Change from Baseline HMAT(b)

Therapy	Weeks of Double Blind Treatment	N	Mean	Mean Change	SE	Pairwise p-Value vs. PBO	vs. DLX 20	vs. PRX
PLACEBO	1	88	16.67	-1.10	0.48			
DLX 20 BID		84	16.88	-0.89	0.49	.752		
DLX 40 BID		86	16.16	-1.61	0.49	.445	.285	
PRX 20 QD		84	16.20	-1.57	0.49	.485	.315	.951
PLACEBO	2	81	15.50	-2.27	0.60			
DLX 20 BID		77	14.24	-3.53	0.61	.136		
DLX 40 BID		78	13.17	-4.61	0.61	.006	.204	
PRX 20 QD		75	13.75	-4.02	0.62	.039	.564	.491
PLACEBO	4	76	14.14	-3.64	0.69			
DLX 20 BID		73	12.12	-5.66	0.70	.038		
DLX 40 BID		71	11.50	-6.27	0.70	.007	.529	
PRX 20 QD		70	11.23	-6.54	0.71	.003	.370	.788
PLACEBO	6	65	13.36	-4.42	0.72			
DLX 20 BID		64	10.80	-6.97	0.73	.012		
DLX 40 BID		65	9.31	-8.46	0.72	<.001	.143	
PRX 20 QD		62	11.03	-6.74	0.74	.023	.821	.093
PLACEBO	8 (Visit 8)	54	12.78	-4.99	0.81			
DLX 20 BID		59	10.35	-7.42	0.80	.034		
DLX 40 BID		55	9.16	-8.61	0.81	.002	.293	
PRX 20 QD		54	11.56	-6.22	0.82	.285	.293	.037

Mean change analysis of study HMAT reach similar conclusions with the exception that mean change analysis does not suggest superiority of duloxetine 40-mg BID over paroxetine 20-mg QD.

Table C-1.I.2 Mean Change from Baseline to Endpoint (LOCF) Study HMAT(b)

		Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Placebo	88	17.19	5.11	17.0			13.03	8.21	14.0			-4.16	6.42	-4.0		
DLX 20 BID	84	18.63	5.85	18.5			11.46	8.02	11.0			-7.17	7.97	-7.0		
DLX 40 BID	86	18.06	4.52	18.0			10.34	7.35	7.5			-7.72	7.67	-7.0		
PRX 20 QD	84	17.65	5.13	17.0			11.60	8.67	12.0			-6.06	8.12	-6.5		

Pairwise Comparison of LS Means in LOCF Analysis

DLX20BID-PLACEBO	diff=-2.41	Two-sided 95% CI : (-4.47,-0.35)	t=-2.30	df=1,321	p=0.022
DLX40BID-PLACEBO	diff=-3.11	Two-sided 95% CI : (-5.15,-1.06)	t=-2.98	df=1,321	p=0.003
PRX20QD-PLACEBO	diff=-1.51	Two-sided 95% CI : (-3.56,0.55)	t=-1.44	df=1,321	p=0.150
DLX40BID-DLX20BID	diff=-0.70	Two-sided 95% CI : (-2.76,1.37)	t=-0.66	df=1,321	p=0.508
DLX20BID-PRX20QD	diff=-0.90	Two-sided 95% CI : (-2.98,1.18)	t=-0.85	df=1,321	p=0.395
DLX40BID-PRX20QD	diff=-1.60	Two-sided 95% CI : (-3.66,0.47)	t=-1.52	df=1,321	p=0.129

Observed case analysis provides evidence that duloxetine 40-mg BID is superior to placebo at the study endpoint but neither the 20-mg BID group nor the paroxetine 20-mg group are statistically different from placebo.

C-1.J Conclusions Regarding the Efficacy Outcome in Study HMAT(b)

Study HMAT(b) represents a positive study toward the claim that duloxetine is effective in the treatment of depression.

C-2 F1J-MC-HMAT(a)

Duloxetine Versus Placebo and Paroxetine in the Acute Treatment of Major Depression

Study HMAT(a) was identical in design to HMAT(b) but was carried out at different sites. It did not produce significantly positive results in support of the sponsor's efficacy claim yet the active control (paroxetine) group had significant improvement in primary efficacy parameters with respect to placebo. A brief review of the results of HMAT(a) follows.

C-2.A Patient Disposition HMAT(a)

Table C-2.A enumerates the reasons for patient dropout in study HMAT(a).

Table C-2.A. Reasons for Discontinuation By Decreasing Frequency All Randomized Patients Acute Therapy Phase HMAT(a)

Reason	Placebo N=90 n(%)	DLX 20 BID N=91 n(%)	DLX 40 BID N=84 n(%)	PRX 20 QD N=89 n(%)	Total N=354 n(%)
Any reason	28(31%)	28(31%)	26(31%)	29(33%)	111(31%)
Adverse event	3(3.3%)	11(12%)	13(15%)	10(11%)	37(10%)
Personal conflict or other patient decision	6(6.7%)	7(7.7%)	9(11%)	5(5.6%)	27(7.6%)
Lack of efficacy, patient/MD perception	12(13%)	2(2.2%)	1(1.2%)	6(6.7%)	21(5.9%)
Protocol violation	3(3.3%)	3(3.3%)	2(2.4%)	6(6.7%)	14(4.0%)
Unable to contact patient (lost to follow-up)	3(3.3%)	5(5.5%)	1(1.2%)	2(2.2%)	11(3.1%)
Physician decision	1(1.1%)	0(.00%)	0(.00%)	0(.00%)	1(.28%)

		p-Values*					
	Overall	**1 vs 2**	**1 vs 3**	**1 vs 4**	**2 vs 3**	**2 vs 4**	**3 vs 4**
Any reason	.994	1.00	1.00	.873	1.00	.873	.871
Adverse event	.037	.048	.007	.048	.661	1.00	.503
Personal conflict or other patient decision	.662	1.00	.422	1.00	.602	.767	.270
Lack of efficacy, patient/MD perception	.003	.005	.003	.213		.166	.118
Protocol violation	.548	1.00	1.00	.330	1.00	.327	.279
Unable to contact patient(lost to follow-up)	.460	.720		1.00	.213	.444	
Physician decision							

NOTE: (1) = PLACEBO, (2) = DLX20BID, (3) = DLX40BID, (4) = PRX20QD
*P- values obtained from Fisher's exact test

The overall dropout rate was lower in study HMAT(a) than in the group(b) study. The dropout rate for lack of efficacy in the placebo group is much lower in HAMT(a)-13% as opposed to (b)-26%. The rate at which placebo patients dropped out for adverse events was 9% in HMAT(b) versus 3% in study group (a).

Usually, a lower dropout rate in the placebo group decreases the likelihood of type II error, but, by itself, does not increase the likelihood of type I error. Therefore, this difference between the studies does not account for their differing results.

C-2.B Baseline Demographics/Severity of Illness

No statistically significant differences were observed among treatment groups with regard to age, gender, origin, weight, or height. Patients had a mean age of approximately 44 years, with the majority being Caucasian and female.

A potentially important difference did exist in psychiatric history. There were more duloxetine patients who had previous episodes of depression versus the placebo and paroxetine patients.

Table C-2.B.1 Presence of previous episodes of depression in randomized patients of study HMAT(a)

Previous Episodes	Placebo	DLX 20 BID	DLX 40 BID	PRX 20 QD	Total	p-value
No. Patients	90	91	84	89	354	<.001*
N	25 (27.8)	14 (15.4)	6 (7.1)	28 (31.5)	73 (20.6)	
Y	65 (72.2)	77 (84.6)	78 (92.9)	61 (68.5)	281 (79.4)	

*Fisher's Exact Test

This may be a factor in this study failing to show significant improvement in the duloxetine groups. There were, however, no differences in the baseline mean rating scale scores.

C-2.C Concomitant Medications During Double Blind Treatment

Non-narcotic analgesics (ASA, paracetamol) were used more often than other concomitant medications in this study. Paracetamol was used more frequently in the duloxetine groups than in the placebo or paroxetine groups; ASA was used more frequently by the paroxetine group than the duloxetine groups. It is unlikely that paracetamol or ASA were related to the outcome of the study.

C-2.D Efficacy Results for HMAT(a)

Tables C-2.D.1 and 2 display the repeated measures analysis (primary efficacy analysis) and the LOCF analysis respectively.

C-2.C.1 Repeated Measures Analysis of All Randomized Patients
HAM-D_{17} Total Score Change from Baseline HMAT(a)

Therapy	Visit (DB treatment weeks)	N	LSMean	LSMean Change	SE	Pairwise p-Val vs. 1)	vs. 2)	vs. 3)
1)PLACEBO	4(1)	89	15.85	-1.74	0.51			
2)DLX20BID		90	16.13	-1.45	0.50	.685		
3)DLX40BID		81	16.14	-1.44	0.53	.682	.988	
4)PRX20QD		86	15.58	-2.00	0.52	.710	.439	.442
1)PLACEBO	5(2)	87	14.77	-2.82	0.57			
2)DLX20BID		83	14.27	-3.31	0.58	.539		
3)DLX40BID		75	14.38	-3.20	0.61	.642	.894	
4)PRX20QD		80	13.05	-4.53	0.59	.036	.138	.114
1)PLACEBO	6(4)	79	13.92	-3.66	0.65			
2)DLX20BID		77	12.90	-4.69	0.66	.266		
3)DLX40BID		70	12.98	-4.60	0.69	.319	.930	
4)PRX20QD		76	13.07	-4.51	0.67	.360	.849	.921
1)PLACEBO	7(6)	68	12.60	-4.98	0.64			
2)DLX20BID		67	11.48	-6.11	0.65	.216		
3)DLX40BID		63	11.85	-5.73	0.67	.420	.684	
4)PRX20QD		66	11.80	-5.78	0.66	.381	.721	.956
1)PLACEBO	8(8)	62	12.80	-4.78	0.68			
2)DLX20BID		65	11.41	-6.18	0.68	.143		
3)DLX40BID		61	11.28	-6.31	0.70	.116	.896	
4)PRX20QD		62	10.18	-7.40	0.69	.007	.202	.261

Table C-2.C.2 Mean Change from Baseline to Endpoint (LOCF) Study HMAT(a)

		Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
Placebo	89	17.79	4.73	18.0			13.51	6.76	13.0			-4.28	6.89	-4.0		
DLX 20 BID	90	17.47	5.20	18.0			12.04	6.31	11.0			-5.42	7.12	-5.5		
DLX 40 BID	81	17.44	5.16	18.0			11.90	6.63	11.0			-5.54	6.68	-5.0		
PRX 20 QD	87	17.97	5.87	18.0			11.77	7.68	11.0			-6.20	6.97	-6.0		

Pairwise Comparison of LS Means

DLX20BID-PBO	diff=-1.17	Two-sided 95% CI : (-3.05,0.71)	t=-1.22	df=1,326	**p=0.222**
DLX40BID-PBO	diff=-1.46	Two-sided 95% CI : (-3.38,0.47)	t=-1.49	df=1,326	**p=0.138**
PRX20QD-PBO	diff=-1.83	Two-sided 95% CI : (-3.72,0.06)	t=-1.90	df=1,326	**p=0.058**
DLX40BID-DLX20BID	diff=-0.29	Two-sided 95% CI : (-2.21,1.63)	t=-0.30	df=1,326	**p=0.768**
DLX20BID-PRX20QD	diff=0.66	Two-sided 95% CI : (-1.23,2.55)	t=0.69	df=1,326	**p=0.493**
DLX40BID-PRX20QD	diff=0.37	Two-sided 95% CI : (-1.57,2.31)	t=0.38	df=1,326	**p=0.707**

The LOCF analysis of study HMAT(a) does not demonstrate a statistically significant difference between placebo and paroxetine. The results of the primary analysis portrays the study as "negative" because paroxetine treated patients did show significant improvement by the repeated measures analysis. The LOCF analysis portrays the study as a "failed study" that lacked the sensitivity to make predictions either way.

C-2.D Conclusions Regarding Efficacy in Study HMAT(a)

When one weighs the results of the LOCF analysis along with the disproportionately higher number of patients with recurrent major depression in the duloxetine treatments groups, I view study HMAT(a) as a failed study as opposed to a negative study. From this point of view, study HMAT(a) neither supports or refutes the results of study HMAT(b). In any case, study HMAT(a) does not support the sponsors claim that duloxetine is effective in the treatment of depression.

C-3 F1J-MC-HMBH (a) Duloxetine Once-Daily Dosing Versus Placebo in the Acute Treatment of Major Depression. Protocol HMBH was used to perform two identical studies. Sites were randomized to study groups (a) and (b). A non-randomized switch in site assignment was performed by the sponsor. Sites 101 and 122 were switched from study group A to study group B. Study group (a) was over enrollment quotas while group (b) was not meeting enrollment projections. The sites were changed to balance enrollment in the studies and were performed before any study data was unblinded. Because of this switch these two sites were visited by the Division of Scientific Investigations for routine audit of records as part of this NDA review.

C-3.A Investigators and Sites for HMBH(a)

Investigators and site addresses along with respective patient enrollment may be found in the appendix in Table C.

C-3.B Objectives

The primary objective of study HMBH(a) was to assess the efficacy of duloxetine 60 mg once daily (QD) compared with placebo in reducing mean total score of the 17-item Hamilton Depression Rating Scale (HAMD17) in patients who met criteria for major depressive disorder as defined in the DSM-IV.

C-3.C Study Population

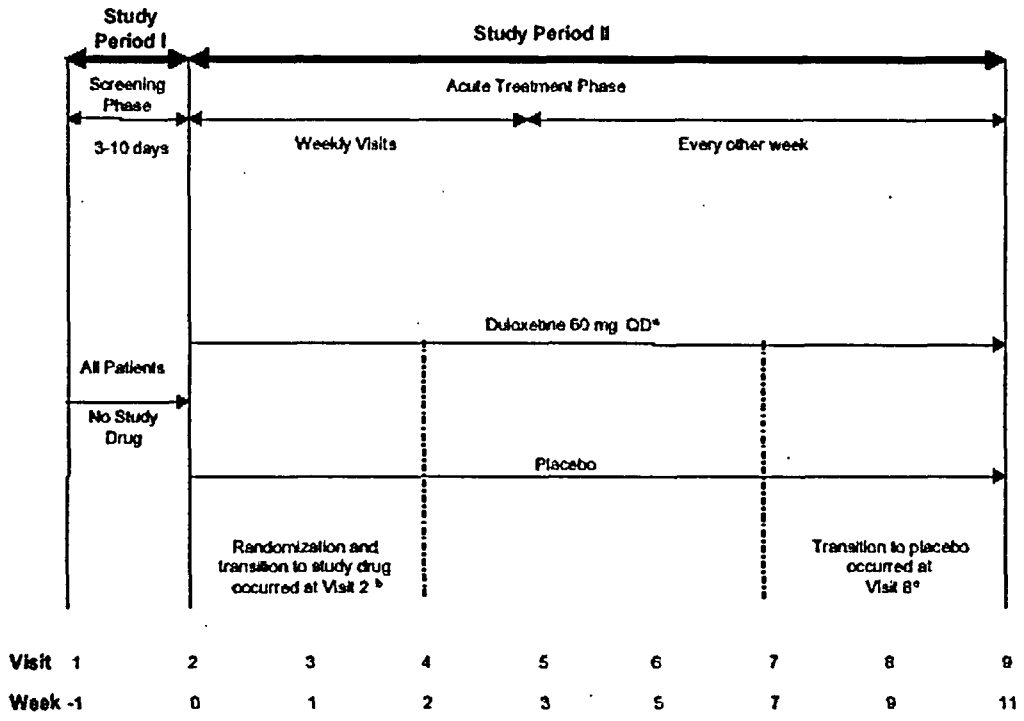
The study population of HMBH (a) and (b)was to include outpatients aged at least 18 years with a primary diagnosis of major depression as defined by the DSM-IV, and confirmed by use of the Mini International Neuropsychiatric Interview (MINI). Patients were required to have a 17-Item Hamilton Depression Rating Scale (HAMD17) total score $\geq$15 and a Clinical Global Impressions of Severity Scale (CGI-Severity) total score $\geq$4 at both screening and baseline (Visits 1 and 2). The inclusion criteria for protocol HMBH is identical to HMAT. The exclusion criteria for HMBH has only minor editorial differences with HMAT. Please refer to the inclusion/exclusion criteria for HMAT in the appendix.

C-3 D Design

This study was comprised of two identical, parallel, double-blind, placebo-controlled studies [groups (a) and (b)] of 480 enrolled patients (240 enrolled patients per study) who met the (DSM-IV) diagnostic criteria for major depressive disorder. Patients who met entry criteria in Study Period I (1-week screening phase) were randomly assigned to receive either duloxetine 60 mg once daily (QD) or placebo. Following the screening phase, patients were treated in a double-blind manner for 11 weeks (Study Period II).

This study design employed double-blind, pseudo-variable-duration placebo lead-in and lead-out periods to blind patients and investigators to the start and end of active therapy. In other words the protocol stated that patients would begin double blind therapy sometime between visit 2 (week 0) and visit 4 (week 2) but in truth, all patients started receiving active treatment at visit 2. Likewise, all patients began tapering active treatment at visit 8 (week 9). This maneuver was performed with the goal of decreasing the chance of investigators' bias toward rating patients as more depressed at study entry so that they would meet entry criteria. There were no circumstances to the sponsors knowledge under which investigators or site personnel knew the complete details of the study design.

A schematic representation of the study design follows in Figure C-3.D.



[a] Patients who had difficulty tolerating duloxetine 60 mg QD (three capsules) may, at the investigator's discretion, have had the number of capsules reduced to the equivalent of 40 mg QD (two capsules) at any time up to Visit 5. Investigator should have attempted to escalate dose back to 60 mg QD within 3 days. Dose must have returned to 60 mg QD after Visit5.
[b] Investigators were told that transition to study drug could occur anytime between Visits 2 and 4. Randomization actually occurred at Visit 2 for all patients.
[c] Investigators were told that subjects could be switched from active treatment to placebo between Visits 7 and 9. All patients actually transitioned to placebo starting at Visit 8 (Week 9).

C-3.E Assessments for Protocol HMBH

The primary efficacy variable was the HAM-D_{17} change from baseline to endpoint versus placebo in the ITT patient population. A schedule of events in the appendix (table C-3.E) gives a detailed listing of assessments and when they were performed.

C-3.F Patient Disposition in Study HMBH group(a)

A total of 341 patients were screened for the study. Of these 341 patients, a total of 96 patients failed to meet entry criteria or declined to participate in the study. The remaining 245 patients were randomized to either placebo or duloxetine at Visit 2. There were no deaths. There were three serious adverse events (pneumonia, emphysema, and hernia) none of which were likely to be drug related.

Table C-3.F.1 Reasons for Discontinuation in Study HMBH group (a)

Primary Reason for Discontinuation	Placebo (N=122) n (%)	DLX 60 QD (N=123) n (%)	Total (N=245) n (%)	p-Value*
Adverse event	3 (2.5)	17 (13.8)	20 (8.2)	**.002**
Lack of efficacy, patient and physician perception	10 (8.2)	4 (3.3)	14 (5.7)	.107
Unable to contact patient (lost to follow-up)	9 (7.4)	8 (6.5)	17 (6.9)	.807
Personal conflict or other patient decision	9 (7.4)	10 (8.1)	19 (7.8)	1.00
Physician decision	1 (0.8)	1 (0.8)	2 (0.8)	
Protocol Violation	4 (3.3)	3 (2.4)	7 (2.9)	.722
Patients completing	86 (70.5)	80 (65.0)	166 (67.8)	.413

* Fisher's Exact Test

Significantly more patients in the duloxetine 60-mg QD group discontinued due to adverse events in group (a).

C-3 G Baseline Demographics/Severity of Illness

There were no significant differences between the two treatment groups in age, gender, origin, weight, or height. Patients had a mean age of 42 years, with the majority being Caucasian and female. Table C-3.G in the appendix gives a detailed overview of demographic characteristics of patients in HMBH(a).

There was one difference in treatment groups with respect to psychiatric history. Of the patients with recurrent episodes of depression, the mean time between episodes was significantly shorter in the duloxetine treatment group (62 weeks versus 157 weeks in the placebo group). There were no significant group mean differences in baseline HAM-D_{17} or CGI. This difference does is not likely to bias the study in favor of duloxetine.

C-3.H Concomitant Medications

Generally speaking concomitant psychotropic drugs were not allowed. There were no significant differences in the types or amounts of concomitant medications used with the exception of zolpidem being used by 10 (8%) of placebo patients versus 4 (3%) of duloxetine patients. This difference is not likely to bias the study results in favor of duloxetine.

C-3.I Efficacy Results

The repeated measures analysis of the change from baseline to endpoint HAM-D17 total score of the ITT population was primary efficacy analysis. This analysis demonstrated significantly greater decrease in the HAM-D 17 total score in the duloxetine 60-mg QD patient group over placebo. LOCF and OC analyses replicated the results of the repeated measures analysis.

Table C-3.I.1 HAM-D_{17} Total Score Repeated Measures Analysis

Therapy	Visit(Weeks of Treatment)	N	LSMean	LS Mean Change	SE	p-value vs. 1)
1)Placebo	3(1)	115	18.77	-2.50	0.37	
2)DLX 60 QD		121	18.37	-2.89	0.36	.435
1)Placebo	4(2)	110	17.87	-3.39	0.50	
2)DLX 60 QD		112	15.55	-5.72	0.49	<.001
1)Placebo	5(3)	103	16.69	-4.58	0.54	
2)DLX 60 QD		105	13.90	-7.37	0.53	<.001
1)Placebo	6(5)	101	15.53	-5.74	0.60	
2)DLX 60 QD		100	12.50	-8.76	0.60	<.001
1)Placebo	7(7)	93	15.45	-5.82	0.65	
2)DLX 60 QD		91	11.33	-9.93	0.64	<.001
1)Placebo	8(9)	89	15.21	-6.05	0.69	
2)DLX 60 QD		84	10.35	-10.91	0.70	<.001

Table C-3.I.2 LOCF Mean Change HAM-D_{17} from Baseline Analysis of HMBH(a)

	Baseline					Endpoint					Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	p-value vs Placebo
1) Placebo	115	21.09	3.71	21.0			15.93	7.04	16.0			-5.16	6.91	-5.0			
2) DLX 60 QD	121	21.50	4.10	21.0			12.25	7.65	11.0			-9.25	7.27	-9.0			**<0.001**

C-3.J Efficacy Conclusions for Study HMBH Group(a)

Based on the results of the two different analytical approaches to the primary efficacy variable I conclude that study HMBH group(a) represents a positive study. The sponsor claims that the decision to switch sites 101 and 122 to group (b) was to bolster the enrollment of group(b). Since group (b) also produced positive results it is difficult to create a scenario where these site changes to group (b) would bias study group(a) in a positive way.

C-4 F1J-MC-HMBH Group (b) Duloxetine Once-Daily Dosing Versus Placebo in the Acute Treatment of Major Depression

A listing of investigators, sites, and the number of patients enrolled at each site for study HMBH group(b) in listed in the appendix in table C. The objectives, design, study population, and schedule of assessments are identical to group(a); descriptions of these may be be found in subsection C-3.B through E.

Sites 101 and 122 were switched from study group A to study group B. Study group (a) was over enrollment quotas while group (b) was not meeting enrollment projections. The sites were changed to balance enrollment in the studies and were performed before any study data was unblinded. Because of this switch these two sites were visited by the Division of Scientific Investigations for routine audit of records as part of this NDA review.

C-4 A. Patient Disposition in Study HMBH group(b)

A total of 367 patients entered the screening phase of the study. Of these 367 patients, a total of 100 patients failed to meet entry criteria or declined to participate in the study. The remaining 267 patients were randomized to placebo or duloxetine 60 mg QD. Study sites 101 and 122 contributed 75 patients (n=37-duloxetine 60-mg and 38-placebo) to study group (b).

The following table enumerates reasons for dropout in study group(b).

Table C-4.A Reasons for Discontinuation in study HMBH group (b)

Primary Reason for Discontinuation	Placebo (N=139) n (%)	DLX 60 QD (N=128) n (%)	Total (N=267) n (%)	p-Value*
Adverse event	6 (4.3)	16 (12.5)	22 (8.2)	.024
Lack of efficacy, patient and physician perception	19 (13.7)	7 (5.5)	26 (9.7)	.037
Unable to contact patient (lost to follow-up)	13 (9.4)	12 (9.4)	25 (9.4)	1.00
Personal conflict or other patient decision	8 (5.8)	6 (4.7)	14 (5.2)	.787
Protocol violation	3 (2.2)	9 (7.0)	12 (4.5)	.075
Patients completing	90 (64.7)	78 (60.9)	168 (62.9)	.529

Noteworthy differences are evident in the dropout rate due to adverse events, lack of efficacy, and protocol violation. Results from LOCF analysis shall be helpful in examining the effects of these patient dropouts on the study results.

C-4.B Baseline Demographics/Severity of Illness

The majority of patients were Caucasian and female with a mean age of 41 years. There were no significant differences in weight, age, sex, height, age of onset of symptoms, duration of the current depressive episode, number of total episodes of depression, or baseline rating scale scores on primary and secondary efficacy scales.

C-4.C Efficacy Results for HMBH group(b)

Duloxetine treated patients showed significant improvement in HAM-D 17 total score by both repeated measures and LOCF mean change from baseline analysis. Tables C-4.C 1 and 2 respectively demonstrate the results of these analyses.

Table C-4.C.1 Repeated Measures Analysis of HAM-D 17 Total Score Change from Baseline for Study HBMH group(b)

Therapy	Visit (Weeks of treatment)	N	LS Mean	LS Mean Change	SE	p-value vs. placebo
Placebo	3(1)	136	17.83	-2.64	0.36	
DLX 60 QD		123	17.58	-2.89	0.38	.601
Placebo	4(2)	129	16.05	-4.43	0.45	
DLX 60 QD		109	14.93	-5.54	0.48	.071
Placebo	5(3)	122	14.42	-6.06	0.52	
DLX 60 QD		108	13.65	-6.82	0.55	.287
Placebo	6(5)	111	13.27	-7.20	0.62	
DLX 60 QD		98	11.89	-8.58	0.66	.116
Placebo	7(7)	97	12.78	-7.69	0.65	
DLX 60 QD		89	10.34	-10.14	0.69	.008
Placebo	8(9)	90	12.18	-8.29	0.67	
DLX 60 QD		81	10.01	-10.46	0.71	**.024**

Table C-4.C.2 LOCF Mean Change from Baseline to Endpoint of HAM-D 17 Total Score

		Baseline					Endpoint					Change					
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	p-value
Placebo	136	20.49	3.42	20.0			13.25	7.37	14.0			-7.24	7.79	-6.0			
DLX 60	123	20.28	3.32	20.0			11.37	7.12	10.0			-8.90	6.76	-10.0			**0.048**

These analyses produce results that are marginally positive. CGI-Severity scores do not show a significant change over placebo but are numerically superior (p=0.22). PGI was significantly positive in the LOCF and repeated measures analysis (p=0.025 and 0.014 respectively). LOCF mean change from baseline analyses of QLDS Score shows a significant improvement in the duloxetine treated group (p=0.032).

Conclusions on the Efficacy Results in Study HMBH group(b).

There are no data analyses presented without sites 101 and 122. It is doubtful that the study would produce positive results without these 75 additional patients provided by the two study sites. Therefore, addition of the two sites definitely contributes to the study's positive result; however, this does not appear to have been done in a biased or otherwise unreasonable fashion.

The results of this study are significantly in favor of duloxetine 60-mg/day over placebo as a treatment for Major Depression. There is not a marked difference between the LOCF and repeated measures analysis for the HAM-D 17 or PGI. The mean treatment effect for the duloxetine group is almost identical between groups (a) and (b) [group (a) duloxetine =-10.9 vs

group(b) duloxetine = –10.5] but the placebo group showed a –8.2 change in HAM-D versus -6.0 change. The duloxetine group did not outperform the placebo group with respect to CGI; however, the PGI and QLDS were significantly better in duloxetine treated patients over placebo patients. In the end, the study supports the sponsor's claim that duloxetine 60-mmg/day is effective in treating Major Depression. The results are very close to $p<0.05$ yet are positive.

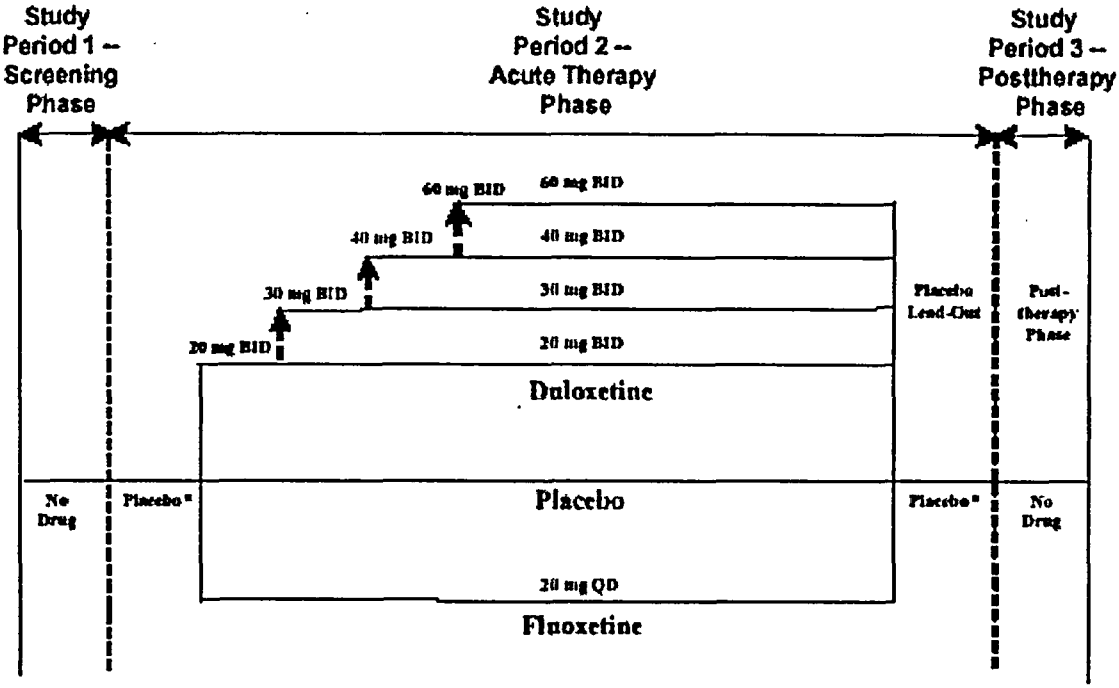
C-5 F1J-MC-HMAQ Duloxetine Versus Placebo in the Treatment of Major Depression groups (a) and (b). Like protocols HMAT and HMBH protocol HMAQ was divided into to study groups [likewise (a) and (b)]. Neither HMAQ (a) nor (b) produced significantly positive results. These studies are therefore reviewed together.

C-5.A Investigators and Sites are listed in table C in the appendix.

C-5.B Objectives
The primary objective was to demonstrate that duloxetine 20 mg to 60 mg twice daily was superior to placebo in the acute treatment of patients with DSM-IV–defined major depression.

C-5.C Study Population
The defined study population was the same as the populations studied under protocols HMAT and HMBH without any substantive differences. HMAQ included outpatients aged at least 18 years with a primary diagnosis of major depression as defined by the DSM-IV, and confirmed by use of the Mini International Neuropsychiatric Interview (MINI). Patients were required to have a 17-Item Hamilton Depression Rating Scale (HAMD17) total score $\geq$15 and a Clinical Global Impressions of Severity Scale (CGI-Severity) total score $\geq$4 at both screening and baseline (Visits 1 and 2). Please refer to the inclusion/exclusion criteria for HMAT in the appendix.

C-5.D Design of protocol HMAQ
These were two identical 8-week, placebo and fluoxetine controlled, double blind, parallel group, multicenter, flexible dose studies. Doses of duloxetine ranged from 20-mg to 60-mg BID. Fluoxetine was fixed at 20-mg/day. The following schematic represents the study design in protocol HMAQ.



			Randomization										
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13
Week	-2	-1	0	1	2	3	4	5	6	7	8	9	10

= Earliest visit at which dose may be escalated.

a- Patients and investigators were told that randomization could occur as early as Visit 2 and as late as Visit 4. All patients were actually given placebo from Visits 2 to 3, with randomization occurring at Visit 3 for all patients.
b- Patients and investigators were told that active therapy would continue until Visit 12. All patients actually entered a placebo lead-out from Visit 11 to Visit 12.

C-5.E Assessments
A schedule of assessments may be found in the appendix in table C-5.E. The primary efficacy variable was the mean change form baseline to endpoint of the clinical rated HAM-D 17 total score.

C-5.F.1 Patient Disposition in Study HMAQ group(a)
A total of 275 patients entered the screening phase of the study. Of these 275 patients, a total of 102 patients failed to meet entry criteria or declined to participate in the study. The remaining 173 patients were randomized to either placebo, duloxetine, or fluoxetine.

Reasons for dropping out before the of the study follow in table C-5.F.1.

Table C-5.F.1 Reasons for Discontinuation in Study HMAQ group (a)

Primary Reason for Discontinuation	Placebo (N=70) n (%)	Dulox (N=70) n (%)	Fluox (N=33) n (%)	Total (N=173) n (%)	p-Value*
Adverse event	3 (4.3)	7 (10.0)	1 (3.0)	11 (6.4)	.417
Lack of efficacy, patient and physician perception	10 (14.3)	2 (2.9)	3 (9.1)	15 (8.7)	.047
Unable to contact patient (lost to follow-up)	6 (8.6)	1 (1.4)	2 (6.1)	9 (5.2)	.147
Personal conflict or other patient decision	3 (4.3)	9 (12.9)	5 (15.2)	17 (9.8)	.099
Protocol Violation	2 (2.9)	5 (7.1)	1 (3.0)	8 (4.6)	.572
Patients completing	46 (65.7)	46 (65.7)	21 (63.6)	113 (65.3)	.956

C-5.F.2 Patient Disposition in Study HMAQ group(b)

A total of 308 patients entered the screening phase of the study. Of these 308 patients, a total of 114 patients failed to meet entry criteria or declined to participate in the study. The remaining 194 patients were randomized to one of three treatment groups: placebo, duloxetine, or fluoxetine.

Table C-5.F.2 Reasons for Discontinuation in Study HMAQ group (b)

Primary Reason for Discontinuation	**Placebo (N=75) n (%)**	**Dulox (N=82) n (%)**	**Fluox (N=37) n (%)**	**Total (N=194) n (%)**	**p-Value***
Adverse event	5 (6.7)	8 (9.8)	3 (8.1)	16 (8.2)	.839
Lack of efficacy, patient and physician perception	7 (9.3)	4 (4.9)	2 (5.4)	13 (6.7)	.566
Unable to contact patient (lost to follow up)	6 (8.0)	1 (1.2)	5 (13.5)	12 (6.2)	.015
Personal conflict or other patient decision	8 (10.7)	5 (6.1)	1 (2.7)	14 (7.2)	.334
Physician decision	1 (1.3)	1 (1.2)	0	2 (1.0)	
Protocol Violation	4 (5.3)	6 (7.3)	3 (8.1)	13 (6.7)	.807
Patients Completing	44 (58.7)	57 (69.5)	23 (62.2)	124 (63.9)	.354

C-5.G. Baseline Demographics/Severity of Illness for HMAQ groups (a) and (b)

There were no significant inter-group differences in baseline demographics, concomitant medication use, or severity of disease in either study group (a) or (b).

C-5.H. Efficacy Results and conclusions for HMAQ (a) and (b)

Neither study showed significant differences in groups treated with duloxetine or fluoxetine versus placebo. Results of the LOCF mean change from baseline of the HAM-D 17 total score may be found in the appendix in tables C-5.H.1 and 2.

Both studies showed smaller treatment effects than studies in HMAT and HMBH. Treatment changes in both placebo and active treatment were approximately 7 points while in HMAT(b) and HMBH duloxetine groups had changes of approximately 8-10 points in HAM-D_{17} total score in the face of placebo changes of 5-6 total points. There is no clear explanations for this differences in study outcomes. The study populations were nearly identical to protocols HMBH and HMAT. HMBH was a flexible dose study and was positive in both groups while the fixed dose study had mixed results, yet HMAQ, a flexible dose study with the same dose range as HMBH did not show separation from placebo. Fluoxetine did not separate from placebo in HMAQ groups. Therefore these studies represent failed studies as opposed to negative studies.

D. Efficacy Conclusions

The sponsor presents six well designed and adequately controlled studies three of which provide evidence of efficacy. Studies HMAT (b), HMBH (a) and (b) show significant improvement over placebo in the HAM-D_{17} total score. Studies HMAT(a), HMAQ(a) and (b) are failed studies and do not provide adequate sensitivity to either argue for or against duloxetine's efficacy in the treatment of depression.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Duloxetine is adequately safe to use in the treatment of major depressive disorder. As with almost any drug, there are some adverse events that will not be tolerable for some patients. The adverse event profile for duloxetine appears to be similar to that of other SNRI drugs with some exceptions.

B. Description of Patient Exposure

A total of 2314 duloxetine patients were included in the primary safety database. 1032 of these patients were randomized to duloxetine in placebo-controlled trials in the primary safety database, and 1282 patients were enrolled in the open-label (uncontrolled) Study HMAU. 704 patients have received duloxetine for at least 180-days. 520 patients were exposed to duloxetine in study HMAU for 1 year or more. The 2314 patients in the primary safety database represent approximately 754 patient-years exposure to duloxetine.

In the combined primary and secondary databases 3490 patients were exposed to duloxetine therapy. The bulk of the long-term exposure at relevant doses was obtained in study HMAU. The HMAU final report was submitted with the 120-day safety update. It included the following exposure data.

Table VII. C.1 Duration and Extent of Exposure to Duloxetine in Study HMAU

Days on Therapy	No. Patients N=1279
0	3 (0.2)
>0 - <30	245 (19.2)
30 - <60	70 (5.5)
60 - <90	43 (3.4)
90 - <120	60 (4.7)
120 - <150	76 (5.9)
150 - <180	45 (3.5)
180 - <210	35 (2.7)
210 - <240	32 (2.5)
240 - <270	31 (2.4)
270 - <300	27 (2.1)
300 - <330	20 (1.6)
330 - <360	72 (5.6)
360 - <390	321 (25.1)
>=390	199 (15.6)
Modal Dose-mg (BID)	
>0 - <39	33 (2.6)
40 - <59	597 (46.8)
>=60	647 (50.7)
Unspecified	2

This exposure meets ICH guidelines.

C. Methods and Specific Findings of Safety Review

C-1. Methods of Review and Assignment of Studies to Primary and Secondary Safety Databases

The sponsor based the assignment of studies to either a primary or secondary safety database from an Agency guidance meeting of June 12, 2001. The primary safety database included duloxetine-treated patients from all completed double-blind (depression and stress urinary incontinence [SUI]) studies who remained on the therapeutically relevant dose range (40 to 120 mg/day) throughout the trial. Patients in the placebo and active comparator arms from these studies were also included in the primary safety database. A limited set of analyses excluding the SUI patients were done to ensure the results including SUI patients were appropriate for making inferences regarding the safety of duloxetine in patients with MDD. The primary safety database therefore includes patients from HMAQ (a) and (b), HMAT (a) and (b), HMBH (a) and (b), an interim data lock of open-label Study HMAU (all data reported through 6 April 2001) and SAAW for patients taking 40-mg/day and above.

The primary safety database was reviewed for deaths, serious adverse, events and adverse dropouts, both qualitatively on a case by case basis and quantitatively using pooled data from controlled clinical trials. A quantitative review of comparisons of trends in treatment related adverse events, changes in clinical labs, vital signs, and ECG was performed on pooled data from controlled studies.

The secondary safety database included patients from on-going studies (except HMAU), Japanese studies, clinical pharmacology studies, and studies (or treatment arms within a study) where patients did not remain on dosages within the therapeutically relevant dose range throughout the trial. The secondary safety database was reviewed on a qualitative case by case basis for deaths, serious adverse events and adverse dropouts.

C-2 Deaths

There were five total deaths in the entire duloxetine development program. Three occurred in duloxetine treated patients and two in imipramine treated patients. There were no deaths that were likely related to duloxetine treatment.

There were two deaths in the primary safety database; one of which was in the controlled trial population. Neither death was likely related to drug treatment. Patient 035- 4418 in study HMAT(a) was a 77-year old male who had a cardiopulmonary arrest 4-days after discontinuing duloxetine 40-mg BID. It is unlikely that this event was drug related. Patient 102-1208 in open-label study HMAU was struck by a train and subsequently died.

In the secondary safety database one duloxetine treated patient died. Patient A10301 completed suicide by jumping from her window. It is unlikely that this was a drug related event. Two patients in the imipramine treatment groups of Japanese studies died. Patient 4304 completed suicide by hanging and 4703, a 61 year-old female, died of pneumonia.

There were no deaths in the phase I studies.

C-3 Serious Adverse Events

There were four serious adverse events in the entire development program that I considered possibly drug related. These SAE occurred in the secondary database; therefore there are no quantitative comparisons with control groups to be made.

The adverse event of "liver function tests abnormal" for patient A09505 appears to be considered serious because it was associated with an overdose. This patient was enrolled in one of the Japanese studies. No quantitative lab data is available either in the report or in the translated CRF. There is no report of jaundice.

Likewise with patient E00301 no quantitative lab data was available in the report or the CRF. No jaundice was reported. Treatment related trends in liver function tests shall be discussed in the section of this review devoted to clinical laboratories.

Two serious cases of hypotension were reported. Treatment related trends in vital signs are discussed in the section devoted to vital signs in this review.

Possibly drug related SAEs in Secondary database of completed studies

F1J-MC-SBAW 102-6104	Dulox 40-mg BID	Orthostatic Hypotension	64 year-old Caucasian female, receiving Duloxetine 40 mg BID, was discontinued from the study on [redacted] due to the serious adverse event of orthostatic hypotension. Patient had a history of hypertension and had been treated with Atenolol, Lotrel, and Imdur since 1997. The patient first experienced orthostatic hypotension on [redacted], 6 days after receiving study drug. Patient was enrolled into study on 9-Aug-01. Patient went to the Emergency room on [redacted] complaining of weakness and nausea. Her blood pressure was 80/55. The patient was admitted to the hospital on [redacted] for orthostatic hypotension and discharged from the hospital on [redacted] The date of the patient's last dose of study drug was 14-Aug-01. The adverse event was reported as resolved on 18-Aug-01.
F1J-MC-SBAY 146-5604	Dulox 40 mg BID	Hypotension	78-year old white female patient in stress incontinence study was randomized on April 2001 and had a QTc of 532 msec on [redacted] but it was not noted by the visit nurse. The coordinator became aware of this on [redacted]. Patient was to stop study drug and have a repeat ECG. She had received 4 doses (2-days) of study drug when she contacted to stop taking study drug. Repeat ECG on [redacted] and her QTc was 470 msec. The patient was hospitalized for hypotension from [redacted] ·BP leading to hospitalization not available.
F1J-JE-321G A09505	30 mg	Liver Function Tests Abnormal	On 8 September 2000, 28 days after starting study drug, and in the middle of the month, the patient took large quantities of other drugs, including antidepressants, anti- anxiety agents and hypnotics. The treatment was discontinued on [redacted] when the site learned of this. (Patient took the study drug until [redacted]) A blood test on [redacted] showed elevated liver functions. Another blood test on [redacted] showed the event had improved. In the opinion of the investigator, the event was causally related to study drug because event improved following discontinuation; however, the investigator could not rule out causality to the large quantities of the other drugs that the patient had ingested.

Possibly drug related SAEs in Secondary database of completed studies

F1J-JE-324G E00301	10 mg	Depression, Tremor, ECG Abnormal, Abnormal Lab Value, Bilirubinemia	The patient was taking study drug from — to — — Seven days after starting drug (— the patient developed tremor. On — the patient couldn't stand up due to this symptom. On — the patient went to the hospital, study drug was discontinued, and the patient was admitted to the hospital due to worsening of depression. In the opinion of the investigator, tremor was not serious but was related to study drug. The patient experienced ST segment decrease on ECG, and abnormal lab value (elevated bilirubin, GPT, TC, BUN and ketonuria and hematuria) on — ST segment revealed normal upon re-assessment on — Lab value revealed normal upon re-assessment on — In the opinion of the investigator, ST segment decrease and abnormal lab value, excluding TC was not serious but related to study drug. The investigator further stated that the event of tremor might have been related to the washout of previously prescribed medications, which had been performed in accordance with the protocol procedures.

There were no serious adverse events (SAE) in the in the primary safety database that were likely to be drug related. Listings of the SAE for controlled trials may be found in table VII.C-3.1 and for the uncontrolled trial HMAU may be found in the appendix.

C-4 Adverse Events Leading to Study Dropout

Dropouts associated with adverse events were reviewed in all databases. Line listings of adverse dropouts were reviewed for adverse events of potential concern. The primary controlled safety database offered the opportunity to compare rates of occurrence of adverse dropouts with placebo. The following table provides an enumeration of adverse dropouts in the primary controlled-studies safety database.

Enumeration of dropouts due to adverse events where there were ≥ 2 more dropouts for any reason than for placebo in the primary placebo controlled safety database

Adverse Events	Placebo (N=723)		Duloxetine (N=1032)		P-value Fishers Exact Test (2 Tail)	P-value for General CMH Association
	n	(%)	n	(%)		
Total Patients Discontinued	36	(5.0)	151	(14.6)	<.001	<.001
Nausea	2	(0.3)	25	(2.4)	<.001	<.001
Dizziness (excluding vertigo)	1	(0.1)	11	(1.1)	.019	.032
Diarrhoea NOS	0	(0.0)	2	(0.2)	.515	.314
Somnolence	2	(0.3)	10	(1.0)	.138	.128
Insomnia NEC	1	(0.1)	8	(0.8)	.090	.099
Fatigue	1	(0.1)	6	(0.6)	.251	.150
Syncope	0	(0.0)	2	(0.2)	.515	.213
Sexual Dysfunction Grouped	0	(0.0)	10	(1.0)		
Anorgasmia	0	(0.0)	3	(0.3)	.273	.110
Ejaculation failure	0	(0.0)	3	(0.3)	.273	.083
Erectile disturbance	0	(0.0)	2	(0.2)	.515	.213
Impotence	0	(0.0)	2	(0.2)	.515	.223
Hypertension NOS	1	(0.1)	4	(0.4)	.654	.277
Blood pressure increased	0	(0.0)	2	(0.2)	.515	.314
Central nervous system stimulation NOS	0	(0.0)	2	(0.2)	.515	.227
Irritability	1	(0.1)	4	(0.4)	.654	.356
Feeling jittery	0	(0.0)	2	(0.2)	.515	.225
Palpitations	0	(0.0)	2	(0.2)	.515	.226
Anxiety NEC	0	(0.0)	3	(0.3)	.273	.117
Migraine NOS	0	(0.0)	2	(0.2)	.515	.158
Headache NOS	3	(0.4)	6	(0.6)	.744	.647

Adverse events in duloxetine treated patients that lead to dropout at a rate of >1% and at least twice the placebo rate were nausea, dizziness, somnolence and sexual dysfunction.

Adverse events leading to dropout in primary uncontrolled database where the event occurred at a rate of ≥1%

	(N=1282)	
	n	(%)
Total patients discontinued	196	(15.3)
Nausea	19	(1.5)
Somnolence	17	(1.3)
Vomiting NOS	12	(0.9)

There were 9 cases (0.7%) of some type of sexual dysfunction that lead to dropout in the primary uncontrolled database.

Cases of hypertension are of interest because this is a dose related adverse event for venlafaxine, a currently marketed SNRI. There were three dropouts due to hypertension in the secondary database. Visit-by-visit vital signs were obtained for these three cases. None appear to be drug related. Perturbations in blood pressure are not marked and blood pressure readings are more or less consistent from baseline to on drug conditions. Patients 002-1879 and 803-8101 had prior histories of hypertension. Though patient 049-2413 was ostensibly discontinued for hypertension the recorded blood pressures were all within the limits of normal. The site recorded "mild hypertension" on . ——— , but there was no recorded value. The patient terminated the study on 17 March 1999 and no vital signs were obtained.

Two patients dropped out due to elevated liver function tests (LFT). Neither patient became jaundiced or had an abnormal total bilirubin. Both patients exhibited a similar pattern of LFT elevation GGT approximately 2-7 times normal, ALT approximately three times normal, and AST no more than 1.5 times normal. Both patients had labs return to normal after the drug was discontinued; neither patient had positive work-ups for gall bladder disease or infectious hepatitis. This pattern is consistent with hepatic steatosis that most commonly occurs in association with heavier alcohol use and may be associated with drug hepatotoxicity.

Patient 912-9235 dropped out due to akathisia. He started "pacing 7-days after commencing duloxetine treatment. He paced at home and during the clinic visit. After stopping duloxetine he stopped pacing at home and was observed to not pace on the follow-up clinic visit. This event was likely to be drug related.

Patient 14449-403 experienced oliguria and dropped out of the study after7-days. This is of potential concern since duloxetine is used to treat urinary incontinence. Reboxetine another SNRI that is marketed in Europe is associated with urinary retention. Unfortunately concomitant

treatment with diphenhydramine, an agent with anticholinergic properties and associated urinary retention complicate this case and no conclusion can be drawn.

C-5 Special Searchs

C-5.A Treatment Emergent Self-directed Harm

The sponsor considered suicide attempt, suicidal ideation, and self-injurious ideation as "self-directed harm". These are events associated with depression and therefore can only be meaningfully explored only in the controlled database.

No patients in the placebo-controlled database attempted suicide. The incidence of suicide ideation and self-injurious ideation were 0.2% and 0.1% for duloxetine-treated patients and 0.3% and 0.0 for placebo-treated patients. In repeated measures analyses of mean change on HAMD item 3 (suicide), the duloxetine-treated groups had a significantly greater mean reduction (advantage) over the placebo groups in 4 of the 6 trials in MDD; the other two trials showed numerically greater reduction in item three scores that did not reach significance. There is no evidence for increased risk of self-directed harm with duloxetine treatment in this population.

C-5.B Treatment Emergent Changes in ECG

ECGs

A total of 75 subjects from single-dose studies and 89 subjects from multiple dose studies had ECG assessments in phase I studies. PK studies attempted to measure ECG and at tmax and steady state trough times(6 and 12 hours after dosing on a BID schedule).

Four single-dose studies, F1J-LC-HMAX, F1J-LC-HMBA, F1J-LC-HMBG, and F1J-LC-HMBJ, took ECG measurements pre- and post-dose of a single-dose administration of duloxetine. Studies F1J-LC-HMAP, F1J-FW-HMAR, F1J-LC-HMAZ, F1J-BD-HMBD, F1J-BD-HMBF, F1J-LC-HMBN, and F1J-BD-O001 measured ECGs at baseline or on placebo and during multiple dose treatment at steady state levels.

Distribution of subjects and dose levels over phase I multiple dose PK studies of duloxetine where ECG were measured

Study Identification	Number of Patients	Duloxetine dose regimen	Number of dosing days
HMAP	12	20 mg BID	7
		30 mg BID	7
		40 mg BID	6.5
HMAR	12	Duloxetine 20 mg to 80 mg, given twice daily for daily doses ranging from 40 mg to 160 mg	20
HMAZ	16	40 mg BID	6
		60 mg BID	15
HMBD	16	Duloxetine 60 mg BID	7.5
HMBF	10	Duloxetine 60 mg BID	4.5
HMBN	11	Duloxetine 60 mg QD and Duloxetine 60 mg BID	7.5
O001	12	Duloxetine 80 mg/day given in one single dose, or 120 mg/day given in two doses.	6.5
Total	89		

QTc was plotted against plasma concentration and a tendency toward decreased QTc (Fredericia) with increased plasma concentration was observed. QTc was also evaluated by dose group. There was no evidence for QTc increase even when using the Bazett correction in single or multiple dose phase I studies. Duloxetine leads to increases in heart rate with increasing dose (see section VII C-7) so that with the Bazett correction, QTc will more likely be overestimated. Given this overly conservative correction, neither single nor multiple dose PK studies at tmax produced a signal for QTc prolongation with duloxetine. More likely, the opposite appeared to be the case.

Post-baseline ECGs were collected only in studies HMAU, HMATa, and HMATb of the phase III controlled trial database.

Central Tendency

There were statistically significant changes in several ECG parameters in the controlled studies. QT and QRS changed in directions and quantities that were not of clinical concern. Mean Heart rate increased by 4.4 bpm versus placebo 0.9 bpm. This mean change is not of clinical significance.

Mean Changes in ECG Parameters for Duloxetine versus Placebo in Placebo Controlled Studies HMAT (a) and (b)

Variables Analyzed		Baseline			Change to Endpoint		- p-Values --	
	Therapy	n	Mean	SD	Mean	SD	Therapy Int*1	Pairwise *2
QT	PLA	75	377.32	42.95	-4.01	33.00	.020	
	DLX	143	380.00	40.43	-10.35	24.05	(.004)	.020
QTCB	PLA	75	403.55	27.28	0.69	21.68	.884	
	DLX	143	402.71	29.85	1.45	22.67	(.028)	.884
QTCF	PLA	75	394.56	29.13	-0.82	22.35	.202	
	DLX	143	395.00	30.21	-2.70	19.10	(.002)	.202
PR	PLA	75	153.31	33.72	-2.12	18.18	.676	
	DLX	142	152.61	26.71	-2.13	14.93	(.237)	.676
QRS	PLA	75	84.44	13.46	0.36	9.76	.064	
	DLX	143	84.20	11.62	-1.15	8.82	(.103)	.064
HR	PLA	75	70.56	13.03	0.93	10.37	.006	
	DLX	143	68.97	12.03	4.43	10.01	(.120)	.006

*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=inv., treatment, and interaction.
*2 Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
HR Heart Rate
PR PR Interval
QRS QRS Interval
QT Uncorrected QT Interval
QTCB Bazetts Corrected QT Interval
QTCF Fridericias Corrected Qt Interval

Baseline to Endpoint Changes in ECG Parameters in Open-Label Study HMAU

	Baseline			Endpoint			Change						
	N	Mean	SD	N	Mean	SD	N	Mean	SD	T	DF	Lower	Upper	P-
PR	127	153.0	21.3	114	147.9	18.5	114	-4.50	12.89	-3.73	113	-6.89	-2.11	<.001
QRS	127	84.29	9.82	114	84.27	11.1	114	-0.12	7.99	-0.16	113	-1.61	1.36	0.870
QT	127	397.3	33.3	114	393.5	28.8	114	-3.29	33.70	-1.04	113	-9.54	2.96	0.300
QTcB	127	418.2	17.8	114	421.0	21.6	114	2.79	20.11	1.48	113	-0.94	6.52	0.141
QTcF	127	411.1	17.8	114	411.6	19.1	114	0.71	19.71	0.39	113	-2.94	4.37	0.700

Analysis for Outliers

Limits for the PCS values for the QTc intervals were any postbaseline value >450 msec for males or >470 msec for females, with an increase in QTc of >30 msec from baseline.

No patients met this PCS criteria for QTc in studies HMAT (a & b), so a second analysis was conducted in which patients were identified as having an abnormal increase if the change from baseline was >30 msec. In this analysis 4.2% of duloxetine-treated patients had abnormal increases compared with 5.3% of placebo-treated patients.

In study HMAU (uncontrolled) two patients (N=127) met the outlier criteria. Neither experienced any clinical symptoms.

Patients Meeting Outlier Criteria in HMAU

Site	Patient	Therapy	Age	Gender	Visit	QTCF	QTCB
131	5102	Duloxetine	59.9	F	1	430.9	447
					6	403.3	422
					13	488.1	521
	5145	Duloxetine	43.6	M	1	423.3	431
					6	350.7	367
					13	467.4	479

There is no indication that duloxetine leads to clinically significant changes in ECG or risk of serious arrhythmia. There was a statistically significant mean increase in heart rate in duloxetine treated patients but there was not a disproportionate increased rate of PCS heart rates in duloxetine treated patients.

C-5.C Treatment Emergent Changes in Blood Pressure

Venlafaxine, another SNRI is associated with hypertension in a dose dependent fashion. It is for this reason that treatment related changes in blood pressure is a special safety topic in this review.

There were two cases of hypotension in the secondary safety database that were considered serious and likely to be drug related. The following table enumerates the dropouts in the placebo controlled primary database due to blood pressure related events (regardless of their causal likelihood).

Table C-5.C.1 Dropouts in the Placebo Controlled Primary Database Due to Blood Pressure Related Events

Event	Placebo (N=723)	Duloxetine (N=1032)	P-value Fishers Exact Test (2 Tail)
Hypertension NOS	1 (0.1)	4 (0.4)	.654
Blood pressure increased	0 (0.0)	2 (0.2)	.515
Syncope	0 (0.0)	2 (0.2)	.515

Table C-5.C.2 enumerates blood pressure related treatment adverse events in the placebo controlled primary safety database regardless of the causal likelihood.

Table C-5.C.2 Blood Pressure Related Treatment Adverse Events in the Placebo Controlled Primary Safety Database

Event	Placebo (N=723)	Duloxetine (N=1032)	P-value Fishers Exact Test (2 Tail)
Hypertension NOS	7 (1.0)	8 (0.8)	.793
Hypotension NOS	0 (0.0)	2 (0.2)	.515
Postural hypotension	0 (0.0)	1 (0.1)	1.00
Blood pressure increased	3 (0.4)	12 (1.2)	.117
Syncope	0 (0.0)	6 (0.6)	.046

Mean changes in blood pressures associated with duloxetine treatment do not show trends toward decreases, in fact they show small and consistent but clinically insignificant increases when compared to placebo treated patients.

Table C-5.C.3 Mean Changes in Blood Pressure with Duloxetine Treatment in the Placebo Controlled Primary Safety Database

Variables	Therapy	n	Mean	SD	Mean Change	SD
Systolic BP						
Standing	Placebo	138	117.870	12.990	-0.754	10.086
	Duloxetine Forced Titration	149	119.322	14.651	1.611	11.783
Supine	Placebo	698	120.497	13.672	-1.372	12.059
	Duloxetine 20-mg bid	305	119.357	13.937	0.210	12.435
	Duloxetine 60-mg qd	244	122.090	13.135	0.344	12.527
	Duloxetine 40-mg bid	299	119.946	13.643	2.344	13.183
	Duloxetine Forced Titration	149	121.732	13.786	2.295	11.787
Diastolic BP						
Standing	Placebo	138	76.746	9.095	-0.428	7.994
	Duloxetine Forced Titration	149	78.208	8.962	1.470	8.538
Supine	Placebo	698	74.903	9.998	0.175	8.809
	Duloxetine 20-mg bid	305	74.882	8.884	1.275	8.456
	Duloxetine 60-mg qd	244	75.152	9.624	1.299	9.922
	Duloxetine 40-mg bid	299	76.304	9.128	1.318	8.414
	Duloxetine Forced Titration	149	76.510	8.815	1.644	8.752

Patients had potentially clinically significant (PCS) changes in blood pressure at roughly equivalent rates. The rates at which placebo patients had PCS low standing diastolic BP was numerically greater than in the duloxetine treatment groups 2.2 vs 0.7% but standing systolic BP occurred numerically more often in the duloxetine groups than in the placebo group (2.1 vs. 1.4%). PCS criteria and rates of PCS occurrence may be found in the appendix in table C-5.C.4.

The rate of treatment related elevated blood pressure was greater in the duloxetine treated patients and appears to increase in a dose dependent fashion (Table C-5.C.5). Elevated blood pressure did not require as high a value as the PCS criteria and was defined as systolic BP $\geq$140 and an increase of $\geq$10-mmHg and diastolic $\geq$90 and an increase of $\geq$10-mmHg.

Table C-5.C.5 Treatment Emergent Elevated Blood Pressure in the Primary Placebo Controlled Safety Database

		Placebo			Duloxetine (mg/day)											
					40			60			80			120		
Vital Statistic	Direction	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
Supine Diastolic BP	High	654	53	8	289	36	13	226	29	13	272	25	9	135	25	19
Supine Systolic BP	High	627	59	9	284	41	14	216	36	17	273	41	15	135	33	24

In summary, there are at least two cases of hypotension that appear to be drug related; however, other cases had extenuating circumstances associated with treatment that make me doubt that duloxetine was causally related. Hypotension does not appear to be common or dose related. The occurrence rates for potentially clinically significant hypotension and hypertension are roughly equivalent between placebo and duloxetine. Mild hypertension, on the other hand, appears to be common and dose dependent. Since duloxetine will probably be given chronically, I that recommendations for monitoring patients' blood pressures over time be placed in product labeling.

C-5.D Urinary Retention

Duloxetine is under development for the treatment of urinary incontinence in women. Another SNRI marketed in Europe but not currently marketed in the US, reboxetine, is associated with urinary retention in men. Based on this, I chose to specifically examine the data for reports of urinary retention. The primary controlled database was searched for reports of adverse event terms that might be associated with urinary retention or prostatic hypertrophy.

Table C-5.D Spontaneously reported adverse events of perceived disruption of urinary flow in the primary placebo controlled database (not corrected for sex)

	Placebo N=723		Duloxetine N=1032		p-value Fisher's Exact
Event	n	%	n	%	
Difficulty in micturition	0	(0.0)	5	(0.5)	.082
Urinary hesitation	0	(0.0)	5	(0.5)	.082
Urinary retention	0	(0.0)	2	(0.2)	.515

The two cases of urinary retention were rated as mild one in occurred in the 40-mg/day group and the other in the 60-mg/day group with no reports on the 80 or 120-mg/day groups. 14/1282 (1%) patients in the uncontrolled primary safety database reported urinary retention.
5 were rated as mild, 7 as moderate and 2 as severe. There was only one dropout because of urinary retention (patient 300-3005) but this was a placebo treated patient.

In Study F1J-MC-SAAI: Duloxetine Hydrochloride Versus Placebo in Patients with Irritative Symptoms of Benign Prostatic Hyperplasia (BPH), there was only one dropout due to urinary retention in 69 males treated with duloxetine for 4-weeks. Treatment-emergent adverse events occurring in at least 5% of duloxetine-treated patients were abnormal ejaculation, diarrhea, dizziness, and somnolence.

There is a small signal for urinary retention with duloxetine treatment. There is no evidence for dose dependence. Generally speaking, patients with BPH tolerated the drug fairly well. This was a small but pertinent study because this group is at a high risk for urinary retention.

C-5.E Discontinuation-Emergent Adverse Events

C-5.E.1 Dropouts During Placebo Lead-out Phase

699 duloxetine treated patients and 492 placebo patients were followed after discontinuation in placebo controlled studies. Only one placebo treated patient dropped out during this lead-out phase versus 17 duloxetine treated patients. Patients were discontinued from their treatments without tapering. The following table enumerates reasons for discontinuation.

Table C-5.E.1 Reason for Dropout During Placebo Controlled Lead-out

	Placebo N=492		Duloxetine N=699		Fisher's Exact
	N	%	N	%	p-value
Total Patients	**1**	**(0.2)**	**17**	**(2.4)**	**.001**
Dizziness (exc vertigo)	0	(0.0)	4	(0.6)	.147
Irritability	0	(0.0)	2	(0.3)	.515
Abdominal pain upper	0	(0.0)	1	(0.1)	1.00
Abnormal dreams	0	(0.0)	1	(0.1)	1.00
Anxiety NEC	0	(0.0)	1	(0.1)	1.00
Diarrhoea NOS	0	(0.0)	1	(0.1)	1.00
Dizziness postural	0	(0.0)	1	(0.1)	1.00
Headache NOS	0	(0.0)	1	(0.1)	1.00
Hypertension NOS	0	(0.0)	1	(0.1)	1.00
Muscle weakness NOS	0	(0.0)	1	(0.1)	1.00
Nausea	0	(0.0)	1	(0.1)	1.00
Paraesthesia NEC	0	(0.0)	1	(0.1)	1.00

Table C-5.E.2. enumerates the rates of drug-discontinuation emergent adverse events in the placebo controlled primary database.

Table C-5.E.2 Adverse Events Associated with Discontinuation
(Occuring >1% and at least twice placebo)

	Placebo (N=492)		Duloxetine (N=699)		P-value Fishers Exact Test (2 Tail)
	n	(%)	n	(%)	
Dizziness (exc vertigo)	3	(0.6)	69	(9.9)	<.001
Nausea	3	(0.6)	33	(4.7)	<.001
Headache NOS	6	(1.2)	30	(4.3)	.002
Paraesthesia NEC	1	(0.2)	17	(2.4)	.001
Insomnia NEC	3	(0.6)	14	(2.0)	.050
Diarrhoea NOS	3	(0.6)	13	(1.9)	.076
Vomiting NOS	2	(0.4)	13	(1.9)	.033
Irritability	1	(0.2)	12	(1.7)	.019
Nightmare	0	(0.0)	10	(1.4)	.007
Vertigo NEC	0	(0.0)	10	(1.4)	.007
Fatigue	3	(0.6)	9	(1.3)	.378
Sweating increased	1	(0.2)	8	(1.1)	.090
Flatulence	1	(0.2)	7	(1.0)	.150
Somnolence	0	(0.0)	7	(1.0)	.046
Tinnitus	1	(0.2)	7	(1.0)	.150

In study HMAP, 11 healthy volunteer men received placebo or escalating BID 20, 30, and 40-mg doses of duloxetine for one week. Duloxetine administration was generally well tolerated but associated with a small increase in recumbent systolic and diastolic blood pressure, and a small decrease in recumbent heart rate. Duloxetine had no clinically important effects on electrocardiograms or on cardiac intervals. No major effects of duloxetine on urine flow were observed. Mild withdrawal symptoms (e.g., insomnia and abnormal dreams) and a small increase in recumbent heart rate occurred in several subjects when duloxetine was abruptly discontinued at the end of the study. Based on this study the sponsor concluded that tapering the dose of duloxetine might be advisable when discontinuing from doses greater than 80 mg per day.

Conclusions Regarding Discontinuation
Discontinuing treatment with duloxetine is associated with symptoms that are qualitatively similar to other antidepressants such as SSRIs. Though no real comparative statements can be made about the intensity of withdrawal to SSRIs, it appears that the symptoms are relatively mild and reliably predictable for a significant minority of patients. Tapering duloxetine at discontinuation appears to be advisable for optimal patient comfort, but not tapering does not appear to pose any serious risk.

C-5.F Sexual Dysfunction
Most antidepressant medication has some effect on sexual function. It appears that duloxetine is not an exception. Table C-5.F.1 outlines these spontaneously reported adverse events. This data did not appear to be corrected for sex. Differences in spontaneous report rates of sexual