CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-733

MEDICAL REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE:	September 3, 2004
DRUG:	Cymbalta (duloxetine HCl, 20-, 30-, and 60-mg capsules)
NDA:	21-733
NDA Code:	Type 6P NDA
SPONSOR:	Eli Lilly and Company
INDICATION:	For the management of neuropathic pain associated with diabetic peripheral neuropathy

Eli Lilly and Company has submitted NDA 21-733 in support of marketing approval for Cymbalta, an orally administered reuptake inhibitor of both serotonin and norepinephrine. In addition to this application for the treatment of pain caused by diabetic peripheral neuropathy (DPN), Cymbalta has also been under development for the treatment of major depressive disorder, stress urinary incontinence and fibromylagia. The NDA for depression recently received marketing approval from the Division of Neuropharmacological Drug Products (DNDP). An application for stress urinary incontinence received an approvable action in August 2003

Review of the CMC, pharmacology and toxicology portions of this application were performed by the reviewers in DNDP during review of the depression application. The primary review of the clinical pharmacology and biopharmaceutics data in the application was also completed by DNDP. David Lee, Ph.D. and He Son, Ph.D. provided

additional review applicable to this application. A statistical review and evaluation was completed by Mahboob Sobhan, Ph.D. Consultation on this application was obtained from the Controlled Substances Staff, the Division of Drug Marketing, Advertisement and Communications, and the Office of Drug Safety.

The sponsor has submitted two studies (HMAW and HMAV) in support of efficacy. A detailed review of these studies and of the clinical safety data was performed by Howard Josefberg, M.D., with the supervision of Rigoberto Roca, M.D.

Efficacy:

Both Studies HMAW and HMAV were randomized, placebo-controlled, double-blind, multicenter trials that compared Cymbalta to placebo. Subjects at least 18 years of age with a clinical diagnosis of diabetic peripheral neuropathy for at least six months, a score of at least 3 on the Michigan Neuropathy Screening Instrument (MNSI) and a mean of at least 4 on an 11-point Likert scale of pain, were randomized to twelve weeks of treatment. In Study HMAW, subjects were randomized to Cymbalta 20 mg qd, 60 mg qd, or 60 mg bid, or placebo. Subjects randomized to the 60-mg bid group initiated treatment with 40 mg bid for 3 days before increasing to the 60-mg bid dose. In Study HMAV, subjects were randomized to Cymbalta 60 mg qd or 60 mg bid, or placebo. Subjects randomized to the 60-mg bid group initiated treatment with 60 mg qd for 3 days before increasing to the 60 mg qd dose. A maximum Hgb A1c of 12% was allowed for inclusion. After completing the double-blind period, subjects then became eligible for inclusion in a 52-week open-label extension study.

The primary efficacy outcome measure was the change from baseline to endpoint in the weekly mean score of the 24-hour average pain measure, collected in a daily diary by patients on an 11-point Likert scale (0 = no pain, 10 = worst pain imaginable). The outcomes were compared in two separate statistical analyses: 1) an ANCOVA model including terms for treatment, center, treatment-by-center interaction, and the baseline pain score; and 2) a likelihood-based, mixed-effects repeated measures model (MMRM). The sponsor employed a LOCF methodology for imputation of missing data in the ANCOVA analyses. The sponsor's MMRM analyses were essentially "evaluable analyses," as missing values were not imputed. Dr. Sobhan also performed analyses of the data using a more conservative Baseline Observation Carried Forward (BOCF) methodology at the request of the clinical review team.

Comparison between the 60-mg bid dose group and the placebo group was defined as the protocol-specified primary outcome in order to avoid adjustments for multiplicity. The ANCOVA analysis was specified as the primary analysis in HMAV and the MMRM in HMAW. The other pair-wise comparisons were considered to be supportive.

The secondary outcome measures included:

- Response (at least ≥30% reduction from baseline to endpoint) and sustained response (at least ≥30% reduction for at least 2 weeks and 20% reduction maintained between every week thereafter) rates.
- Weekly means of night and worst daily pain from the daily diary
- Brief pain Inventory (BPI) of Severity and Interference: Measured by patient on an ordinal scale ranging from 0 (no pain) to 10 (pain as bad as one can imagine).
- Clinical Global Impression of Severity (CGI-Severity): Administered by a physician investigator with score ranging from 1 (normal) to 7 (most severe illness).
- Patient Global Impression of Improvement (PGI-Improvement): Completed by the patient with a score ranging from 1 (normal) to 7 (most severe illness).
- Sensory portion of the Short-Form McGill Pain Questionnaire (SF-MPQ): Completed by the clinician using 11 pain descriptors with scores ranging from 0 (none) to 3 (severe).
- 36-item Short-Form Health Survey (SF-36)
- EQ-5D version of the Euro-Qol Questionnaire
- Resource Utilization Questionnaire
- Hamilton depression scale measuring depression symptom severity using 17-item scale score each ranging from 0 (no depression) to 52 (severely depressed).
- Beck Depression Inventory-II (BDI-II)
- Beck Anxiety Inventory (BAI)
- Allodynia Measures: Measuring a painful reaction to a normally non-painful stimulus.

Patient disposition is summarized in Dr. Sobhan's Table 3.1.4.1.

The results of the primary efficacy (ANCOVA) analyses are summarized in Dr. Sobhan's Table 3.1.4.2, reproduced below:

Table 3.1.4.2
Primary Efficacy: 24-hour Average Pain Score Change from Baseline to Endpoint: Intent-to-treat Population*

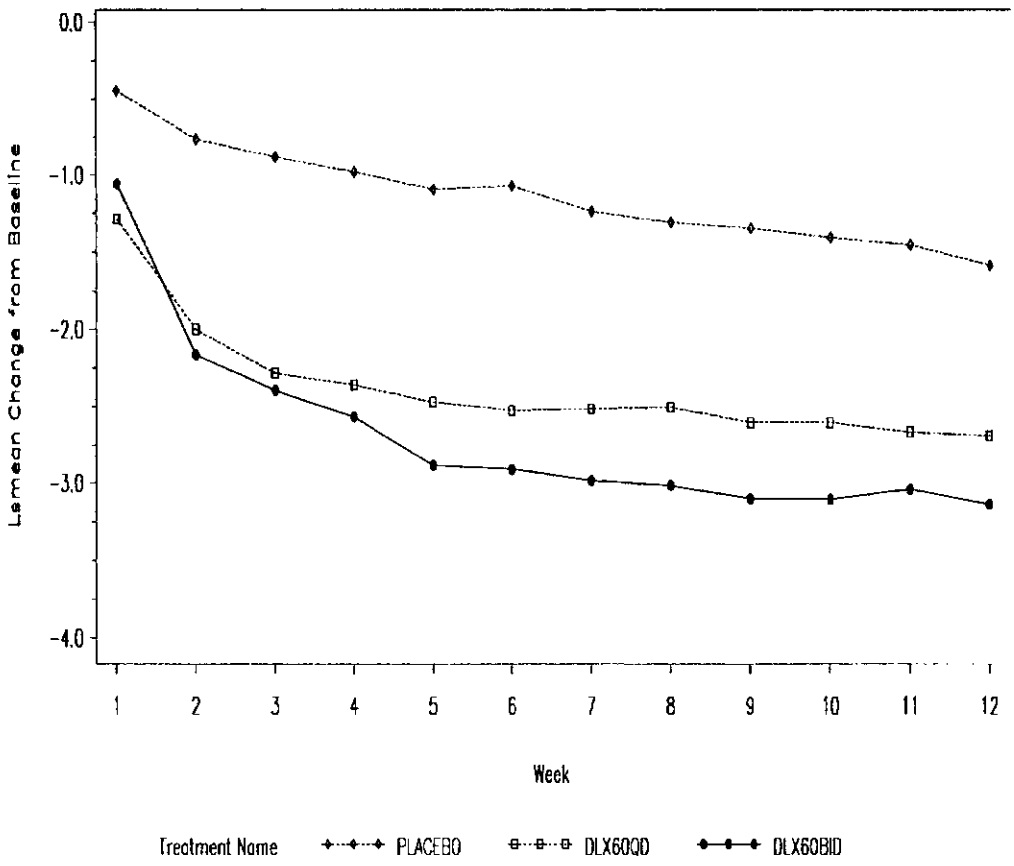
Study	Treatment Groups	N	24-Hour Average Pain Score			P-value (Pair-wise comparison)		
			Baseline Mean	LS Mean **	SE	Placebo vs. DLX20QD	Placebo vs. DLX60QD	Placebo vs. DLX60BID
HMAV	1) Placebo	106	5.8	-1.4	0.23			
	2) DLX60QD	110	6.1	-2.7	0.22	--	<.001	--
	3) DLX60BID	111	6.2	-2.8	0.23		--	<.001
HMAW	1) Placebo	111	5.7	-1.9	0.22			
	2) DLX20QD	111	5.8	-2.3	0.21	0.13	--	--
	3) DLX60QD	112	6.0	-2.9	0.22	--	<.001	--
	4) DLX60BID	109	5.8	-3.2	0.23	--	--	<.001

* Excluding patients with no post-baseline score and Last observation carried forward
** Estimates from ANCOVA model in Study HMAV and from Repeated Measures Analysis in Study HMAW
Source: Table HMAW 11.8, Page 87 and Table HMAV 11.9, Page 118

In both studies, Cymbalta 60 mg qd and 60 mg bid showed a statistically superior treatment effect compared to placebo (p-value less than 0.01). There was a statistically significant treatment-by-center interaction for one center in Study HMAV. However, this effect actually comprised no reduction in pain for the study drug group while pain for the placebo group was improved. Therefore, the overall treatment effect would not have been biased towards Cymbalta by this anomaly.

The results of the primary efficacy (MMRM) analyses are summarized in Dr. Sobhan's Figures HMVa 11.1 and HMAW.11.1 (copied from the sponsor's study reports), reproduced below:

Weekly 24-hour Average Pain Score
Least Square Mean Changes from Repeated Measures Analysis
All Randomized Patients
F1J-MC-HMAV(A) Acute Therapy Phase



Model: change from baseline in WKAVRGPS=THERAPY WEEK POOLINV THERAPY*WEEK BASELINE BASELINE*WEEK
Covariance Structure: Unstructured
Program: RMP.F1JSHMAV.SASPGM(PLAPSA1A) RMQCA700
Data: RMP.SAS.F1JM.L.MCHMAVSW.INTRIMA1

Figure HMAVa.11.1. 24-hour average pain score least-squares mean change from repeated measures analysis of change by visit for all randomized patients in acute therapy phase.

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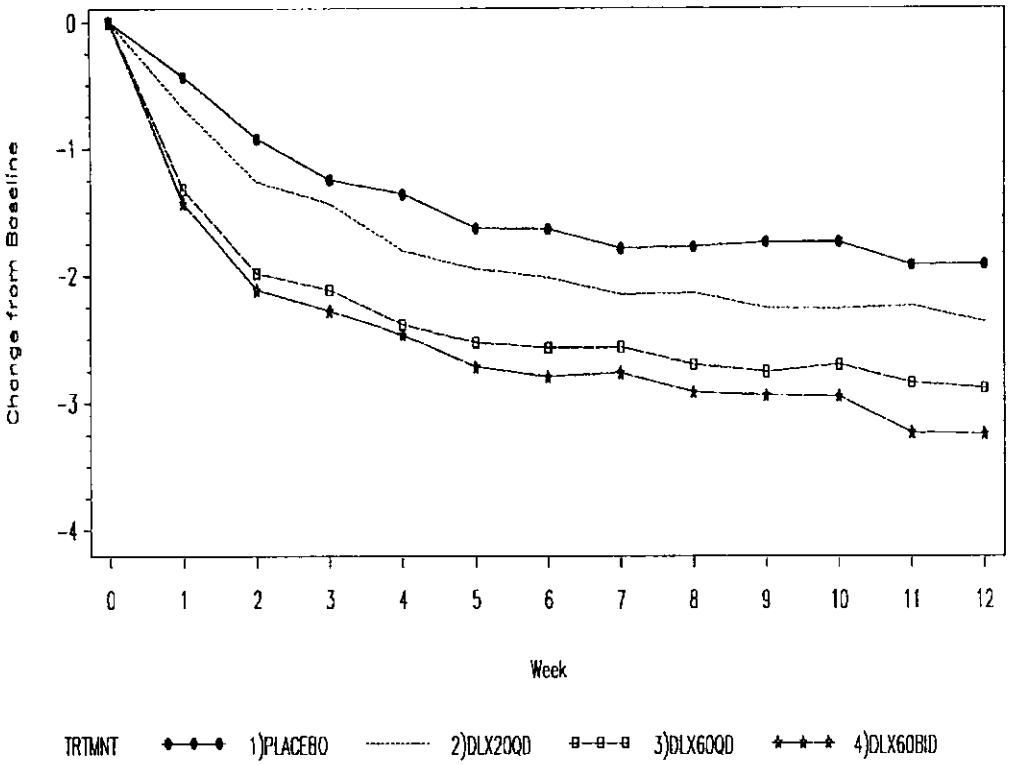
24 Hour Average Pain Severity
Plot of Least Square Mean Change from Baseline
All Randomized Patients
F1J-MC-HMAW Acute Therapy Phase



Model: change from baseline in VIAVRGPS=trtmnt poolinv visit trtmnt*visit basval basval*visit; cov. structure=UN
Note: At Week 0, value 0 was assigned
Program: RMP.F1JSHMAW.SASPGM(RMPLTS1A) QCA700
Data: RMP.SAS.F1JM.MCHMAWSW.INTRIM1

Figure HMAW.11.1. Plot of mean change on 24-hour average pain severity for all randomized patients in acute therapy phase of Study HMAW.

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These MMRM analyses also showed statistically significant treatment effects for Cymbalta 60 mg qd and 60 mg bid at all weeks of treatment for both studies.

Dr. Sobhan's analyses using the BOCF methodology for imputation of missing data confirmed the results of the sponsor's analyses for both the ANCOVA and MMRM assessments.

Pairwise comparisons of Cymbalta 20 mg qd and placebo did not show statistical significance by any of the analyses. In addition, no statistically significant additional efficacy was demonstrated for Cymbalta 60 mg bid when compared to 60 mg qd.

The sponsor also performed a series of post-hoc responder analyses. Response was defined as a 30% reduction in pain during the double-blind period, and sustained response as a 30% reduction from baseline to endpoint, with a corresponding 30% reduction from baseline at a visit at least 2 weeks prior to the last visit and at least a 20% reduction maintained at every visit in-between. The results of these analyses are summarized in Dr. Sobhan's Table 3.1.4.3. A greater percentage of subjects achieved responder status in the Cymbalta 60-mg bid and 60-mg qd groups compared to the placebo group. The differences were statistically significant.

The results of the sponsor's secondary analyses are summarized in Dr. Sobhan's Table 3.1.4.4. These analyses were generally supportive of the primary analyses.

Clinical Safety:

Across all indications, 8447 subjects were exposed to at least one dose of Cymbalta. In the DPN development program, 1074 subjects were exposed to at least one dose of Cymbalta. As of March 1, 2004, 484 subjects were exposed for greater than or equal to six months and 158 were exposed for greater than or equal to 12 months. The table on page 93 of Dr. Josefberg's review summarizes the dose by exposure data for all DPN studies. Four hundred eighty-four subjects were exposed to a 120-mg total daily dose for greater than or equal to six months and 220 subjects were exposed to that dose for greater than or equal to 12 months.

The approved labeling for the major depression indication identifies the following safety concerns: elevation of serum transaminases, increases in blood pressure, the potential for hydrolysis of the active ingredient to naphthol in patients with slow gastric emptying, mydriasis in patients at risk for narrow-angle glaucoma, and potential drug-drug interactions with CYP1A2 and CYP2D6 inhibitors.

Twenty-one Cymbalta-exposed subjects died during the development program. None of these deaths were assessed as likely to be drug related by the clinical review team. While there was an increased incidence of deaths in the DPN population, the majority of those

subjects died due to cardiac causes not uncommon in this population. One subject in a high-dose, clinical pharmacology study committed suicide. Based on this subject's psychiatric history and other confidential information, the DNDP clinical review team assessed this death as not related to exposure to Cymbalta.

Three percent of all Cymbalta-exposed subjects experienced a serious adverse event. In the DPN studies, 9% of the Cymbalta-exposed subjects experienced a serious adverse event. In the DPN controlled clinical trials, 3.3% of Cymbalta-exposed subjects and 4.5% of placebo-exposed subjects experienced a serious adverse event. The most common serious adverse events in Cymbalta-treated subjects in the DPN controlled trials that occurred with a frequency greater than placebo occurred in only one or two patients (per each event), and the majority were either expected in this patient population or unlikely to be related to drug exposure. There were one or two events each of hip fracture, ankle fracture, femur fracture, fall, traffic accident and concussion, raising the possibility that the CNS-related side effects of Cymbalta increase the risk of falls, injuries and accidents. However, the numbers were small and the overall adverse event data does not support this notion. The most common serious adverse events occurring in the DPN population of all Cymbalta-exposed subjects are listed in the table on page 102 of Dr. Josefberg's review. None of these events occurred with an incidence greater than 0.7%, and none were unexpected in this patient population.

The frequency of discontinuation due to adverse events in the overall DPN population (19.4%) was similar to the frequency in the overall, all-indications database (18.5%). In the placebo-controlled DPN trials, the frequency of discontinuation due to adverse events was 14% for the Cymbalta-treated subjects and less than 7% for the placebo-treated subjects. The most common adverse events (occurring in 1% or greater of subjects) resulting in study discontinuation in the DPN population of all Cymbalta-exposed subjects were: nausea (3%), dizziness (2%), somnolence (1%) and fatigue (1%). The most common adverse events resulting in discontinuation in the controlled clinical trials were nausea, dizziness and somnolence. The table on page 105 of Dr. Josefberg's review summarizes these data by dose group.

In the DPN population of all Cymbalta-exposed subjects, 92.5% of patients experienced an adverse event. Events reported with an incidence of greater than or equal to 5% in this population included: nausea, somnolence, dizziness, insomnia, constipation, diarrhea, fatigue, dry mouth, hyperhidrosis, decreased appetite, asthenia and anorexia. In the placebo-controlled trials, 88% of the Cymbalta-treated subjects and 78% of the placebo-treated subjects experienced an adverse event. The most common adverse events in the Cymbalta-treated subjects in these trials were: nausea, somnolence, dizziness, insomnia, constipation, diarrhea, fatigue, dry mouth, hyperhidrosis, asthenia, decreased appetite and anorexia. The table on page 111 of Dr. Josefberg's review lists the incidences of these events by treatment arm.

Nonclinical Safety:

No significant new information was submitted to this application. The materials in this application included confirmatory pharmacology studies and pharmacokinetic data.

Biopharmaceutics:

The materials submitted were follow-up data from studies that were previously reviewed in either DNDP or DRUDP, correction of certain analyses from previously reviewed studies, conformational studies of in vitro metabolism, and information on studies that were prematurely discontinued. No additional data was submitted to this application that provided new insights into the clinical biopharmaceutics of Cymbalta.

Chemistry, Manufacturing and Controls:

No new data was submitted to this application.

Discussion

The clinical data submitted in this application clearly supports the sponsor's claim that Cymbalta is safe and effective as a treatment for the pain associated with diabetic peripheral neuropathy at a total daily dose of 60 mg. The development program also established that doses up to 120 mg per day are reasonably safe in patients with pain due to DPN. While a statistically significant increase in efficacy over the 60-mg dose was not demonstrated at a total daily dose of 120 mg, there was a clear trend of increasing efficacy noted from 20 mg qd through 120 mg qd.

An increasing incidence of adverse events was also noted as exposures increased from 20 mg qd to 120 mg qd. These increases in adverse events were not, however, of such clinical concern that they necessarily preclude use of the higher doses in all patients. Based on these results, it is appropriate to conclude that, as analgesic drug products are most frequently administered to patients based on a dosing paradigm that allows increases based on a reasonable balance of effectiveness and tolerance, it would not be inappropriate for Cymbalta to be prescribed within a range of doses that may provide efficacy and that are unlikely to result in clinically unacceptable levels of toxicity.

Thus, the product labeling for Cymbalta should allow some leeway for prescribers in choosing an appropriate dosing regimen for their patients. While the data from the studies submitted to this application will only allow clear assurance to those prescribers of efficacy at 60 mg qd, it would be imprudent to limit prescribing to that dose considering the highly variable pharmacokinetics of this product, the well-recognized

variability of pain patients in response to analgesic therapeutics, and the safety profile of the product, especially with respect to drug-drug and drug-disease interactions.

Certain specific safety concerns, particularly applicable to the diabetic patient population, must, however, be clearly addressed in the product labeling. Based on the pharmacokinetics of Cymbalta, patients with diabetes induced renal disease are likely to have higher levels of duloxetine exposure and, consequently, higher incidences of adverse events. Drug-drug interactions are likely to occur in patients exposed to CYP2D6 and CYP1A2 inhibitors concomitantly with duloxetine. The potential for alterations in gastric motility to disrupt the product's enteric coating and allow for rapid hydrolysis of the drug to the highly toxic metabolite naphthol is of particular concern in the diabetic population, especially those with peripheral neuropathy who may have also developed gastroparesis. In addition, patients with liver disease will likely be exposed to unacceptable levels of duloxetine even when treated with the approved doses of this product, and elevations in liver enzymes and possible hepatoxicity due to concomitant exposure to Cymbalta and alcohol were seen in the clinical studies. The agreed upon labeling includes adequate information to inform prescribers of these safety concerns, thus allowing us to determine that Cymbalta is safe and effective when used according to the approved labeling.

Action recommended by the Division: Approval

APPEARS THIS WAY
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Bob A. Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-733
Submission Code	N
Letter Date	03/23/04
Stamp Date	03/03/04
PDUFA Goal Date	09/03/04
Reviewer Name	Howard Josefberg, M.D.
Supervisory Review	Rigoberto Roca, M.D.
Review Completion Date	09/03/04
Established Name	Duloxetine hydrochloride
(Proposed) Trade Name	Cymbalta
Therapeutic Class	SSNRI
Applicant	Eli Lilly and Company
Priority Designation	Priority Review
Formulation	Oral Capsule
Proposed Dosing Regimen	60-mg QD —
Indication	Diabetic peripheral neuropathy
Intended Population	Adult

Table of Contents

ABBREVIATIONS

5-HT	5-hydroxytryptamine = serotonin
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BAI	Beck Anxiety Inventory
BDI - II	Beck Depression Inventory - II
BOCF	Baseline observation carried forward
BPI	Brief Pain Inventory
CFR	Code of Federal Regulations
CGI	Clinical Global Impression Scale (includes multiple subscales)
CMC	Chemistry, Manufacturing and Controls
CMH	Cochran Mantel-Haenszel chi-square
CPMP	Committee for Proprietary Medicinal Products
EMEA	European Agency for the Evaluation of Medicinal Products
HGA1c	Glycosylated hemoglobin
LS	Least-squares
LTSDB	Long-term safety database
LOCF	Last observation carried forward
DACCADP	Division of Anesthetic, Critical Care and Addiction Drug Products
DAADP	Division of Anti-Inflammatory and Analgesic Drug Products
DLX	Duloxetine
DM	Diabetes mellitus
DNDP	Division of Neuropharmacologic Drug Products
DPN	Diabetic peripheral neuropathy (abbreviated as DNP by Lilly)
DRUDP	Division of Reproductive and Urologic Drug Products
$HAMD_{17}$	17-item Hamilton Depression Rating Scale
LFT	Liver function tests (includes AST, ALT, SGOT, SGPT, GGT, T. Bili)
MDD	Major depressive disorder
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed-models repeated measures
MNSI	Michigan Neuropathy Screening Instrument
NE	Norepinephrine
PBO	Placebo
PCPSDB	Placebo-controlled primary safety database
PCSSDB	Placebo-controlled secondary safety database
PGI	Patient's Global Impression Scale (includes subscales, i.e. Improvement)
RCCSDB	Routine care-controlled safety database
SF-36	Short Form-36 Health Survey
SF-MPQ	Short-Form McGill Pain Questionnaire
SNRI	Serotonin and norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SPCSDB	Secondary placebo-controlled safety database
SUI	Stress urinary incontinence
TEAE	Treatment Emergent Adverse Event
ULN	Upper limit of normal

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend that the Division take an approval action on NDA 21-733. NDA 21-733 presents adequate data to support the claim that duloxetine is safe and effective in the treatment of diabetic peripheral neuropathic pain. The risks of duloxetine treatment (for up to one year) with daily doses up to 120-mg, in DPN patients without renal or hepatic impairment, are minimal.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

At this time, there is no basis for recommendation of any specific postmarketing risk management activities or programs.

1.2.2 Required Phase 4 Commitments

Two clinical pharmacology studies are currently underway, or have recently been completed. The protocols for these investigations have already received detailed feedback from the Division of Reproductive and Urologic Drug Products and the Division of Scientific Investigations. DNDP has required (in the 7/23/04 approval letter for NDA 21-427) that final study reports be submitted by 12/31/04.

Because of the nature of diabetic peripheral neuropathy, long-term duloxetine therapy is almost certain, in patients for whom it relieves (diabetic peripheral) neuropathic pain, at least until true disease modifying medications are available. Longer-term (six-months to one year) safety evaluation could be indicated. The additional long-term safety data, particularly with respect to glycemic control, diabetic complications (i.e., retinopathy and nephropathy progression) as well as the course of the underlying neuropathy, would be of value in assessing whether genuine long-term use is safe.

Lilly need not be asked, at this time, for any commitments required to comply with the Pediatric Research Equity Act.

1.2.3 Other Phase 4 Requests

- +/- Detailed follow-up information on reported cases of hepatotoxicity (SAEs)

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Lilly conducted three studies specific to the diabetic peripheral neuropathy indication, evaluating three daily doses (20-mg, 60-mg, 120-mg), as summarized in Table 1.2:

- Study HMAW, a 12-week, placebo-controlled efficacy, and dose-ranging study
  HMAW 52-week open-label extension, completed
- Study HMAVa, a 12-week, placebo-controlled efficacy study
  HMAVa 52-week open-label extension, ongoing
- Study HMBT, a 28-week open-label safety study
  HMBT 24-week open-label extension, ongoing

In total 1071 DPN patients received duloxetine (controlled and uncontrolled trials), representing 471.7 patient-years exposure (509.9 including the 120-Day Safety Update). Five-hundred and sixty-eight patients received duloxetine in two double blind, placebo-controlled DPN studies. All 671 patients enrolled in 'long-term' open-label studies, received the highest dose, 120-mg per day; 449 in Study HMBT and 222 in the HMAW-Extension. As of 3/1/2004 (120-Day Safety Update cutoff) 484 patients had received duloxetine for 180 days or more, all at the 120-mg dose; 220 of these received 365 days or more.

Table 1.1: 'Primary Safety Database' – Duloxetine DPN Trials/Exposures

	20 mg/d	60 mg/d	120 mg/d	Placebo	'Routine Care'
HMAVa – Acute	---	114	112	108	---
HMAW – Acute	115	114	113	115	
HMAW - Extension	---	---	222*	---	115
HMBT – 6 month data	---	---	449	---	---
Subtotal, for dose			(896)*		
Subtotal	115	228	731 naive	223	115
Total DLX = 1074					

*In the HMAW Extension Phase, 222 patients received DLX 120 mg/day Source: Reviewer
- 165 of these had been treated with DLX in the HMAW Acute Phase
- 57 were new exposures (received Placebo in Acute Phase, then DLX in Extension)

Lilly has three other active development programs for duloxetine:

- For Major Depressive Disorder (MDD) under NDA 21-427, approved 7/23/04
- For stress urinary incontinence —
- For fibromyalgia —

Overall, 8447 patients have received duloxetine in Lilly and — clinical trials. The bulk of the longer-term exposure in MDD/SUI trials has been at daily doses ≤60-mg.

1.3.2 Efficacy

Duloxetine efficacy for the [redacted] caused by diabetic peripheral neuropathy (as measured by reduction in diary-recorded ratings of "average pain over last 24-hours") has been established in both Lilly efficacy trials: HMAW and HMAVa. HMAW employed fixed duloxetine doses of 20-mg QD, 60-mg QD and 60-mg BID. HMAVa employed only the 60-mg QD and 60-mg BID doses, but was otherwise nearly identical to HMAW. Sixty milligrams QD and sixty milligrams BID appear to exhibit approximately equal efficacy. Patients treated at the higher dose (120 mg/day) did not appear more likely to attain 'clinical response' or 'sustained response' either. Pain score reductions were not greater, on average, at the higher dose, nor was 'time to response' decreased. There is no data, then, demonstrating that doses above 60-mg QD confer additional benefit. Still, it is possible that higher doses could be beneficial for some patients.

Overall, dosing at 20-mg QD did not appear to be more effective than placebo. Dose-ranging was not sufficient for determination of a minimum effective dose. The main efficacy findings are summarized in Table 1.2.

Table 1.2: Summary of Efficacy Findings

Trial	RX Group	Primary Endpoint Δ Pain Score	Endpoint p-value*	Secondary Endpoint % responders	Endpoint p-value**
HMAW	PBO	-1.40	---	30.6	
	20QD	-1.93	0.111	42.3	0.074
	60QD	-2.40	0.002	51.8	<0.001
	60BID	-2.38	0.002	53.2	0.001
HMAV	PBO	-1.36	---	31.1	
	60QD	-2.17	0.006	50.9	0.004
	60BID	-2.25	0.026	54.1	<0.001

*ANOVA (Type II, sums of squares), BOCF analysis for primary endpoint

**'Sustained-responders' at Week 12, Fisher's Exact pairwise comparisons, LOCF analysis for 2° endpoint

1.3.2.1 Efficacy by Diabetes Type and Duration

Type I and Type II diabetics (with DPN) appear to be equally likely to benefit from duloxetine-treatment.

1.3.3 Safety

The most common treatment associated adverse events were nausea, somnolence, dizziness, fatigue and insomnia. These AEs seem to be dose dependent, as does the small increase in blood pressure (≈ 1-2 mm Hg) seen with duloxetine treatment.

Potential liver toxicity (as evidenced by markedly increased transaminases), with, or possibly even without, concomitant ethanol ingestion was of significant concern to DNDP and DRUDP clinical safety reviewers. All but one of the handful of reported cases (four or five occurring in >8000 patients treated in clinical trials) appear to have been associated with substantial ethanol ingestion (chronic daily consumption of five or more drinks +/- superimposed binge drinking). One other case was determined to have been attributable to gallstone pancreatitis. DNDP and DRUDP concerns about the

potential for serious hepatotoxicity have been adequately addressed. Still, small transaminase elevations were found, in duloxetine treated patients, in the DPN population, as well as the MDD population. Approximately 2% of duloxetine-treated patients experience asymptomatic ALT and/or AST elevations to three times baseline. These resolve upon duloxetine discontinuation.

There were increases in fasting glucose in duloxetine treated patients, compared to placebo-treated or 'routine care' treated patients (about 5 to10 mg/dL plasma glucose). Hemoglobin A1c does not change, however, during three month (placebo-controlled trials), or longer-term (12 month open-label) exposures. There was no increase in symptomatic hyperglycemic, or hypopglycemic episodes in DLX treated subjects. Likewise, there was no increase in diabetes-related SAEs (i.e., ketoacidosis) in duloxetine-treated patients.

Retinopathy and renal disease do not appear to progress differentially either. Duloxetine does not appear to alter the course (progression) of underlying neuropathy, over the time period studied, either

1.3.4 Dosing Regimen and Administration

Efficacy at daily doses of 60-mg and 120-mg (for up to 12-weeks) was demonstrated in two placebo-controlled trials. For 'sustained responders' treatment response was usually evident within one to two weeks of duloxetine initiation (both 60-mg QD and 60-mg BID). Most 'sustained responders' (by treatment week 12), had achieved 'clinical response' by the end of the second or third treatment week. Efficacy, as assessed by magnitude of response, or response rate, did not appear to diminish once response was achieved.

The 120-mg dose was not demonstrably better than the 60-mg dose, by any of a number of measures (change in pain scores from baseline to study endpoint, response rate, sustained response rate, time to response). The 120-mg daily dose was, however, associated with increased rates of the most common drug-related adverse events (nausea, dizziness, somnolence, insomnia). There was no apparent increase in SAEs at the higher dose.

The 20-mg daily dose was not statistically significantly superior to placebo. The Applicant did not attempt to determine minimal effective dose. Daily doses between 20-mg and 60-mg were not studied. Duloxetine can be taken with or without food. The 120-mg daily dose can be taken as 120-mg QD or 60-mg BID.

1.3.5 Drug-Drug Interactions

Potential metabolic interactions, primarily via hepatic enzymes (CYP1A2, CYP2D) have been thoroughly evaluated, to the satisfaction of the DNDP and DACCADP reviewers. The potential for hepatotoxicity in the setting of coadministration with other potential hepatotoxic medications was not systematically evaluated.

1.3.6 Special Populations

Duloxetine was approved by the Division of Neuropharmacological Drug Products on August 3, 2004 for the treatment of major depressive disorder. Their label indicates the following:

Age, Sex, Ethnicity-There is no evidence that duloxetine dose, or the choice of duloxetine for treatment, need be modified based on adult patient age (in adulthood), or sex. Pediatric population studies or specific pharmacokinetic studies to investigate the effects of race were not performed.

Pregnancy, Labor, Delivery and Nursing-The effect of duloxetine on pregnancy, labor and delivery in humans is unknown. The recently approved label places it in pregnancy category C, stating "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. The approved label indicates that 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 patients with cirrhosis and moderate liver impairment (Child-Pugh Class B) 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 C_{max} was similar to normal patients 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.

Except for ethnicity, Lilly's evaluation for efficacy and safety differences in special populations appears to have been adequate. The proportion of non-whites (includes Hispanic origin) enrolled in controlled DPN trials was relatively low compared to the US population, though, at only 21.9% (144). The racial distribution within the DPN patient population, (and also within the 'overall duloxetine exposures database') is not necessarily representative of the US population as a whole, or of Americans with diabetes

and peripheral neuropathy. The low absolute number of Non-whites precludes meaningful subgroup analyses, to look for efficacy or safety differences between individual Non-white subgroups and Caucasians. Still, the ramifications for generalizability of the safety and efficacy findings are not clear.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Duloxetine hydrochloride, a new molecular entity, is an orally administered serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI). Its chemical designation is (+)-(*S*)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The applicant, Lilly, seeks FDA approval to market duloxetine under the tradename, Cymbalta®, for the depression and pain indications, which would share a label,

Lilly has — active NDAs and — for duloxetine:

- For major depressive disorder (MDD), NDA 21-427 in the Division of Neuropharmacological Drug Products-DNDP, received approvable actions in 9/2002 and 9/2003, and an approval on 7/YY/2004.
  — mg, the recently approved MDD label states "there is no evidence of increased efficacy at daily doses above 60 mg."
- For stress urinary incontinence (SUI), NDA —
  , received approvable action August 2003. —
- For diabetic peripheral neuropathy (DPN) in adults, NDA 21-733, the subject of this review, in DACCADP. Lilly proposes daily dosing — 60 mg —
- —

Lilly's proposed DPN 'Indication' statement reads as follows:

- Cymbalta is indicated for the — associated with diabetic neuropathy (see CLINICAL STUDIES).

Lilly's proposed DPN 'Dosage and Administration' statement reads as follows:

- Cymbalta should be administered at a total dose of 60 mg/day given once a day, without regard to meals. —
- /

Lilly proposes this DPN 'Maintenance/Continuation/Extended Treatment' statement:

- As the progression of diabetic neuropathy is highly variable and treatment of pain is empirical, the effectiveness of Cymbalta must be assessed individually —

/

2.2 Currently Available Treatment for Indication

At this time, there are no drugs approved specifically for the treatment of diabetic peripheral neuropathic pain, or for the broader class of neuropathic pain. Drugs from

several therapeutic and pharmacologic classes (i.e., TCA antidepressants and occasionally SSRI antidepressants, newer anticonvulsants) are often tried in clinical practice, however, with varying support found in the peer-reviewed medical literature. Still, all such prescribing is off-label. Opioid analgesics are also widely prescribed; NSAIDs much less so.

2.3 Availability of Proposed Active Ingredient in the United States

Duloxetine hydrochloride was approved for the treatment of major depressive disorder 7/23/04.

2.4 Important Issues With Pharmacologically Related Products

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

Neither venlafaxine nor reboxetine has been implicated in any patient suicides. As with other antidepressants, though, the Cymbalta® label carries the current MDD class label language, concerning suicide risk:

> **Clinical Worsening and Suicide Risk** — Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established. **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases**. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Although recent concerns about a possible association between SSRI treatment (not necessarily SSNRIs) and increased suicide rate have generated substantial publicity, those safety signals originated in patients being treated for major depressive disorder. At this time there is no reason to expect that such a link, even if real, would be present in, or relevant to DPN patients (that are not also suffering from MDD).

2.5 Presubmission Regulatory Activity

Lilly opened INDs 37,071 and 38,838, for LY248686 hydrochloride (later named duloxetine) for the indication ' July 1991 and February 1992, respectively, both in the Division of Neuropharmacological Drug Products (DNDP). Investigations conducted under these INDS became the basis for NDA 21-427, initially submitted in November 2001, and (first) deemed approvable September 2002.

The September 2002 approvable action letter outlined several CMC issues that Lilly would have to address prior to approval. The 'clinical issues' identified in the letter would not necessarily have precluded approval. Lilly was asked to provide additional information on six syncope cases, though, and two SAEs suggestive for liver injury. The letter also revised the draft labeling, proposing that 60 mg/day be the maximum recommended dose (Lilly had proposed dosing). In his Division Director memo, Dr. Katz wrote that "this was related to the fact that in a study that compared 40 mg/ day and 80 mg/ day, there was essentially no superiority of the 80 mg/ day dose." A daily dose of 60 mg was not directly compared to any other dose in any study. A Phase 4 study examining (efficacy with) long-term use was suggested as well.

Meanwhile, Lilly had also opened IND duloxetine for stress urinary incontinence, . NDA received an approvable action (August 2003).

Lilly had already planned to begin the study, though. In February 2004 one of the participants, a

nineteen year old healthy (volunteer) female inpatient, with no known psychiatric history, committed suicide (by hanging) on Lilly's clinical pharmacology unit. DNDP safety reviewers believe there to be no causal relationship with duloxetine.

After correction of CMC problems, and re-review of the hepatic safety data, Lilly was granted marketing approval for NDA 21-427 on July 23, 2004 Lilly.

2.5.1 Contact with DACCADP

A pre-IND meeting was held 3/14/01, during which Lilly was advised that duloxetine effects on pain must be demonstrated, independent of effects on mood, and that approval for a , two clinical trials would be required for a DPN indication. IND 62,536 was opened in 4/19/01 with protocol HMAW. At that time Lilly also expressed intent to

In May 2001 DACCADP clinical reviewers requested information on several patients (from MDD trials) with either LFT or CPK elevations, and on one patient with anemia. The 5/01 advice letter reiterated that duloxetine effects on pain would have to be, independent of effects on mood. In August 2001 there was a teleconference in which several details of the initial clinical protocol were discussed. The overall design, and study plan were thought to be acceptable, though.

In February 2003 an advice letter was sent requesting further details on several cases (of mild CPK elevations) reported on in IND submission #22 (1/28). In August 2002 Dr. Comfort reviewed the protocol for HMAVa (submission #037). HMAVa was also considered to be acceptable, with minor revisions to the schedule for monitoring LFTs.

The key points from the 8/8/2002 EOP2 meeting were:

- Two DPN trials would be required, each at least 12-weeks
- The Agency is not persuaded that DLX pain-efficacy effects in some of the MDD trials can be completely distinguished from concurrent effects on mood.
- In the Phase 3 trials it is important to study patients as close to the "real world" population as possible. Lilly was encouraged not to exclude subjects with psychiatric diagnoses in these trials.
- Lilly proposed that the Phase 3 DPN trials evaluate no doses lower than 60-mg QD. The Division found this acceptable.
- Regarding the safety database; there should be ≥1000 DPN patients total, with ≥500 treated to at least six months, and ≥100 treated for at least one year.
- The Divison recommended performing nerve conduction velocities (NCVs) initially, and at appropriate times during the study (middle, end): to insure that disease severity is equally distributed across treatment groups and, to insure that duloxetine efficacy is not actually due to worsening of the patients' nerve function.
- Priority review could be possible

- Lilly asked about how decisions are made about (whether to hold) advisory committees. The Division stated that these decisions are based upon difficult issues or specific questions. An advisory committee meeting would not be necessary for this drug unless there was a particular problem or issue. The Division stated that they make every attempt to issue approval letters during the first review cycle.
- CSS review of materials submitted indicated that duloxetine has no abuse liability.

Much of the discussion at the pre-NDA meeting (7/30/03) concerned the adequacy of the safety database, and the content, structure and format of the NDA and datasets. The key points were:

- The overall design of the electronic submission and datasets should permit the reviewer to recreate all sponsor efficacy and safety results.
- All datasets should have a common unique patient identifier to permit merging datasets and/or tracking individual patients.
- Datasets should include adverse event (AE) preferred and verbatim terms, dates of onset and conclusion of AE, dose at onset of AE, duration on that dose, and duration and outcome of AE.
- The integrated summary of safety (ISS) should include specific section addressing any safety problems found by DNDP and DRUDP during their respective NDA reviews.
- The overall number of patient exposures appears on track to be adequate.
  - The Sponsor stated that the open-label extension phase of the two efficacy studies will provide some data (at 120-mg/day), but that most (approximately 50%) of the data being collected are at the 60-mg dose (target dose).
  - The Division stated that adequate exposure at the highest dose must be provided.
- Biopharmaceutics stated that the Sponsor should conduct a study to evaluate the PK of duloxetine in patients with mild and moderate renal impairment.
- CRFs and narratives for all deaths, SAEs and withdrawals due to AEs from all studies contributing to the safety database are required (completed & ongoing MDD, SUI, and pain studies, as well as — _ trials)
- All CRFs and narratives are required for the three relevant categories (SAEs, discontinuations due to AEs, and deaths) for the — studies.
- Special Vulnerabilities in Diabetics: The Sponsor asked if there were particular aspects of diabetes such as renal failure and neuropathy that should be studied with extra vigilance. Dr. Hertz stated that the Sponsor should evaluate things that are clinically relevant to diabetics such as glucose control. Dr. Rappaport added that the Division will scrutinize the data with respect to these issues and also gave ophthalmic disease as another example.
-

/

Imputation of missing efficacy data was not discussed with Lilly (meetings, letters or phone calls).

2.5.2 Japanese Trials —

— , conducted thirteen duloxetine trials between 1993 and 2002. Data from these trials have not been included in NDA 21-733, or in this review. All of the — trial deaths and serious adverse events from these trials, have been reviewed by DNDP clinical reviewers, and were not thought to be drug related. DNDP had requested additional information for a subset of the SAEs, and determined that duloxetine had not played any contributory role, in any of the cases. The narratives previously requested by the DNDP reviewers, have been included in this NDA.

At the pre-NDA meeting, Lilly informed DACCADP that it does not own the data from studies conducted in Japan. They also have limited ability to alter format of those data, in order to present information on serious adverse events (SAEs), discontinuations due to adverse events (AEs), and deaths for the Japan studies. Lilly proposed to present all information available, upon request by the reviewers, but, in alternative format to traditional CRFs. This was agreed to by DACCADP.

The conditions studied in these protocols were (in translation from Japanese, of course): "Depression and Depressive States/Conditions," " Urinary Incontinence Induced by Increased Abdominal Pressure," and " Urinary Frequency, Urgency and Incontinence Caused by Neurogenic and Unstable Bladder with Uninhibited Contractions." One-thousand two-hundred and seven (1207) patients received duloxetine, representing over 294 patient-years. The doses of duloxetine administered in these studies were 5, 10, 15, 20, 30 and 40 mg/day. There were five deaths, 35 serious adverse events (SAEs) and 116 discontinuations due to adverse events. On the whole, AEs were similar to those reported in NDA 21-427; largely GI and CNS related. The breakdown by dose of the discontinuations due to adverse events is:

5 mg	10 mg	15 mg	20 mg	30 mg	40 mg
16	43	11	25	16	5

The deaths that occurred during — trials are included in the tabulation in Section 7.4 of this review.

2.6 Other Relevant Background Information

As of 3/1/2004 Lilly had — , duloxetine marketing applications under review in the USA, —

—

On 3/24/2004 the CPMP of EMEA issued a *Summary of Opinion* for duloxetine, stating that they had "adopted a positive opinion, recommending to grant a marketing authorization for the medicinal product Ariclaim®, 20 mg and 40 mg capsules intended for treatment of moderate to severe Stress Urinary Incontinence (SUI)." The approved indication statement is: "Ariclaim® is indicated for the treatment of moderate to severe Stress Urinary Incontinence – SUI." Duloxetine's first marketing approval was granted in Mexico on April 16, 2004 for MDD. Table 2.1 summarizes duloxetine worldwide regulatory activity.

Table 2.1: Duloxetine Regulatory Activity (as of 3/04, except USA)

Indication	Country	Date Submitted	Application Status	Estimated Decision Date
MDD	UNITED STATES	12 Nov 2001	**Approval 7/23/04**	
MDD	UNITED STATES	12 Nov 2001	Approvable 9/03	
MDD	UNITED STATES	12 Nov 2001	Approvable 8/02	
MDD	MEXICO	18 Dec 2003	**Approval 3/04**	
SUI	EUROPEAN UNION	7 Feb 2003	**'Recommendation for approval'**	**3/28/04**
SUI	UNITED STATES	30 Oct 2002	Approvable 8/29/03	

Source: Modified from Applicant Table, Volume 57

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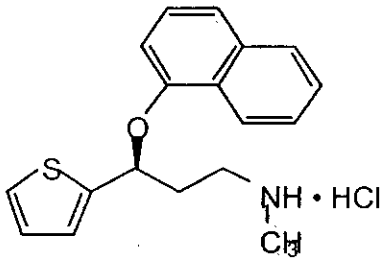
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

All outstanding CMC issues have been resolved to ONDCP satisfaction. The relevant section from the recently approved label appears below.

CYMBALTA®
(duloxetine hydrochloride)
DESCRIPTION

Cymbalta® (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(*S*)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The empirical formula is $C_{18}H_{19}NOS \cdot HCl$, which corresponds to a molecular weight of 333.88. The formula is:



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

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

3.2 Animal Pharmacology/Toxicology

Dr. Thornton-Jones, DACCADP Pharmacology/Toxicology reviewer recommends approval for NDA 21-733, with no recommendations at this time for additional non-clinical studies (8/13/04). She bases her recommendation, in part, on previous Pharmacology/Toxicology reviews from DNDP and DRUDP. She points out that the recent DNDP approval (NDA 21-427) was only for human doses up to 60 mg per day.

Dr. Thornton-Jones' review discusses the DRUDP reviewers' concerns about potential duloxetine hepatotoxicity "either alone, or in combination with ethanol (as evidenced by increased transaminases, in both clinical and non-clinical studies)."

. Dr. Thornton-Jones reviewed the mitochondrial beta-oxidation study results, and writes that "it does appear that duloxetine hydrochloride and its major human metabolites, when given at comparable plasma levels to cultured rat hepatocytes, may lead to mitochondrial beta-oxidation." She goes on to say that the studies as outlined by DRUDP are good basic science, but they may not provide any advantage in assessing human risk (over actual human exposure). Her conclusion is that "There are no known *in vivo* non-clinical models that can adequately assess the interaction of duloxetine/ethanol and the relevance of the findings to humans." Dr. Thornton-Jones believes that any outstanding liver toxicity concerns (either as a direct affect of duloxetine or via interaction with ethanol) can be addressed with appropriate labeling and post-marketing surveillance, the approach taken with DNDP's recent duloxetine approval.

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4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

New Drug Application 21-733 was received on March 2, 2004, and deemed acceptable for filing. All required items were included with the original NDA submission. The individual study reports and the ISE and ISS sections were consistent with US regulatory requirements.

This review is based on information included in the following submissions:

- NDA 21-733, submitted electronically (03/02/04) (including individual study reports, ISS and ISE, datasets, and CRFs): \\CDSESUB1\N21733\N_000\2004-03-02
- 4/26/04, Abuse liability assessment package
- 5/05/04, Reformatted safety datasets: \\CDSESUB1\N21733\N_000\2004-05-05
- 5/11/04, Corrected ISS dataset Q403SAE.xpt: \\CDSESUB1\N21733\N_000\2004-05-11
- 6/02/04, Additional CRFs as requested: \\CDSESUB1\N21733\N_000\2004-06-02
- 07/01/04, 120-day Safety Update: \\CDSESUB1\N21733\N_000\2004-07-01
- 07/26/04, Response to clinical request with baseline-observation-carried-forward (re)analysis of primary efficacy data: \\CDSESUB1\N21733\N_000\2004-07-26
- 08/27/04, Response to clinical request with baseline-observation-carried-forward (re)analysis of primary efficacy data: \\CDSESUB1\N21733\N_000\2004-08-30
- DNDP reviews in DFS, clinical, safety, biopharm., pharm/tox and Division Director and Team Leader memos
- DRUDP bioparm. and pharmacology/toxicology reviews, and Division Director memo.

4.2 Review Strategy

The clinical reviews written by Drs. Andreason and Racoosin (DNDP review cycles one and two), served as the starting point for review of NDA 21-733 (specifically, the safety findings). Otherwise, this clinical review is based on material in the NDA submission, the 120-Day Safety Update, the revised datasets (5/4/04 and 5/11/04), and the Applicant's responses (7/27/04 and 8/27/04) to specific questions.

The bulk of this review was divided into two general sections; the efficacy review and the safety review. The review of efficacy focused on the two 12-week efficacy studies, HMAW and HMAVa. Efficacy data from these two trials were pooled for subgroup analyses (Section 6.7) by demographic and disease characteristics (DPN duration, DM type).

Review of the Applicant's safety data started with the integrated summary of safety (ISS). Deaths and serious adverse events were then reviewed, initially for the overall duloxetine exposures database, and then, with greater scrutiny, those from the primary DPN database. Study dropouts were then reviewed, as well as discontinuations (attributed by the Applicant, or not) to adverse events (within the DPN population). Data from controlled DPN clinical trials were pooled, for some analyses, to explore common and drug related adverse events, and possible treatment-related changes in laboratory analytes, ECGs and vital signs.

4.3 Data Quality and Integrity

The NDA submission was evaluated, prior to the filing decision, for data integrity and quality, by detailed review and re-tabulation of selected tables summarizing the major efficacy and safety findings. The electronic datasets were evaluated for completeness, coherence, consistency and accuracy. Attempts were made to reproduce selected tables from the text of NDA study reports and the ISS, using the electronic datasets (i.e. dose-by-duration, frequency of serious adverse events and treatment emergent common adverse events), with varying success. The adverse event tabulations in particular were difficult to replicate.

Line-by-line examination of the electronic datasets revealed a variety of problems. Overall, the format and structure were not consistent with CDER guidance documents for electronic submissions. Specifically:

- The Agency requirement, reiterated at the pre-NDA meeting, that "All datasets should have a common unique patient identifier to permit merging datasets and/or tracking individual patients" was not met. Patients had not been assigned unique patient identifiers, anywhere in the collection of datasets.
- Most datasets did not contain the basic demographic (sex, age, race) or treatment information stipulated in the CDER guidance documents.
- 'Adverse events,' 'secondary conditions,' and 'historical diagnoses' were all considered to be 'events,' and all represented within the same dataset(s). Individual rows did not correspond to single AEs, secondary conditions, or historical diagnoses, though. One unique historical diagnosis (or AE, or secondary condition) could be represented in one, or five, or fifteen rows in a dataset, depending upon when it was recorded on a case report form, on how many additional pages were added to the CRF subsequently, and also upon whether or not the individual adding blank CRF pages re-listed 'events' recorded on preceding pages.
- The Division had made the point (at the pre-NDA meeting) that "The overall design of the electronic submission and datasets should permit the reviewer to recreate all sponsor efficacy and safety results." As submitted, the safety data could not have been used for even rudimentary tabulations (i.e., adverse events, exposure duration, patient disposition, etc.).

Aside from fundamental inadequacies, and an unorthodox and unwieldy dataset structure, there were numerous errors, missing values and inconsistencies, predominantly in the safety datasets. For example:

- The classification and coding of 'events' as 'adverse events,' 'secondary conditions,' or 'historical diagnoses' seemed inconsistent in many cases, and sometimes just incorrect.
- In some cases, within one dataset, the same (unique) event, was classified in some rows as a "secondary condition," or as a 'historical diagnosis,' but in other rows as a new adverse event, all with the same date and time of onset (and resolution).
- There were also many obvious treatment-emergent adverse events with 'onset dates' twenty or thirty years past.
- 'Events' like 'chronic back pain' were sometimes coded as 'new' and as 'adverse events," but had 'onset date' ten weeks into the twelve week study, and no matching or related 'historical diagnosis' or 'secondary condition.'
- Some datasets contained only missing values for all AE Preferred Terms and SOC codes.
- Four patients had (derived) values for DPN duration < 0.0 years.

Reformatted and corrected datasets were provided 5/04/07, but initial review of the main ISS dataset listing SAEs (Q403SAE.XPT) revealed persistent errors. That particular dataset was re-corrected, and submitted 5/11/04. The other corrected datasets appeared to be free of gross errors. Several months of scrutiny revealed persistent (but less abundant and more manageable) problems, though.

Within the text of the NDA itself there were also errors and inconsistencies. Some safety tables appeared incorrect, or inconsistent with the accompanying text. For example Table ISS.6.3.3 was mislabeled, as to the patient population reported on, and Table ISS.6.3.4 had incorrect labeling of both axes. Table APP.20.3 (dose-by-duration for the placebo-controlled DPN patients) was inconsistent with most of the other exposure tables.

Overall, the data errors and inconsistencies do not appear to be attributable to attempts at fraud, though.

4.4 Compliance with Good Clinical Practices

Each study report (HMAW, HMAVa and HMBT) included the following statement: "This study was conducted in accordance with applicable laws and regulations, good clinical practice (GCP), and the ethical principles that have their origin in the Declaration of Helsinki. The PI or designee promptly submitted the protocol to applicable ERBs for approval." My review of the study reports suggests this to be the case.

Because duloxetine hydrochloride was classified as a new molecular entity (until 7/23/04) DACCADP requested that Division of Scientific Investigations (DSI) conduct an inspection under the PDUFA 'routine inspection' program. Two clinical sites were chosen, because they had each enrolled relatively high numbers of patients (> than average), not because of any specific concerns at those sites.

DSI inspectors visited two domestic clinical sites; Dr. Eugene Blonsky in Chicago (Investigator #2359, site #004, enrolled 17 subjects) and Dr. Louise Beckitt in Oklahoma City (Investigator #32957, site#003 enrolled 31 subjects).

There were no problems found with Dr. Beckett's clinical study conduct. There were two minor problems found at Dr. Blonsky's site. The DSI assessment stated that neither of the problems would appear to increase the safety risk to subjects, or affect the validity of the study results. From the data reviewed during the inspections, DSI concluded that the data from both clinical sites could be used to support an approval decision for the NDA.

4.5 Financial Disclosures

Three investigators are reported as having Disclosable Information [redacted] The NDA only contains the required disclosure for Dr. [redacted], however. Dr. [redacted] an investigator at [redacted] stated that he holds approximately $55,000 in Lilly shares [redacted] was one of [redacted] investigators in [redacted] His site enrolled [redacted], less than 4% of the total. The data from this site were consistent in general with the overall patterns seen in the

— , data. Dr. — site also enrolled — — or 3.5% of the total). Again, the data for — , from site — were consistent with the overall — data.

My audit of the listings of participating clinical investigators found only one investigator, for whom the required financial disclosure appeared to be missing. Interestingly enough, this was Dr. Louise Beckett, at the site visited by DSI inspectors. The DSI inspectors audited the records of ten patients (out of 31 total) enrolled in HMAVa through Dr. Beckett's site. No problems were found at Dr. Beckett's site. There were no discrepancies between source data and that recorded in the case report forms. Adverse events from source documents were compared with those reported by the sponsor. There was no evidence of under-reporting of AEs. There were no serious adverse events (SAEs) occurring during the acute phase of the study. The one SAE, occurring in the (ongoing) extension phase (hospitalization for bypass surgery), was appropriately reported. Drug accountability was adequate, and all informed consents were signed prior to subjects entering into the study. Lack of the required financial disclosure statement by Dr. Beckett is unlikely to have had any bearing on data reported from her site, especially in light of the problem-free (coincidental) audit.

All other participating clinical investigators have filed the required documentation indicating that they have no potential conflicts of interest, except for two investigators, in Argentina — at sites — . In the Financial Disclosure these sites are reported together, both under Dr — The total number of patients enrolled at those two sites, was 31 and 28, respectively (into open-label study HMBT), by twenty-two investigators.

Lilly appears to have adequately disclosed all financial arrangements with clinical investigators, as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. Lilly's arrangements with their investigators (as disclosed) raise no concerns about the integrity of the duloxetine data. Review of the NDA Financial Disclosure Section indicates that Lilly appears to have exercised due diligence in obtaining all required information (The specifics of the procedures used are contained within the NDA.)

5 CLINICAL PHARMACOLOGY

Text in this section was excerpted from DNDP clinical pharmacology reviews for NDA 21-427 (Dr. Kavanagh, 8/02 and 8/03).

5.1 Pharmacokinetics

Duloxetine is well absorbed after oral administration (>72% in Study SAAZ). It is extensively (over 80%) metabolized to numerous (more than eleven) 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.

The t_{max} for duloxetine is approximately 6-hours. Steady state concentrations are achieved within three days of daily dosing. The elimination half-life of duloxetine ranges from 8.1 to 17.4 hours (mean of 12.1 hours, 5^{th} to 95^{th} percentile) and the apparent plasma clearance ranges from 33 to 261 L/ hr (mean of 101 L/hr, 5^{th} to 95^{th} percentile). Total radioactivity half-life ($t_{½}$) is substantially longer than the duloxetine $t_{½}$ (120 hours versus 10.3 hours).

In clinical pharmacology Study SBAA, food did not affect the maximum plasma concentration (C_{max}); marginally decreased AUC (11%); and delayed T_{max} by about 4 hours. Bedtime administration decreased C_{max} (26%) and AUC (17%); and delayed T_{max} 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 (an H2-antagonist) and Mylanta® (an antacid) did not change duloxetine pharmacokinetics. In contrast, activated

charcoal significantly decreased duloxetine plasma concentrations and $t_{1/2}$, 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 plus duloxetine resulted in numerically worse performance, compared to ethanol alone or to duloxetine plus 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 (plus 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. Patients of African and Asian descent only constituted a small portion of the HMBA study population. The DNDP reviewer concluded that no meaningful assessment of pharmacokinetic differences could be performed for these ethnic subgroups.

5.2 Pharmacodynamics

Dose tolerability for the MDD indication 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 (E_{max} 19.6 bpm; EC50 71.8 ng/mL).

5.3 Exposure-Response Relationships

The applicant's submission did not contain any concentration-exposure relationship data. The phase 3 clinical trials only assessed the dose-response relationship. The efficacy findings will be discussed further in this review (Section 6.1.5 – Efficacy Findings).

6 INTEGRATED REVIEW OF EFFICACY

Duloxetine efficacy in patients with diabetic neuropathic pain was evaluated (in comparison to placebo) in two very similar 12-week (acute therapy phase) clinical studies, HMAW and HMAVa. Both were multicenter, double-blind, fixed-dose, parallel group studies. HMAW and HMAVa were alike in most aspects, employing the same eligibility criteria, efficacy and safety measures, and assessment schedules. HMAW incorporated one additional treatment arm, though, and employed non-US study sites. The major differences are outlined in Table 6.1 below.

Table 6.1: Major Differences Between Efficacy Studies HMAW and HMAVa

Trial Characteristic	HMAW	HMAVa
Treatment Arms	Duloxetine 60 mg BID (n=113)* Duloxetine 60 mg QD (n=114) Duloxetine 20 mg QD (n=115) Placebo (n=115)	Duloxetine 60 mg BID (n=112)* Duloxetine 60 mg QD (n=114) Placebo (n=108)
Treatment Duration	12 weeks	12 weeks + 1 week taper
Analysis Plan	MMRM then ANCOVA	ANCOVA then MMRM
Clinical Sites	22 USA (+ 1 in PR) 1 Canada, 2 Argentina	26 USA (+ 2 in PR)
OL Safety Extension	Data submitted	Ongoing, data not submitted
Duration	One year	One year
Treatment Arms	DLX60BID vs. routine care	DLX60BID vs. routine care (if 60BID not tolerated, ↓ to 60QD)

*Up-titration for 60-mg BID arm; in HMAW 40-mg BID first 3 days, in HMAVa 60-mg QD first 3 days
Source: Clinical reviewer

In HMAW patients were randomized to one of four (equally sized) treatment arms; duloxetine 60 mg BID, duloxetine 60 mg QD, duloxetine 20 mg QD or placebo. Patients assigned to receive 60-mg BID in HMAW initiated therapy at 40-mg BID for the first three days, and then increased to 60-mg BID on the fourth day, which they continued until their final study day. There was no post-treatment taper period in HMAW.

In HMAVa patients were assigned to one of three (equally sized) treatment arms; duloxetine 60 mg BID, duloxetine 60 mg QD, or placebo. Patients assigned to the 60-mg BID group took 60-mg QD for their first three days before increasing to the 60-mg BID dose. All HMAVa patients (still in the study) continued for a 13th study week, during which they underwent a duloxetine taper. The 60-mg BID patients tapered to 60-mg QD for their final week. Patients assigned to the 60-mg QD dose in HMAVa, also tapered for their 13th treatment week, to 30-mg QD. (Data from the 13th treatment week are not included in efficacy analyses).

Patients who completed the acute therapy phase in either study were eligible to enroll in an optional one-year open-label follow-up. HMAW-Extension has completed, but HMAVa-Extension was still ongoing at the time of NDA submission (HMAVa-Extension data are NOT included in the NDA 21-733 safety databases). In the HMAW open-label follow-up patients were re-randomized to receive either duloxetine 60 mg BID, or routine care (for the 52 weeks of open-label treatment). Patients who were rerandomized (for the extension) to duloxetine 60 mg BID started at 40 mg BID for 3 days and then increased to 60 mg BID. Patients enrolling in the HMAVa follow-up are re-randomized to either duloxetine 60 mg BID, or to 'routine care' meaning no duloxetine, in a 2:1 ratio, although "patients in the duloxetine treatment group, who were unable to tolerate 60 mg BID, per the clinician's judgment, were allowed to reduce their dose to 60 mg QD." If a dose reduction occurred, the patient remained on 60 mg QD for the duration of the open-label extension. If still unable to tolerate duloxetine at the lower dose the patient would be discontinued from the study.

Both HMAW and HMAVa used the same primary efficacy measure, reduction of pain severity as measured by the weekly mean of the (daily diary-recorded) 24-hour average pain scores (on an 11-point Likert scale). Both studies also included numerous secondary efficacy measures, detailed below. (The same instruments and assessment schedules were used in both trials, with a few minor exceptions.)

Between the two trials, then, oral duloxetine doses of 20 mg once daily, 60 mg once daily, and 60 mg twice daily, were evaluated for efficacy. According to Lilly the 60 mg QD and 60 mg BID doses were chosen for Phase 3 efficacy trials "because they were found to relieve pain in depression studies" and the 20 mg/day dose was included in Study HMAW "so as to establish a subtherapeutic dose of duloxetine in the treatment of DPN."

One other Phase 3 study, HMBT, also evaluated duloxetine in patients with DPN. HMBT, an open-label 28-week safety study (with its own ongoing 24-week extension phase), "had the secondary objective of observing duloxetine's efficacy" according to Lilly. In HMBT patients received either duloxetine 60 mg BID or duloxetine 120 mg QD. Because HMBT was not a controlled study, efficacy measures from HMBT, limited to the Brief Pain Inventory (BPI) and the Clinical Global Impressions of Severity (CGI-Severity) scales, were not considered in this review of efficacy.

In all three DPN studies (HMAW, HMAVa, and HMBT), study inclusion required a diagnosis of bilateral peripheral neuropathy caused by Type 1 or Type 2 diabetes mellitus. Pain was to have begun have in the feet, with relatively symmetrical onset, and to have been present for at least six months. A score of at least three on the Michigan Neuropathy Screening Instrument (MNSI) was also required for inclusion. The minimum age for inclusion in all studies was 18. There was no maximum age limit. Lilly states that they to ensure "a homogenous population of DPN patients, achieving a balance between the pragmatics of protecting vulnerable patient groups and the generalizability and validity of the results."

Noteworthy exclusion criteria common between Studies HMAW and HMAVa were as follows: current (within the past year) Axis I diagnosis of major depressive disorder, dysthymia, generalized anxiety disorder, alcohol or eating disorders as determined by the Mini-International Neuropsychiatric Interview (MINI) or a previous diagnosis; any present or previous diagnosis of mania, bipolar disorder, or psychosis; a history of substance abuse or dependence within the past year; serious or unstable cardiovascular, hepatic, renal, respiratory, or hematologic illness, symptomatic peripheral vascular disease, or other medical condition; ALT > 1.5 times upper limit of normal (ULN); prior renal transplant, current renal dialysis, or met criteria for abnormal serum creatinine; previous exposure to drugs known to cause neuropathy or a history of a medical condition, including pernicious anemia and hypothyroidism, that could be responsible for neuropathy; pain that could not be clearly differentiated from or conditions that interfere with the assessment of DPN.

As noted above, HMAW utilized clinical sites in the USA (with PR), Canada and Argentina. HMAVa utilized sites only in the USA (with PR). HMBT was performed in Australia, North and South America, and Taiwan.

6.1 Indication

The sponsor's proposed indication statement reads "Cymbalta is indicated for the —— (see CLINICAL STUDIES)."

6.1.1 Methods

Some efficacy results presented in this review were adapted from those reported by the Applicant. In those cases, Lilly defined the analysis populations. All Lilly efficacy analyses utilized a last-observation-carried-forward (LOCF) scheme for imputation of missing data. Baseline-observation-carried-forward (BOCF) analyses were performed (for HMAW and HMAVa) for the primary outcome measure, and are reported side-by-side with the Lilly analyses. Dr. Mahboob Sobhan, statistical reviewer also replicated Lilly's primary efficacy analyses for HMAW and HMAVa, using LOCF imputation. His analyses confirmed Lilly's.

Table 6.2: Replication of Primary Efficacy Analyses (Dr. Sobhan)

			p-value	vs.	Placebo
Study	**Population**	**N**	**vs. 20QD**	**vs. 60QD**	**vs. 60BID**
HMAW	ITT Population (LOCF)	443	0.19	<0.001	<0.001
	Discontinued	(113)?			
	Completers Only	347	0.13	<0.001	<0.001
	'Modified ITT'	443	0.13	<0.001	<0.001
HMAVa	ITT Population (LOCF)	327	--	<0.001	<0.001
	Discontinued	(86)?			
	Completers Only	245	--	<0.001	<0.001
	'Modified ITT'	326	--	<0.01	<0.03

Source: Statistical reviewer, Dr. Sobhan

6.1.2 General Discussion of Endpoints

Eleven-point Likert scales are often used to assess degrees of pain, and relief from pain, in clinical studies. The clinical relevance of these types of scales must always be considered in clinical trial design, however. In analgesic efficacy trials, it's especially important to consider what amount of change would be "clinically meaningful" for most patients in the target population (in absolute as well as proportional terms).

These questions have been addressed by many investigators, and several well accepted concepts, and instruments, have emerged. One widely referenced article, examining data from 2724 patients participating in 10 pain studies, demonstrated that a 30% decrease in a linear pain scale corresponded with a two-point reduction in the Patient's Global Impression of Change scale (itself considered to be well validated), representing a "clinically important" difference (Farrar, et al. 2001). Another study showed that a 20% reduction in a linear 11-point numeric rating scale corresponded to "minimal" improvement, but a 35% reduction corresponded to "much" improvement (Cepeda et al. 2003). The 30% reduction had also been agreed upon at the August 2002 end-of-phase-2 meeting.

Lilly's two DPN efficacy trials, HMAW and HMAVa used the same primary efficacy endpoint; the reduction in pain severity, as measured by the weekly mean of the daily '24-hour average pain' scores (recorded daily in a diary). An 11-point Likert scale, allowing scores from 0 ('no pain') to 10 ('worst possible pain') was used for pain ratings.

'Clinical response' was (pre)defined as a $\geq$ 30% reduction from baseline, on the 24-hour average pain severity score (at each specified endpoint). 'Sustained response' was defined as a $\geq$ 30% reduction from baseline to endpoint in the 24-hour average pain severity, at study completion, with a $\geq$ 30% reduction from baseline at a visit other than the last visit, and at least $\geq$ 20% reduction maintained at every study visit between the first visit at which the patient achieves 'clinical response' and study endpoint.

Secondary efficacy measures used in both HMAW and HMAVa included:

- weekly means of night pain and 24-hour worst pain, from the daily diary
- BPI-Severity and Interference
- CGI-Severity
- Patient Global Impression of Improvement (PGI-Improvement) scale
- Sensory portion of the Short-form McGill pain questionnaire
- Dynamic allodynia, assessed by the clinician using a brush stroke (to the same body location at baseline and endpoint), to elicit a pain rating (on a four point, zero to three scale).

Although HMAW and HMAVa both excluded patients meeting diagnostic criteria for major depression, they incorporated 'paper-and-pencil' depression assessment instruments, throughout both acute-therapy and open-label follow-up phases. (Lilly intended "to examine whether the pain inhibitory effect assessed by the weekly mean of the 24-hour pain average severity scores was a direct pain inhibitory effect of duloxetine therapy and not dependent upon the improvement of depression or anxiety symptoms.")

Study HMAW used the Beck Depression Inventory (BDIII) and the Beck Anxiety Inventory (BAI). Study HMAVa used the 17-item Hamilton Depression Rating Scale ($HAMD_{17}$).

The HMAW and HMAVa study reports also state that "Although not specified as a secondary outcome measure in the protocols, concomitant use of acetaminophen was collected in patient diaries in Studies HMAW and HMAVa, and the analysis of these data was specified in the protocols."

Health outcome measures (both studies) included the Short Form-36 (SF-36) and the EQ-5D version of the EuroQoL instrument.

6.1.3 Imputation of Missing Data

For both HMAW and HMAVa, several efficacy analyses were undertaken. The Applicant prospectively identified as the outcome of primary interest a comparison across treatment groups of the *final (endpoint) weekly mean pain score*, defined as the mean of all available daily pain diary entries since the prior (weekly) visit. If less than three daily entries were available, though, the weekly mean would be considered missing (for that week). Where patients did not continue until the final study week, the last available (weekly) mean pain scores were used.

This last-observation-carried-forward (LOCF) approach in chronic pain studies has a number of drawbacks. For instance, patients achieving adequate symptom control but experiencing intolerable side effects often terminate a study with "good" pain scores, which are carried forward in the LOCF analysis. However, these subjects are true treatment failures because they were unable to tolerate the dose necessary to achieve symptom control. Therefore, the LOCF analysis may overestimate the benefits of a drug, when many patients drop-out due to intolerable side effects. If a patient terminates prior to study end, but a baseline observation is carried forward, the change from baseline is, by definition, zero, and the patient would categorized as a non-responder.

The Agency's thinking has evolved regarding efficacy analyses for chronic pain trials, and at present, emphasis is placed on evaluation of responder rates, calculated using a BOCF imputation strategy. This preference was not communicated to Lilly during protocol review, or prior to NDA submission, however. Consequently, all Lilly efficacy analyses utilized a last-observation-carried-forward scheme for imputation of missing data.

In the review below, I present the Applicant's original analyses followed by the BOCF analyses conducted at Agency request (after NDA filing). In no case, does the (primary) efficacy conclusion change as a result of the BOCF analysis.

6.1.4 Study Design

Both efficacy studies submitted in support of the DPN indication, HMAW and HMAVa, conformed with the regulations on the design of "adequate and well-controlled studies" as stipulated in 21CFR 314.126. Although allowing for a reasonable assessment of

duloxetine benefit in the treatment of pain cause by diabetic peripheral neuropathy, dose finding efforts may have been less than ideal, however.

6.1.5 Efficacy Findings (with Individual Study Descriptions)

6.1.5.1 Study HMAW

Title: A Dose-Response Study of Duloxetine vs. Placebo in Patients with Painful Diabetic Neuropathy.

Protocol HMAW was submitted March, 2001. The first patient was enrolled on June 14, 2001 and the last patient completed (the acute phase of) the study on March 30, 2002. There were no formal protocol amendments to HMAW.

6.1.5.1.1 Objectives, Population and Design

6.1.5.1.1.1 Objectives

The protocol specified primary objective of HMAW was "to assess the efficacy of duloxetine 60 mg BID compared with placebo in reducing pain severity in patients with painful diabetic neuropathy at the last visit of a 12-week, double-blind, acute therapy phase." The primary outcome measure was the weekly mean of the 24-hour average pain severity scores recorded daily on an 11-point Likert scale.

The secondary objectives of HMAW were:

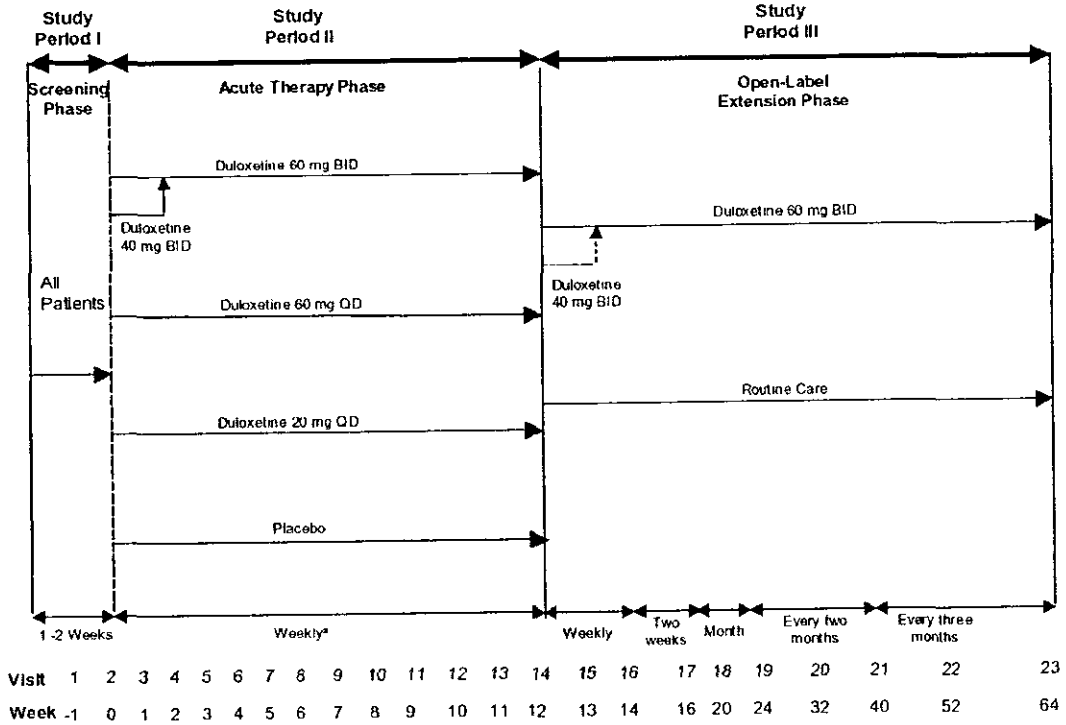
- To evaluate the dose-response relationship at the last visit of the acute therapy phase among duloxetine 20 mg once daily (QD), 60 mg QD, and 60 mg BID in terms of reducing the pain severity as measured by the weekly mean of the 24-hour average pain severity scores.
- To assess the efficacy of duloxetine 60 mg BID, 60 mg QD, and 20 mg QD versus placebo over a 12-week acute therapy phase as measured by:
  - Clinical Global Impression of Severity (CGI-Severity)
  - Patient Global Impression of Improvement (PGI-Improvement) scale
  - Brief Pain Inventory (BPI) of Severity and Interference (Cleeland and Ryan 1994)
  - Weekly means of night pain and worst daily pain from the daily diary
  - Sensory portion of the Short-Form McGill Pain Questionnaire (SF-MPQ) (Melzack 1987).
  - Dynamic allodynia
  - Static allodynia (assessed only at a subset of study sites)
- To evaluate whether the analgesic effect assessed by the weekly mean of the 24-hour pain average severity scores is a direct analgesic effect of duloxetine therapy and not dependent upon the improvement of depression or anxiety symptoms (that is, a pseudospecific effect). Depression and anxiety symptoms were assessed using the Beck Depression Inventory (BDI-II) (Beck et al. 1996) and the Beck Anxiety Inventory (BAI) (Beck et al. 1988).
- To evaluate the safety of duloxetine 60 mg BID, 60 mg QD, and 20 mg QD versus placebo over a 12-week acute therapy phase as measured by:
  - Discontinuation rates

- Treatment-emergent adverse events (TEAEs)
- Laboratory assessments, including lipid profile and glycosylated hemoglobin
- Vital signs Electrocardiograms, (ECGs) and "significant hypoglycemic events."

- To evaluate the safety of up to one year of exposure to duloxetine 60 mg BID with regard to the progression of diabetic complications, as measured by the Michigan Neuropathy Screening Instrument (MNSI) (neuropathy progression) (Feldman et al. 1994), microalbumin/creatinine ratio (nephropathy progression), and an ophthalmologic exam with retinogram (retinopathy progression).
- To assess the impact of treatment with duloxetine 60 mg BID, 60 mg QD, and 20 mg QD versus placebo over the acute therapy phase of the study on patient-reported health outcomes, as measured by the:
  - Short Form 36 (SF-36®) (Ware et al. 1993)
  - EQ-5D® version of the Euro-QoL instrument (Kind 1996).

6.1.5.1.1.2 Study Design

HMAW was to be a multicenter, parallel group, double-blind, randomized, placebo-controlled study. The acute treatment period was to last for twelve weeks, and then be followed by a one-year, open-label extension period.



Source: Sponsor Diagram HMAW.9.1

6.1.5.1.1.3 Study Population

Inclusion Criteria

Patients would be eligible to enroll only if they met **all** of the following criteria:

1. Male or female outpatients at least 18 years of age.
2. Presents with pain due to bilateral peripheral neuropathy caused by Type 1 OR Type 2 diabetes mellitus. Pain must have begun in the feet with relatively symmetrical onset. Daily pain present for at least six months. Diagnosis must be confirmed by a score of at least three on the MNSI.
3. Glycosylated hemoglobin (HgbA1c) = 12% at Visit 1
4. Mean pain score of at least 4 on the 24-hour average pain severity score from the patient diary at Visit 2
5. Full completion of the daily diaries for at least 80% of the days
6. Educational level and degree of understanding such that the patient could communicate intelligibly with the investigator and study coordinator
7. Judged to be reliable and agree to keep all appointments for clinic visits, tests, and procedures required by the protocol.

Exclusion Criteria

Patients were to be excluded if they met **any** of the following criteria:

1. Are investigator site personnel directly affiliated with the study, or are immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
2. Women who were pregnant or breast-feeding; women of child-bearing potential who were not using a medically accepted means of contraception when engaging in sexual intercourse (including IUD, oral contraceptive, implant, Depo-Provera®, or barrier devices with spermicide).
3. Current (≤1 year) DSM IV Axis I diagnosis of depression, major depressive disorder, depression-partial remission, dysthymia, generalized anxiety disorder, or alcohol or eating disorders as determined by the Mini-International Neuropsychiatric Interview (MINI).
4. Any current or historical diagnosis of mania, bipolar disorder, or psychosis, as determined by the MINI.
5. Serious cardiovascular, hepatic, renal, respiratory, or hematologic illness, symptomatic peripheral vascular disease, or other unstable medical (including unstable hypertension) or psychological conditions that in the opinion of the investigator would compromise participation or be likely to lead to hospitalization during the duration of the study.
6. Total bilirubin > 1 times upper limit of normal range and/ or ALT > 1.5 times upper limit of normal, based on Lilly reference ranges.
7. Prior renal transplant, current renal dialysis, or serum creatinine laboratory value outside of Lilly reference range at Visit 2.
8. Abnormal thyroid-stimulating hormone (TSH) concentrations. Note: Patients previously diagnosed with hyperthyroidism or hypothyroidism who had been treated on a stable dose of thyroid supplement for at least the past 3 months, had medically appropriate TSH concentrations, and were clinically euthyroid were allowed.
9. Pain that cannot be clearly differentiated from, or conditions that interfere with the assessment of the diabetic neuropathy pain. Examples of painful conditions that could

be confused with diabetic neuropathy pain include peripheral vascular disease (ischemic pain); neurological disorders unrelated to diabetic neuropathy (for example, phantom limb pain from amputation); skin condition in the area of the neuropathy that could alter sensation (for example, plantar ulcer); and other painful conditions (for example, arthritis).

10. Historical exposure to drugs known to cause neuropathy (for example, vincristine), or a history of a medical condition, including pernicious anemia and hypothyroidism, that could have been responsible for neuropathy.
11. Patients who had previously completed or withdrawn from this study or any other study investigating duloxetine.
12. Treatment within the last 30 days with a drug that had not received regulatory approval at the time of study entry.
13. Treatment within the last 30 days with a drug that had not received regulatory approval at the time of study entry.
14. Patients taking protocol-excluded medications(s) within seven days of Visit 2.
15. Treatment with a monoamine oxidase inhibitor (MAOI) or fluoxetine within 30 days of Visit 1.
16. Opioid use during the three days prior to Visit 1.
17. History of substance abuse or dependence within the past year, excluding nicotine and caffeine.
18. A positive urine drug screen for any substances of abuse. Note: If the patient has a positive drug screen at Visit 1, a retest could be performed prior to Visit 2 if the positive test was for a prescribed medication that may not have had an adequate wash-out period. If the retest was positive, the patient was excluded.
19. Frequent and/ or severe allergic reactions with multiple medications.

6.1.5.1.2 Treatments

During the 12-week, randomized, double-blind phase, patients were to receive one of four treatments; duloxetine 60 mg BID, duloxetine 60 mg QD, duloxetine 20 mg QD, or placebo. Patients assigned to duloxetine 60 mg BID were to initiate therapy with duloxetine 40 mg BID for 3 days before titrating up to the 60 mg BID dose.

6.1.5.1.3 Efficacy Variables (HMAW)

The weekly mean of the '24-hour average pain' score, recorded daily on the 11-point Likert scale, was to serve as the primary efficacy measure.

The following secondary efficacy measures were also to be performed (see detailed Study Schedule):

- **Pain Severity for average, worst pain and night pain** as measured by an 11-point Likert scale, completed daily by the patient in a diary. This is an ordinal scale with scores from 0 (no pain) to 10 (worst possible pain).
- The **Clinical Global Impression of Severity** (CGI-Severity) scale was to be administered by a physician investigator overseeing the clinical care of the patient in the presence of the patient. The CGI-Severity evaluates the severity of illness at the time of assessment. The score ranges from 1 (normal) to 7 (most severe illness).

- The **Patient Global Impression of Improvement** (PGI-Improvement) scale was to be completed by the patient to measure the degree of improvement at the time of assessment. The score ranges from 1 (normal) to 7 (most severe illness).
- The **Brief Pain Inventory (severity scales)** was to be completed by the patients to measure the severity of pain, and the interference of pain on function. Both scores range from 0 to 10.
- **Beck Depression Inventory-II** (BDI-II) was to be completed by the patient to rate the severity of depressive symptoms and any improvement during the course of the study. The total score ranges from 0 to 63; the higher the score, the more severe the depressive symptoms.
- **Beck Anxiety Inventory (BAI)** was to be completed by the patient to rate severity of anxious symptoms and any improvement during the course of the study. The total score ranges from 0 to 63; the higher the score, the more severe the anxiety symptoms.
- **Sensory Portion of the Short Form McGill** Pain Questionnaire was to be completed by the patient. This instrument consists of 11 pain descriptors, each of them scored from 0 (none) to 3 (severe).
- **Allodynia** as measured by:
  - Dynamic allodynia was to be assessed by the clinician using a brush stroke (to the same body location at baseline and endpoint) to elicit from the patient the pain severity. The score ranges from 0 (no pain) to 3 (severe)
  - Static allodynia was to be assessed (at selected sites only) as the highest pressure applied by von Frey hairs (to the same body location at baseline and endpoint) before producing pain.

6.1.5.1.4 Analysis Plan (HMAW)

When a total score was to be calculated from individual items, it would be considered missing if any of the individual items were missing. No adjustments for multiple comparisons were to be made. No justification was to be made for any of the pairwise comparisons, "given that the interests of the study are to evaluate each individual duloxetine dose versus placebo in terms of efficacy."

The HMAW analysis plan stated "the main interest of the study is to evaluate the efficacy of each duloxetine dose, especially the duloxetine 60 mg BID, versus placebo in the treatment of pain due to diabetic neuropathy. Therefore, the treatment group comparison for efficacy analyses, except for dose response evaluation, will be the pairwise comparison between each duloxetine dose group and placebo treatment group. Unless stated otherwise, the phrase " to evaluate treatment group differences" in this section implies that the treatment group difference in each pair of duloxetine dose group (60 mg BID, 60 QD, and 20 mg QD) and placebo group will be assessed by the corresponding contrast in the specific statistical model, or by the specific test."

6.1.5.1.4.1 Analysis Plan, Primary Efficacy Measure

The primary efficacy measure was to be the weekly mean of the 24-hour average pain severity score (on the 11-point Likert scale), which would be computed from the daily diary scores. The primary efficacy analysis would test the difference in the 24-hour

average pain score, between the duloxetine 60 mg BID and placebo treatment groups, at the last visit of the acute therapy (after accounting for differences in baseline scores). A likelihood-based, mixed-effects repeated measures analysis of all weekly data, after randomization, would be used. The model was to include the fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline score and baseline-by-visit interaction.

6.1.5.1.4.2 Analysis Plan, Secondary Efficacy Measures

Secondary efficacy measures were to include:

- Weekly mean score of the 24-hour *worst* pain severity on the 11-point Likert scale
- Weekly mean score of the average *night* pain severity in the 11-point Likert scale
- Weekly Brief Pain Inventory (BPI): Severity (4 items: worst, least, average, and current) and Interference (7 items: general activity, mood, walking ability, normal work, relations to others, sleep, and enjoyment of life)
- PGI-Improvement (All post-baseline data)
- Monthly CGI- Severity and PGI- Improvement scores
- Monthly total Beck Depression Inventory (BDI) and total Beck Anxiety Inventory (BAI) scores
- The sensory portion of Short- Form McGill Pain Questionnaire (SF-MPQ) assessment at the randomization visit and at the last visit of the acute therapy phase (the sensory component consists of 11 pain descriptors: throbbing, shooting, stabbing, sharp, cramping, gnawing, hot- burning, aching, heavy, tender, splitting)
- Dynamic allodynia (measuring the response to the touch of brush) and static allodynia (measuring the pressure threshold before painful response to Von Frey hairs test) assessment at the randomization visit and at the last visit of the acute therapy phase

Pain Severity for average, worst and night pain (as measured by 11-point Likert scale), and BPI, CGI, BDI and BAI scores as measured by an 11-point Likert scale, were to be analyzed by the repeated measures analysis described above

PGI-Improvement was to be analyzed primarily by a repeated measures analysis, similar to the one described above, with the modifications that there would be no baseline and baseline-by-treatment effects in the model. In addition, the observed scores at each post-baseline visit were to be analyzed an ANOVA model.

Change from baseline to endpoint in the 24-hour *worst pain*, *least pain* and *night pain* scores was to be analyzed using an ANCOVA model. Within-group change was to be analyzed by Student's t-test.

'Response' and 'sustained response' rates (defined above) based on *the average 24-hour pain severity*, were to be summarized by treatment group. The proportions were to be analyzed by Fisher's Exact test.

Kaplan-Meier survival curves of time-to-event were to be calculated, by treatment group, for

time to 'sustained response' and *to first 30% reduction* in the 24-hour pain severity. In the calculation, patients who do not have the event were to be considered as right-censored observation. The comparison of the survival curves among and between treatment groups was to be conducted using log-rank test and Wilcoxin tests.

6.1.5.1.4.3 Sample Size

Approximately 440 patients in total were to be enrolled, into four treatment groups (placebo, duloxetine 20 mg QD, 60 mg QD, 60 mg BID). With 110 patients per arm, the study would have at least 90% power to detect a treatment group difference of -1.20 points in the weekly mean of the 24-hour average pain severity, between duloxetine 60 mg BID and placebo (after three months of acute therapy). The sample size was determined using a two-sided test with $\alpha = 0.05$, assuming a common standard deviation of 2.2 and a discontinuation rate of 35%.

6.1.5.1.4.4 Missing Data

All efficacy analyses (examined in this review) were to utilize data obtained during the 'acute therapy phase,' the time interval in which the randomized treatment was to be administered: from Study Visit 2 through Visit 14. The primary efficacy analysis was to be performed on the set of all randomized patients with a baseline score and at least one post-baseline score. 'Baseline' would refer to the last non-missing observation at or before Visit 2. 'Endpoint' would be the last non-missing observation from Visit 3 through Visit 14.

Patients were to complete diary pain assessments ("worst" "least") daily, but efficacy analyses were to be conducted using weekly means. The baseline values (for each diary pain assessment) were to be the average of the last three non-missing diary scores before the randomization visit (Visit 2). Pain diary scores for each of the weekly post-baseline visits, was to be the average of all scores recorded since the last weekly visit, up to seven daily scores for each diary parameter. If less than three daily observations were recorded since the last visit (out of seven possible), the score for that week (for that parameter) would be considered missing.

6.1.5.1.4.5 Planned Analyses for Dose-Response Relationship

The dose-response relationship among duloxetine 20 mg QD, 60 mg QD, and 60 mg BID was to be "primarily evaluated using appropriate treatment contrast in the repeated measures analysis," described above, for the 24-hour average pain score at the last visit of the acute therapy phase. The appropriate treatment contrast in the ANCOVA model for the change from baseline to endpoint in 24-hour average pain score was to be the second evaluation. In both analyses, the contrast was to use 20, 60 120 as the scale. In addition, the proportion of responders and sustained responders in duloxetine 20 mg QD, 60 mg QD, and 60 mg BID treatment groups were to be "analyzed by the CMH non-zero correlation test controlling for investigator to evaluate the dose- response trend."

6.1.5.1.4.6 Sample Size

Approximately 440 patients in total were to be enrolled, into four treatment groups (placebo, duloxetine 20 mg QD, 60 mg QD, 60 mg BID). With 110 patients per arm, the

study would have at least 90% power to detect a treatment group difference of -1.20 points in the weekly mean of the 24-hour average pain severity, between duloxetine 60 mg BID and placebo (after three months of acute therapy). The sample size was determined using a two-sided test with $\alpha = 0.05$, assuming a common standard deviation of 2.2 and a discontinuation rate of 35%.

6.1.5.1.5 Detailed Schedule of Assessments and Study Events

See diagram above 'Study Population' section above.

6.1.5.1.6 Concomitant Medications

In general, concomitant medications with primarily central nervous system activity were not to be allowed in the acute phase. Several medications were to have fewer restrictions in the extension phase than in the acute phase.

6.1.5.1.7 Protocol Amendments, Changes in Study Conduct

6.1.5.1.7.1 Protocol Amendments

There were no formal amendments to protocol HMAW

6.1.5.1.7.2 Changes in Study Conduct

Static allodynia measures were to be obtained at two of the study sites. According to the sponsor, the two sites selected were chosen because they were the only ones in possession of the necessary equipment. Study staff had received appropriate training in use of this equipment (prior to and independent from, participation in this study) at only one of the two sites, however. The sponsor's plan was for the 'trained' staff, at allodynia site #1, to train the study staff at allodynia site #2. According to the sponsor, "Due to other circumstances," the site responsible for training the second site was not selected for the study. The only study site having the necessary equipment, and still participating in the trial, did not have staff trained to use this equipment, then, so "static allodynia was not performed in this study."

Protocol HMAW called for the data for the primary efficacy measure, the 24-hour average pain severity, to be collected by an interactive voice response system (IVRS) at each visit, and monitored using the "triangular test" to determine if an interim analysis would be needed. According to the sponsor "While the data were collected via IVRS, the data monitoring was not done and no interim analysis was completed. This monitoring was planned to provide guidance for planning other studies, however, when this study was implemented it was determined that no monitoring would be necessary and that other studies would be planned using other available information."

6.1.5.1.7.3 Changes in Planned Analyses

Due to the low number of patients from non-Caucasian populations, Lilly's subgroup analysis for ethnic origin used only two sub-groups; Caucasian and non-Caucasian.

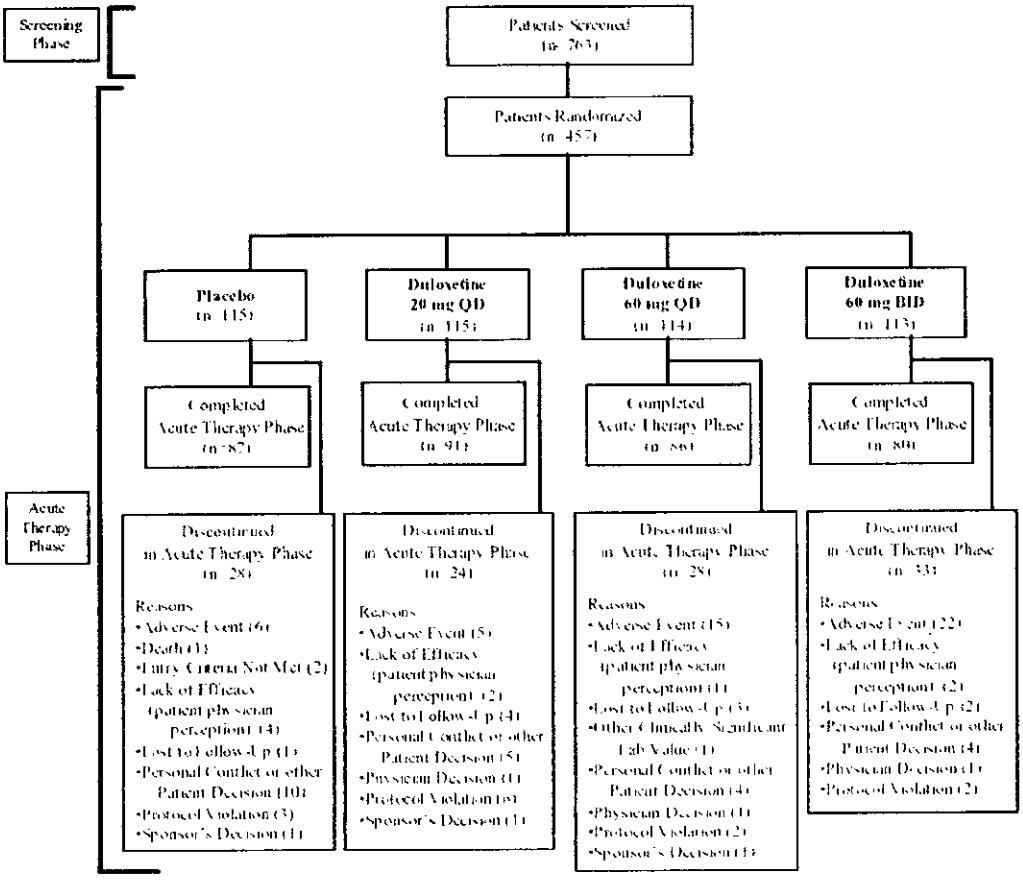
Also, in addition to the planned categorical analysis of acetaminophen usage, an analysis of variance was performed on the average acetaminophen use. The ANOVA model included terms for therapy and investigator.

6.1.5.1.8 Study Conduct

6.1.5.1.8.1 Subject Disposition

The figure below summarizes patient disposition during the screening and acute therapy phases. Seven-hundred and sixty-three patients entered the screening phase. Of these patients, 457 patients met entry criteria and were randomly assigned to one of four treatment groups. The number of patients that discontinued during the acute therapy phase, 113 (24.7%), was not exceptionally high for a twelve-week DPN (pain treatment) trial. A total of 344 (75.3%) patients completed the acute therapy phase (87 [75.7%] placebo-treated, 91 [79.1%] duloxetine 20 mg QD-treated, 86 [75.4%] duloxetine 60 mg QD-treated and 80 [70.8%] duloxetine 60 mg BID treated). The reasons for patient disposition (completed acute therapy phase, discontinued due to adverse events, discontinued due to lack of efficacy, etc.) were summarized by percentages within each treatment group. The treatment group differences were evaluated using a Fisher's exact test.

HMAW Patient Disposition (per Applicant)



Source: Applicant Diagram HMAW.10.1

6.1.5.1.8.2 Reasons for Discontinuation

The applicant's assessment for reason for discontinuation are in the table below.

HMAW Applicant Assessment of Reasons for Discontinuation

Primary Reason	Placebo n=115(%)	DLX20QD n=115	DLX60QD n=114	DLX60BID n=113	Total n=457
AE ** (p<0.001)	6 (5.2)	5 (4.3)	15 (13.2)	22 (19.5)	48 (10.5)
Death	1 (0.9)	0	0	0	1 (0.2)
Lost to Follow-up	1 (0.9)	4 (3.5)	3 (2.6)	2 (1.8)	10 (2.2)
Personal Conflict/ Patient Decision	10 (8.7)	5 (4.3)	4 (3.5)	4 (3.5)	23 (5.0)
Entry Criteria Not Met	2 (1.7)	0	0	0	2 (0.4)
Sponsor Decision	1 (0.9)	1 (0.9)	1 (0.9)	0	3 (0.7)
Physician Decision	0	1 (0.9)	1 (0.9)	1 (0.9)	3 (0.7)
Clin. Significant Lab Value	0	0	1 (0.9)	0	1 (0.2)
Protocol Violation	3 (2.6)	6 (5.2)	2 (1.8)	2 (1.8)	13 (2.8)
Lack of Efficacy	4 (3.5)	2 (1.7)	1 (0.9)	2 (1.8)	9 (2.0)
Complete Acute, No Ext.	2 (1.7)	3 (2.6)	2 (1.8)	1 (0.9)	8 (1.8)
Complete/Continuing Ext.	85 (73.9)	88 (76.5)	84 (73.7)	79 (69.9)	336 (73.5)

DLX60QD vs. DLX60BID, all pairwise comparisons, p>0.37
**Fisher's Exact Test
Source: Applicant Table HMAW.10.1

6.1.5.1.8.3 Protocol Deviations and Violations

Relatively few patients (≈13/457 or 2.8%) (were) discontinued during the acute therapy phase because of protocol violations. These protocol violations appear to have been distributed across treatment arms, and no changes in the analysis plan were taken.

Table 6.YY: HMAW Protocol Deviations and Violations
(Subjects not randomized due to failure to meet inclusion criteria, included)

Deviation/Violation	Total	Excluded	Placebo	20QD	60QD	60BID
Inadequate informed consent	29	2	8	7	9	3
Drug accountability issue	9	0	0	4	3	2
Entry criteria error	7	0	1	2	1	3
"Lab issues"	21	4	1	6	5	5
Visit schedule inadherence	18	2	4	6	3	3
Assessment schedule errors	35	1	10	7	8	9
Excluded medication use	9	0	2	5	2	0
Significant diary errors	4	Site 110	1	2	0	0

Source: Compiled from HMAW data listings (pages 2075-2078)

Only patients with baseline (10-point Likert scale) pain scores of 4 or higher were supposed to be enrolled. The tabulations of baseline disease characteristics showed that a number of patients with scores below 4 were included, however.
There were 17 patients enrolled in HMAW that appear not to have met inclusion criteria for (diary rated) baseline mean pain score. The table below shows the baseline pain scores of the protocol violations, by treatment arm.

Baseline 24-hour average pain scores not meeting inclusion criteria

Baseline	Placebo	20 mg QD	60 mg QD	60 mg BID	Total
1.33	0	1	0	0	1
3	1	0	1	0	2
3.33	2	2	1	2	7
3.67	1	3	3	0	7

These patients were also distributed roughly equally across treatment arms. Only one patient had a baseline score below 3. These protocol violations were also unlikely to have introduced any bias.

HMAW Protocol Deviations and Violations

(Subjects not randomized due to failure to meet inclusion criteria, included)

Deviation/Violation	Total	Excluded	Placebo	20QD	60QD	60BID
Inadequate informed consent	29	2	8	7	9	3
Drug accountability issue	9	0	0	4	3	2
Entry criteria error	7	0	1	2	1	3
"Lab issues"	21	4	1	6	5	5
Visit schedule inadherence	18	2	4	6	3	3
Assessment schedule errors	35	1	10	7	8	9
Excluded medication use	9	0	2	5	2	0
Significant diary errors	4	Site 110	1	2	0	0

Source: Compiled from HMAW data listings (pages 2075-2078)

The protocol deviations and violations were distributed roughly equally across treatment arms, and were unlikely to have introduced any bias.

6.1.5.1.9 Datasets Analyzed (by Applicant)

All analyses were conducted on an intent-to-treat (ITT) basis. All randomly assigned patients with at least one post-baseline follow-up were included in Lilly's efficacy analyses. All randomized patients were included in all safety analyses.

6.1.5.1.9.1 Excluded Patients

HMAW patients excluded from primary efficacy analysis (missing post-baseline data, for 24-hour average pain score).

HMAW Patients Excluded

Patient (Investigator)	Treatment	Baseline

1208 (102)	DLX60BID	8.00
1221 (102)	DLX60QD	5.67
1230 (102)	Placebo	6.33
1322 (102)	DLX20QD	4.00
1413 (103)	Placebo	5.33
1617 (104)	Placebo	6.33
2002 (106)	DLX60BID	5.33
2013 (106)	DLX60BID	9.00
2827 (110)	DLX60QD	8.33
3428 (113)	DLX20QD	6.67
4026 (116)	DLX60BID	7.33
4033 (116)	DLX20QD	8.00
4822 (120)	DLX20QD	10.00
6201 (505)	Placebo	8.00

Source: Applicant Table HMAW.16.2.4

6.1.5.1.10 Patient Demographics/Group Comparability

The tables below summarize patient demographics (age, gender, ethnic origin) and disease characteristics (type of diabetic mellitus, duration of diabetes, duration of diabetic neuropathy, and baseline neuropathic pain) for all randomized patients.

There was a statistically significant difference between treatment groups in gender ratio (p=.033). While males composed 61.5% (281/457) of the total patient population, the percentage of males in each treatment group varied from 51.3% (59/115) in the placebo group to 69.3% (79/114) in the duloxetine 60 mg once daily (QD) group. Mean patient age at baseline 60.1 years overall, varied little between treatment groups. The mean time since diabetes diagnosis was 11.3 years, overall, with Type 2 diabetes being most prevalent (88% of patients).

The mean of the baseline Michigan Neuropathy Screening Score was 5.2 overall, varying little between treatment groups. Mean time since DPN diagnosis, 2.55 years overall, also varied little between treatment groups. There were, however, two patients whose 'time since DPN diagnosis' was in negative years (-0.31 and -0.07), both in the DLX60QD group.

Lilly analyzed baseline 24-hour average pain score, by treatment group, and by demographic variables (overall treatment group differences were examined using the ANOVA model, with the terms of treatment and investigator for the continuous variables, and the Fisher's exact test for the categorical variables). No differences were found (between treatment groups).

HMAW Baseline Patient Demographics

Characteristic	Placebo n=115	20QD n=115	60QD n=114	60BID n=113	Total n=457
Ethnicity					
African Descent	11 (9.6)	12 (10.4)	8 (7.0)	6 (5.3)	37 (8.1)
Western Asian	0	3 (2.6)	2 (1.8)	1 (0.9)	6 (1.3)
Caucasian	89 (77.4)	85 (73.9)	88 (77.2)	91 (80.5)	353 (77.2)
East/Southeast Asian	2 (1.7)	2 (1.7)	2 (1.8)	0	6 (1.3)
Hispanic	12 (10.4)	12 (10.4)	13 (11.4)	14 (12.4)	51 (11.2)
Other	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)	4 (0.9)
Chi-square (p=0.915)					
Mean Age	60.42	60.31	59.21	60.50	60.11
Median Age	61.25	61.38	59.31	61.94	61.10
Age Range	23.9-80.6	29.9-82.7	30.8-88.8	22.4-79.1	22.4-88.8
ANOVA (p=0.786)					
Female : Male	56 : 59	40 : 75	35 : 79	45 : 68	176 : 281
Chi-square (p=0.033)					

Source: Applicant Tables ISS.6.1.1 and ISS dataset DIABDEMO.XPT

Neuropathy severity

HMAW Baseline Patient DM and DPN Characteristics

Characteristic	Placebo n=115	20QD n=115	60QD n=114	60BID n=113	Total n=457
Type I DM	11 (9.6)	17 (14.8)	14 (12.3)	11 (9.7)	53 (11.6)
Type II DM	104 (90.4)	98 (85.2)	100 (87.7)	102 (90.3)	404 (88.4)
Chi-square (p=0.565)					
DM Duration					
Mean Duration	11.44	12.06	11.42	10.06	11.25
Median Duration	7.52	9.70	9.87	7.49	8.65
Duration Range	0.68-66.49	0.17-40.51	0.35-41.10	0.44-42.77	0.17-66.49
ANOVA (p=0.438)					
DPN Duration					
Mean Duration	4.03	3.65	3.81	3.45	3.74
Median Duration	2.66	2.10	2.56	2.59	2.55
Duration Range	0.02-4.12	0.04-19.87	-0.31*-30.91	0.08-14.06	-0.31*-30.91
ANOVA (p=0.695)					
Baseline 24-Hour Average Pain					
Mean Pain	5.75	5.89	6.03	5.91	5.90
Median Pain	5.33	5.67	6.00	5.67	5.67
Range Pain	2.67*-10.00	1.33*-10.00	3.00-10.00	3.33-10.00	1.33*-10.00
ANOVA (p=0.627)					
Michigan Neuropathy Screen					
Mean	5.13	5.35	5.10	5.29	5.22
Median	5.00	5.00	5.00	5.00	5.00
Range	2.00-9.00	1.00-9.00	1.00-9.00	1.00-9.00	1.00-10.00
ANOVA (p=0.555)					

* These apparent protocol violations are discussed in Section 6

Source: Sponsor Tables HMAW 11.1 and 11.2 and datasets DIABDEMO.XPT

The patient with the baseline score of 2.67 was discontinued (Visit 5). The patient with baseline 1.33 was in the 20 mg QD group, had all subsequent scores below that (last five were 0.857, 0, 0, 0, 0.42).

6.1.5.1.11 Treatment Compliance

During Study Periods II and III (on-treatment), compliance for each visit interval was defined as taking between 80% and 120% of the study medication prescribed for that interval. The protocol required investigative sites to "counsel patients on the importance of study drug compliance and drug accountability," and to repeat this counseling for patients who demonstrated noncompliance. Investigators were allowed to discontinue patients who were "consistently out of the compliance range." Compliance rates did not differ between treatment groups.

6.1.5.1.12 HMAW Applicant's Primary Efficacy Analysis

Protocol HMAW specified the primary efficacy evaluation to be a comparison between treatment groups ("especially the duloxetine 60 mg BID"), of the weekly means of the

24-hour average pain score. The protocol specified use of "a likelihood-based, mixed-effects repeated measures analysis, on all weekly data after randomization." A detailed description of the planned analysis appears in Section 6.1.4.1 above.

The repeated measures analysis (of the weekly means of the '24-hour average pain' scores, only for patients with non-missing pain scores) is presented in Table 6.YY below. Statistically significant treatment-group differences (in the weekly means of the '24-hour average pain' scores), between placebo and duloxetine 60-mg QD, and between placebo and duloxetine 60-mg BID, beginning one-week after initiation of therapy, and persisting through all 12 weeks of the acute phase. That is, duloxetine 60-mg BID and duloxetine 60-mg QD were both (statistically significantly) superior to placebo, at all on-treatment study visits. Duloxetine 60-mg BID was (statistically significantly) superior to duloxetine 20-mg QD at all visits. Duloxetine 60-mg QD was (statistically significantly) superior to duloxetine 20-mg QD at Treatment Weeks 1 through 5 and at Week 11; the treatment effect was in the "predicted" direction for Weeks 6 through 10, and Week 12, with most p-values between 0.05 and 0.10. There were no significant differences in pairwise comparisons between duloxetine 60-mg QD and 60-mg BID, at any of the treatment weeks.

HMAW, Applicant's Primary Efficacy Analysis
Change from Baseline 24-Hour Average Pain Score
Repeated-Measures by Treatment Week (Only Non-Missing Data)

Rx.				LS Mean	Pairwise p-value		
Week	Treatment	N	LS Mean	Change	vs. Placebo	vs. 20QD	vs. 60QD
1	Placebo	111	5.46	-0.43			
	DLX20QD	111	5.21	-0.68	0.173		
	DLX60QD	112	4.57	-1.33	<0.001	<0.001	
	DLX60BID	109	4.46	-1.43	<0.001	<0.001	0.556
2	Placebo	108	4.97	-0.93			
	DLX20QD	107	4.63	-1.27	0.178		
	DLX60QD	105	3.91	-1.99	<0.001	0.004	
	DLX60BID	106	3.78	-2.11	<0.001	<0.001	0.623
3	Placebo	107	4.65	-1.25			
	DLX20QD	106	4.46	-1.4	0.467		
	DLX60QD	101	3.78	-2.11	0.001	0.010	
	DLX60BID	93	3.62	-2.28	<0.001	0.002	0.541
4	Placebo	102	4.54	-1.36			
	DLX20QD	103	4.09	-1.81	0.102		
	DLX60QD	96	3.51	-2.38	<0.001	0.036	
	DLX60BID	92	3.43	-2.47	<0.001	0.018	0.767
5	Placebo	96	4.27	-1.63			
	DLX20QD	100	3.95	-1.95	0.245		
	DLX60QD	94	3.37	-2.53	0.001	0.039	
	DLX60BID	87	3.18	-2.72	<0.001	0.007	0.509

(Table continued on following page)

Source: Modified from Applicant Table HMAW.11.7

HMAW, Applicant's Primary Efficacy Analysis
Change from Baseline 24-Hour Average Pain Score
Repeated-Measures by Treatment Week (Only Non-Missing Data)

Rx. Week	Treatment	N	LS Mean	Change	Pairwise p-value vs. Placebo	vs. 20QD	vs. 60QD
6	Placebo	96	4.26	-1.64			
	DLX20QD	101	3.88	-2.02	0.196		
	DLX60QD	95	3.33	-2.57	0.002	0.061	
	DLX60BID	86	3.10	-2.79	<0.001	0.010	0.458
7	Placebo	92	4.11	-1.79			
	DLX20QD	98	3.75	-2.15	0.229		
	DLX60QD	93	3.33	-2.57	0.010	0.166	
	DLX60BID	83	3.13	-2.76	0.002	0.046	0.524
8	Placebo	91	4.12	-1.78			
	DLX20QD	98	3.76	-2.13	0.223		
	DLX60QD	91	3.20	-2.70	0.002	0.055	
	DLX60BID	84	2.98	-2.92	<0.001	0.009	0.467
9	Placebo	89	4.16	-1.74			
	DLX20QD	93	3.64	-2.26	0.081		
	DLX60QD	87	3.14	-2.76	<0.001	0.093	
	DLX60BID	84	2.95	-2.94	<0.001	0.024	0.544
10	Placebo	90	4.16	-1.74			
	DLX20QD	93	3.64	-2.26	0.079		
	DLX60QD	88	3.20	-2.70	0.002	0.145	
	DLX60BID	82	2.95	-2.95	<0.001	0.025	0.419
11	Placebo	88	3.98	-1.92			
	DLX20QD	90	3.66	-2.24	0.280		
	DLX60QD	88	3.06	-2.84	0.002	0.043	
	DLX60BID	81	2.66	-3.24	<0.001	0.001	0.196
12	Placebo	88	3.99	-1.91			
	DLX20QD	91	3.53	-2.36	0.130		
	DLX60QD	88	3.01	-2.89	0.001	0.082	
	DLX60BID	80	2.66	-3.24	<0.001	0.004	0.251

Source: Modified from Applicant Table HMAW.11.7

6.1.5.1.12.1 Applicant's Additional Analyses of Primary Efficacy Measure (LOCF)

'Baseline-to-endpoint' changes in the weekly means of the '24-hour average pain' scores (mean change analyses) are summarized in the tables below. Again, duloxetine 60-mg BID and duloxetine 60-mg QD were both (statistically significantly) superior to placebo. Both were also (statistically significantly) superior to duloxetine 20-mg QD. Put another way, the following comparisons were statistically significant:

- DLX 60-mg QD ($p<0.001$) and DLX 60-mg BID ($p<0.001$) compared to placebo
- DLX 60-mg QD ($p=0.032$) and DLX 60-mg BID ($p=0.003$) compared to DLX 20-mg QD

Duloxetine 60-mg BID did not differ from duloxetine 60-mg QD.

HMAW, Applicant's Analysis (LOCF), Primary Efficacy Measure
Change from Baseline to Endpoint, Weekly Mean of 24-Hour Average Pain Score

		Baseline		Endpoint		Change	
	n	Mean	Median	Mean	Median	Mean	Median
Placebo	111	5.73	5.3	4.09	3.9	-1.64	-1.3
DLX20QD	111	5.84	5.7	3.69	3.8	-2.16	-1.6
DLX60QD	112	6.01	6.0	3.31	2.9	-2.70	-2.6
DLX60BID	109	5.85	5.7	3.00	2.8	-2.85	-3.0

Source: Modified from Applicant Table HMAW.11.8

Applicant's Results, Using LOCF,
Baseline→Endpoint Change, 24-Hour Average Pain Score
Pairwise Comparisons (LS Means)

	DLX60BID	DLX60QD	DLX20QD
Placebo	<0.001	<0.001	0.189
DLX20QD	0.003	0.032	
DLX60QD	0.403		

Source: Modified from Applicant Table HMAW.11.8
Type II sums of squares from ANOVA

Lilly also calculated, by treatment group, the proportion of 'clinical responders' and 'sustained responders' at endpoint. 'Clinical response' was defined as a reduction in the weekly mean of the 24-hour average pain score, from baseline to endpoint, of 30% or more. 'Sustained response' was defined as a ≥ 30% reduction from baseline to endpoint in the 24-hour average pain severity, at study completion, with a ≥ 30% reduction from baseline at a visit preceding the last visit, and at least ≥ 20% reduction maintained at every study visit between the first visit at which the patient achieves 'clinical response' and study endpoint.

HMAW, Applicant's Results (LOCF), Response Rate at Endpoint
(Response = 24-Hour Average Pain Score Reduced ≥ 30%, Baseline→Endpoint)

			Fisher's Exact Pairwise		
Therapy	**N**	**Responders**	**p vs. Placebo**	**p vs. DLX20QD**	**p vs. DLX60QD**
Placebo	111	52 (46.8%)			
DLX20QD	111	57 (51.3%)	0.591		
DLX60QD	112	72 (64.3%)	0.010	0.080	
DLX60BID	109	71 (65.1%)	0.007	0.041	1.000

Source: Modified from Applicant Table HMAW.11.10

Applicant's Results (LOCF), Sustained-Response* Rate at Endpoint

			Fisher's Exact Pairwise		
Therapy	**N**	**Responders**	**p vs. Placebo**	**p vs. DLX20QD**	**p vs. DLX60QD**
Placebo	111	37 (33.3%)			
DLX20QD	111	51 (45.9%)	0.074		
DLX60QD	112	63 (56.3%)	<0.001	0.141	
DLX60BID	109	61 (56.0%)	0.001	0.141	1.000

*Sustained-response defined in paragraph above table
Source: Modified from Applicant Table HMAW.11.11

6.1.5.1.13 Reviewer Analyses (Primary Outcome Measure – BOCF Analysis)

As discussed above (Section 6.1.3) for efficacy analyses in chronic pain trials, a BOCF imputation strategy offers advantages over LOCF. The table below compares primary efficacy results using each imputation scheme.

HMAW, Primary Efficacy Measure, Change from Baseline to Endpoint, Weekly Mean of 24-Hour Average Pain Score, LOCF Compared with BOCF

LOCF		Baseline		Endpoint		Change	
BOCF	n	Mean	Median	Mean	Median	Mean	Median
Placebo	111	5.73	5.3	4.09	3.9	-1.64	-1.3
DLX20QD	111	5.84	5.7	3.69	3.8	-2.16	-1.6
DLX60QD	112	6.01	6.0	3.31	2.9	-2.70	-2.6
DLX60BID	109	5.85	5.7	3.00	2.8	-2.85	-3.0
Placebo	115	5.75	5.3	4.36	4.1	-1.40	-1.0
DLX20QD	115	5.89	5.7	3.96	4.0	-1.93	-1.1
DLX60QD	114	6.03	6.0	3.63	3.8	-2.40	-1.8
DLX60BID	113	5.91	5.7	3.53	3.4	-2.38	-2.2

Source: Modified from Applicant Table HMAW.11.8 and response (8/27/04)

Change, 24-Hour Average Pain Score (LOCF → BOCF)

	DLX60BID	DLX60QD	DLX20QD	DLX60BID	DLX60QD	DLX20QD
Placebo	<0.001	<0.001	0.189	0.002	0.002	0.111
DLX20QD	0.003	0.032		0.114	0.142	
DLX60QD	0.403		LOCF	0.910		BOCF

Source: Modified from Applicant response (8/27/04) Type II sums of squares from ANOVA

The Table and Diagram on the following page use the agreed upon criteria (≥30% reduction, baseline→endpoint) for 'clinical response' but BOCF for imputation of missing data. Using LOCF, the proportion of 'clinical responders' at endpoint was 46.8% for patients treated with placebo, 51.3% of the 20-mg/day patients, 64.3% of duloxetine 60-mg/day treated patients, and 65.1% of those treated with duloxetine 60-mg BID. All four proportions decrease, with use of BOCF imputation; 38.7% for placebo, 45.9% for 20-mg QD, 55.4% for 60-mg QD, and 56.0% for 60-mg BID.

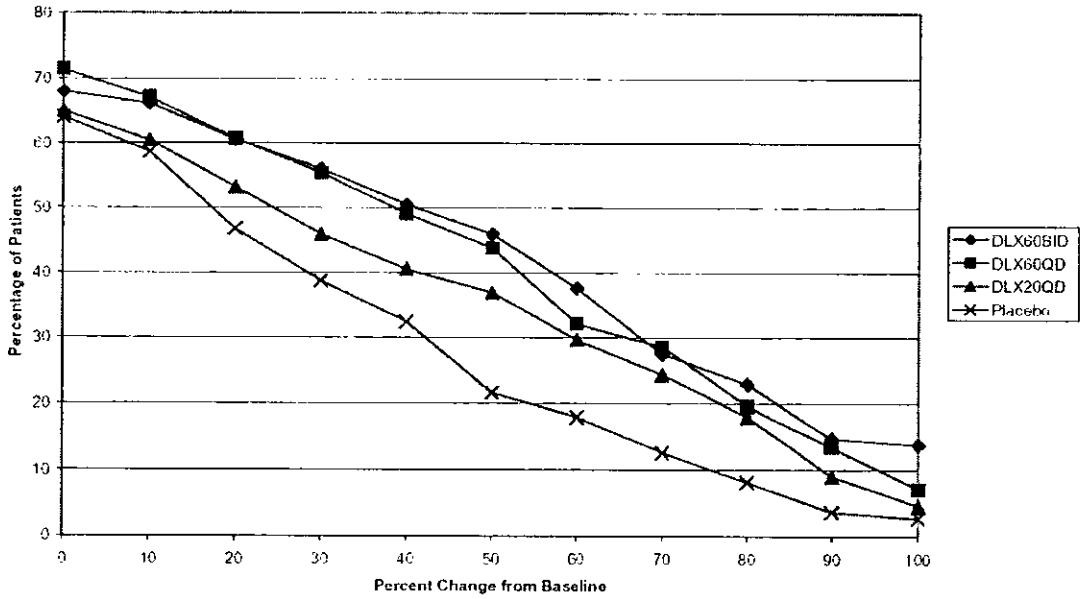
The table and diagram on the next page also demonstrate that as more stringent criteria for 'clinical response' are applied, such as a ≥40% reduction (in 24-hour average pain score from baseline to endpoint), or a ≥50% reduction, 'response rates' decrease, but for all treatment groups. The relative differences between treatment groups are preserved. The response rates in the duloxetine 60-mg QD and 60-mg BID arms remain nearly identical (to each other), and about 50% higher than for the placebo arm (using response thresholds between 20% and 60%). The duloxetine 20-mg/day response rates fall midway between placebo and duloxetine 60-mg QD, over the 20% to 50% range.

HMAW, Baseline Observation Carried Forward
24-Hour Average Pain Score Reduction, Baseline→Endpoint

Pain Score Change From Baseline	Placebo n = 111 (%)	DLX20QD n = 111 (%)	DLX60QD n = 112 (%)	DLX60BID n = 109 (%)
Any increase	13 (11.7)	18 (16.2)	5 (4.5)	5 (4.6)
No change	27 (24.3)	21 (18.9)	27 (24.1)	30 (27.5)
> 0 % decrease	71 (64.0)	72 (64.9)	80 (71.4)	74 (67.9)
≥ 10 % decrease	65 (58.6)	67 (60.4)	75 (67.0)	72 (66.1)
≥ 20 % decrease	52 (46.8)	59 (53.2)	68 (60.7)	66 (60.6)
≥ 30 % decrease (LOCF)	*52 (46.8)*	*57 (51.3)*	*72 (64.3)*	*71 (65.1)*
≥ 30 % decrease (BOCF)	43 (38.7)	51 (45.9)	62 (55.4)	61 (56.0)
≥ 40 % decrease	36 (32.4)	45 (40.5)	55 (49.1)	55 (50.5)
≥ 50 % decrease	24 (21.6)	41 (36.9)	49 (43.8)	50 (45.9)
≥ 60 % decrease	20 (18.0)	33 (29.7)	36 (32.1)	41 (37.6)
≥ 70 % decrease	14 (12.6)	27 (24.3)	32 (28.6)	30 (27.5)
≥ 80 % decrease	9 (8.1)	20 (18.0)	22 (19.6)	25 (22.9)
≥ 90 % decrease	4 (3.6)	10 (9.0)	15 (13.4)	16 (14.7)
= 100 % decrease	3 (2.7)	5 (4.5)	8 (7.1)	15 (13.8)

*Lilly results in the 'LOCF' row; all other rows use BOCF imputation

BOCF, 24-Hour Average Pain Score Reduction, Baseline→Endpoint
Frequency, by Percent-Reduction (X-Axis)



Source, Table and Diagram: Applicant response to Agency request (8/27/2004)

The following table and diagram demonstrate the sustained-responder rate (using the agreed upon definition of 'sustained-response'), by treatment week. The baseline-observation-carried-forward method for imputation of missing data is employed, except in the last row, which shows Lilly's LOCF results.

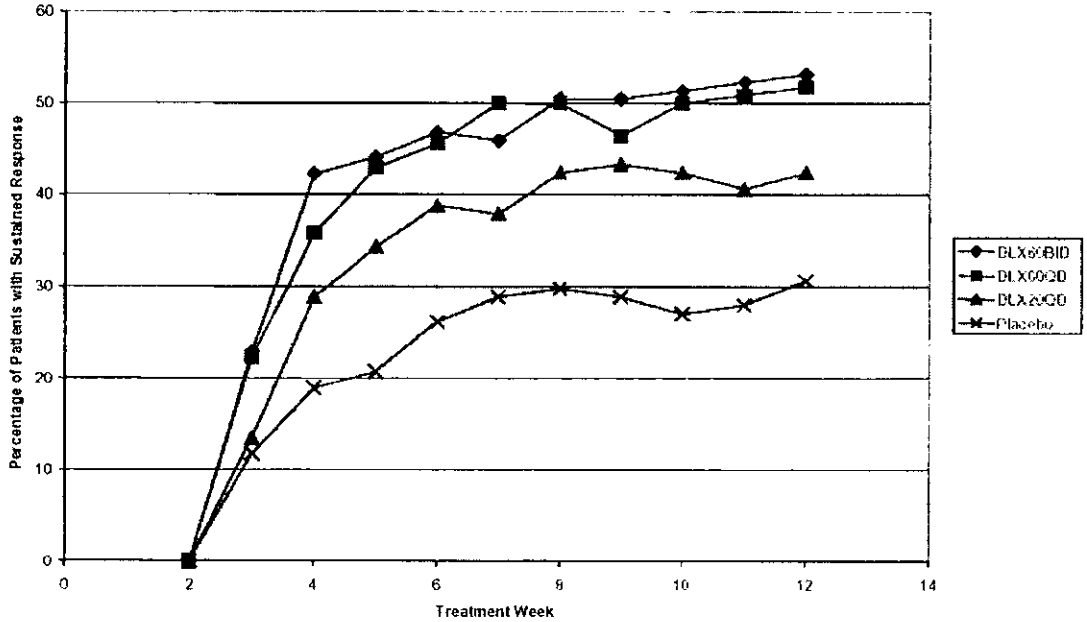
HMAW BOCF, 'Sustained Response' Rate by Treatment Week

Treatment Week	Placebo n = 111 (%)	DLX20QD n = 111 (%)	DLX60QD n = 112 (%)	DLX60BID n = 109 (%)
1	N/A	N/A	N/A	N/A
2	N/A	N/A	N/A	N/A
3	13 (11.7)	15 (13.5)	25 (22.3)	25 (22.9)
4	21 (18.9)	32 (28.8)	40 (35.7)	46 (42.2)
5	23 (20.7)	38 (34.2)	48 (42.9)	48 (44.0)
6	29 (26.1)	43 (38.7)	51 (45.5)	51 (46.8)
7	32 (28.8)	42 (37.8)	56 (50.0)	50 (45.9)
8	33 (29.7)	47 (42.3)	56 (50.0)	55 (50.5)
9	32 (28.8)	48 (43.2)	52 (46.4)	55 (50.5)
10	30 (27.0)	47 (42.3)	56 (50.0)	56 (51.4)
11	31 (27.9)	45 (40.5)	57 (50.9)	57 (52.3)
12 (BOCF)	34 (30.6)	47 (42.3)	58 (51.8)	58 (53.2)
12 (LOCF) *	*37 (33.3)*	*51 (45.9)*	*63 (56.3)*	*61 (56.0)*

* Applicant's LOCF analysis. All other rows use BOCF

Source, Table and Diagram: Applicant's response to clinical reviewer request (7/27/04)

HMAW Sustained Response Rate by Treatment Week, BOCF



Source, Table and Diagram: Applicant response to Agency request (7/27/2004)

The table and the figure above illustrate that there was an early separation in the number of patients that experience a sustained reponse between the treatment arms (all doses of duloxetine) and placebo, and the difference was maintained till the end of the study. This difference was more pronounced for the 60 mg qd and the 60 mg bid treatment group, although there was no difference noted between the two dosage groups.

The following Table and Diagram demonstrate response rate, by treatment week, using the agreed upon definition of 'clinical response,' a 30% reduction in the weekly mean of the '24-hour average pain' score. Again, the baseline-observation-carried-forward method for imputation of missing data was employed, but the last row shows Lilly's LOCF results.

HMAW BOCF, 'Clinical Response' Rate by Treatment Week

Treatment Week	Placebo n = 111 (%)	DLX20QD n = 111 (%)	DLX60QD n = 112 (%)	DLX60BID n = 109 (%)
1	16 (14.4)	16 (14.4)	33 (29.5)	33 (30.3)
2	25 (22.5)	38 (34.2)	46 (41.1)	54 (49.5)
3	36 (32.4)	41 (36.9)	50 (44.6)	49 (45.0)
4	34 (30.6)	46 (41.4)	53 (47.3)	55 (50.5)
5	36 (32.4)	48 (43.2)	60 (53.6)	57 (52.3)
6	39 (35.1)	51 (45.9)	60 (53.6)	58 (53.2)
7	38 (34.2)	51 (45.9)	58 (51.8)	56 (51.4)
8	37 (33.3)	54 (48.6)	58 (51.8)	62 (56.9)
9	36 (32.4)	50 (45.0)	56 (50.0)	55 (50.5)
10	39 (35.1)	49 (44.1)	59 (52.7)	57 (52.3)
11	42 (37.8)	49 (44.1)	63 (56.3)	62 (56.9)
12 (BOCF)	43 (38.7)	51 (45.9)	62 (55.4)	61 (56.0)
12 (LOCF) *	*52 (46.8)*	*57 (51.3)*	*72 (64.3)*	*71 (65.1)*

* Applicant's LOCF analysis. All other rows use BOCF

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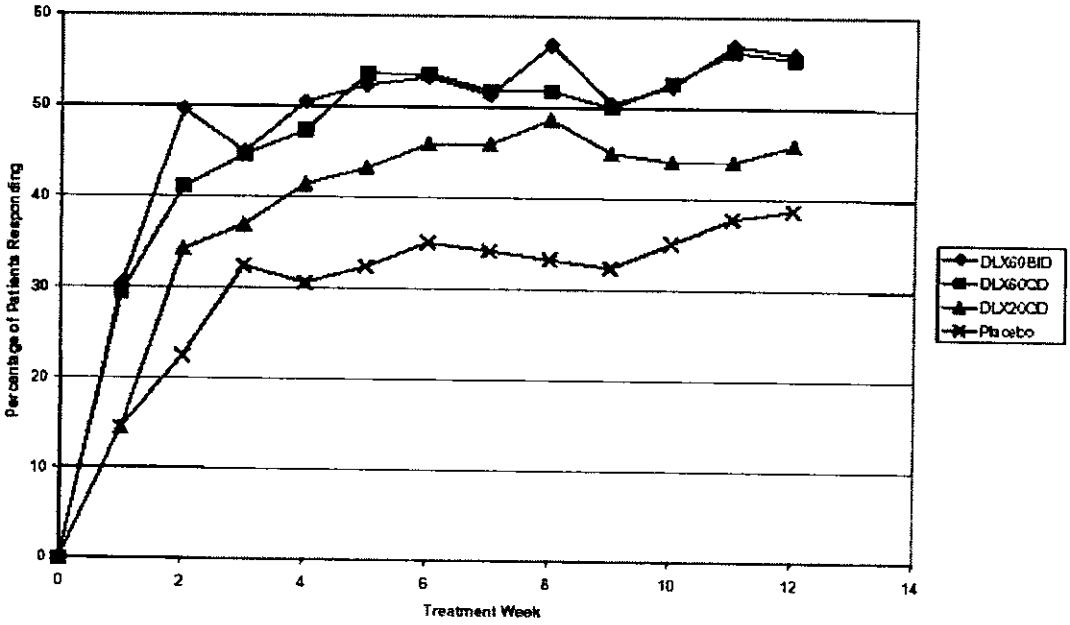
HMAW Response Rate by Treatment Week, BOCF



Source, Table and Diagram: Applicant's response to clinical reviewer request (July 27, 2004)

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The following table tabulates the results, utilizing the BOCF imputation method for missing data. Since all sustained responders, by definition, would have needed to achieve at least a 30% reduction by Week 10, the rows for Weeks 11 and 12 are denoted as "not applicable" (NA).

HMAW, First Week 'Clinical Response' Achieved Sustained Responders at Week-12 (BOCF)

Treatment Week	Placebo N=34 (%)	Duloxetine 20 mg QD N=47 (%)	Duloxetine 60 mg QD N=58 (%)	Duloxetine 60 mg BID N=58 (%)
1	10 (29.4)	14 (29.8)	24 (41.4)	23 (39.7)
2	9 (26.5)	17 (36.2)	15 (25.9)	20 (34.5)
3	6 (17.7)	7 (14.9)	7 (12.1)	4 (6.9)
4	3 (8.8)	2 (4.3)	3 (5.2)	4 (6.9)
5	3 (8.8)	3 (6.4)	5 (8.6)	4 (6.9)
6	2 (5.9)	2 (4.3)	1 (1.7)	2 (3.5)
7	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.7)
8	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
9	0 (0.0)	1 (2.1)	1 (1.7)	0 (0.0)
10	1 (2.9)	0 (0.0)	1 (1.7)	0 (0.0)
11	N/A	N/A	N/A	N/A
12	N/A	N/A	N/A	N/A

Source: Applicant response to Agency request, page 12 (8/27/2004)

The table shows that a higher percentage of "sustained responder" patients in the duloxetine-treated arms achieved their first clinical response early in the study, compared to the placebo group.

6.1.5.1.14 Applicant's Secondary Efficacy Analyses

Lilly's secondary efficacy results from study HMAW consistently support the primary efficacy findings, with few exceptions (most notably, the "pain right now" diary score). In addition to the primary measure, "average pain over the last 24-hours" patients recorded in their diaries "worst pain over last 24-hours," "least pain over the last 24-hours, "night pain over the last 24-hours" and "pain right now." Several widely utilized (and well validated) paper-and-pencil instruments, were also employed, such as the Brief Pain Inventory, and the Clinical Global Impressions Scale, intended in part, to assess overall functional impairment.

- Duloxetine 60-mg QD and duloxetine 60 mg BID both appear to be more effective than placebo in reducing "average," "worst" and "least" pain scores (baseline to endpoint using LOCF).
- Duloxetine 60-mg BID was not more effective than duloxetine 60-mg QD, using the above ratings, or even using ANY of Lilly's other secondary measures.
- Duloxetine 20-mg QD was not superior to placebo on most secondary efficacy measures.

Table 6.XX on the following page summarizes Lilly's key secondary efficacy results.

Table 6.XX: HMAW, Applicant's Secondary Efficacy Results, Baseline to Endpoint Change (LOCF)

Efficacy Measure	Placebo	DLX20QD	DLX60QD	DLX60BID	DLX20QD vs Placebo	DLX60QD vs Placebo	DLX60BID vs Placebo	DLX60QD vs DLX60BID	
24-Hour Average Pain = 1°	n=111	n=111	n=112	n=109	0.189	<0.001	<0.001	0.403	ANCOVA
Mean Baseline (SD)	5.73 (1.52)	5.84 (1.59)	6.01 (1.69)	5.85 (1.38)	0.130	<0.001	<0.001	0.251	MMRM
24-Hour Worst Pain	n=111	n=111	n=112	n=109	0.047	<0.001	<0.001	0.391	ANCOVA
Mean Baseline (SD)	6.51 (1.59)	6.64 (1.65)	6.84 (1.76)	6.75 (1.45)	0.035	<0.001	<0.001	0.223	MMRM
24-Hour Night Pain	n=111	n=111	n=112	n=109	0.649	0.014	<0.001	0.224	ANCOVA
Mean Baseline (SD)	5.72 (2.17)	6.08 (2.01)	6.16 (2.46)	5.86 (2.05)	0.380	0.025	<0.001	0.099	MMRM
BPI Pain Severity	n=112	n=110	n=113	n=109					
Average	5.67 (1.65)	5.75 (1.54)	5.81 (1.77)	5.61 (1.56)	0.460	0.009	<0.001	0.385	MMRM
Worst	6.69 (1.88)	6.76 (1.87)	6.94 (1.96)	6.79 (1.53)	0.220	0.002	<0.001	0.232	MMRM
Least	4.16 (2.46)	4.28 (2.31)	4.20 (2.18)	4.13 (1.91)	0.410	0.032	0.008	0.579	MMRM
Now	4.85 (2.40)	4.77 (2.31)	5.00 (2.26)	5.06 (1.91)	0.652	0.010	<0.001	0.324	MMRM
BPI Interference	3.67 (2.45)	3.65 (1.99)	3.86 (2.31)	3.95 (2.23)	0.916	0.081	0.084	0.994	ANCOVA
(Average All Subscales)					0.992	0.010	0.019	0.873	MMRM
CGI Severity	n=111	n=109	n=109	n=110	0.030	<0.001	<0.001	0.331	ANOVA
					0.004	<0.001	<0.001	0.085	MMRM
PGI-Improvement	n=111	n=108	n=111	n=109	0.638	0.013	0.009	0.908	ANOVA
					0.146	<0.001	<0.001	0.866	MMRM
McGill Pain Total	n=96	n=88	n=95	n=99	0.043	0.001	<0.001	0.286	ANCOVA
Dynamic Allodynia	n=103	n=99	n=98	n=103	0.620	0.103	0.621	0.250	ANCOVA

MMRM ANCOVA

Source: Applicant Table HMAW.11.9

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6.1.5.1.15 Applicant's Dose-Response Analysis

Lilly examined the dose-response relationship among duloxetine 20 mg QD, 60 mg QD, and 60 mg BID "using appropriate treatment contrast in the repeated-measures analysis" The table above, shows the weekly mean 24-hour average pain scores, by treatment week, along with pairwise comparisons. There does appear to be a linear effect of dose.

6.1.5.1.16 HMAW Discussion

- Both 60 mg BID and 60 mg QD appear to be more effective than placebo
- The Applicant's claim that the two higher doses are more effective than 20 mg QD loses statistical significance when BOCF is used instead of LOCF.
- 60 mg BID does not appear to be more effective than 60 mg QD, nor does it hasten time to 'sustained' response.
- Over 75% of patients that achieve 'sustained response' (by Week 12) do so within two weeks of treatment initiation. By the seventh week, nearly all (96%) have.

Using BOCF instead of LOCF duloxetine treatment effect at the two higher doses is still present, although p-values increase slightly. 'Response rate' and 'sustained response rate' at endpoint, decrease (compared to those from the LOCF analysis), but for all treatment groups, including placebo, the overall conclusions are not affected.

6.1.5.2 Study HMAVa

Title: Duloxetine vs. Placebo in the Treatment of Patients with Painful Diabetic Neuropathy.

The initial version of HMAVa was dated May 30, 2002 and submitted. Two protocol amendments were implemented prior to subject enrollment, dated June 19, 2002 (Amendment 1), and June 3, 2002 (Amendment 2).

6.1.5.2.1 Objectives, Population and Design

6.1.5.2.1.1 Objectives

The protocol specified primary objective of HMAVa was "to assess the efficacy of duloxetine 60 mg twice daily compared with placebo, on the reduction of pain severity (as measured by the weekly mean of the 24-hour average pain scores), in patients with painful diabetic neuropathy, during a 12-week, double-blind, acute therapy phase."

The secondary objectives of HMAVa were:

- To assess the efficacy of duloxetine 60 mg QD (once daily) compared with placebo on the reduction of weekly mean for 24-hour average pain in patients with painful diabetic neuropathy during a 12-week, double-blind, acute therapy phase.
- To assess the efficacy of duloxetine 60 mg QD and duloxetine 60 mg BID versus placebo over a 12-week acute therapy period as measured by:
  - Weekly means of night pain and worst daily pain from the daily diary
  - Brief Pain Inventory (BPI) of Severity and Interference (Cleeland and Ryan 1994)
  - Clinical Global Impression of Severity (CGI-Severity) (NIMH 1976)
  - Patient Global Impression of Improvement (PGI-Improvement) (NIMH 1976) scale
  - Sensory portion of the Short-Form McGill Pain Questionnaire (SFMPQ) (Melzack 1987).
- To assess the impact of treatment with duloxetine 60 mg QD and duloxetine 60 mg BID versus placebo over the acute therapy period of the study on patient-reported health outcomes, as measured by:
  - 36-item Short-Form Health Survey (SF-36) (Ware et al. 1993)
  - EQ-5D version of the Euro-QoL Questionnaire (Kind 1996)
  - Resource Utilization Questionnaire (for patients in Study Group A only).
- To evaluate whether the improvement in diabetic neuropathic pain, as assessed by the weekly mean of the 24-hour pain average severity scores, is a direct analgesic effect of duloxetine therapy and is independent of the treatment effect on the mood improvement, as measured by the total score of the first 17 items of the 21-item Hamilton Depression Rating Scale (HAMD17)
- To evaluate the safety of duloxetine 60 mg QD and duloxetine 60 mg BID versus placebo over a 12-week, double-blind acute therapy period as measured by:
  - Discontinuation rates
  - Treatment-emergent adverse events (TEAEs)

- Laboratory assessments, including lipid profile and glycosylated hemoglobin (HbA1c)
- Vital signs (including heart rate and blood pressure)
- Electrocardiograms (ECGs)
- Significant hypoglycemic events
- Electrophysiology assessment.

- To evaluate the safety of duloxetine 60 mg BID over the 52-week, open-label extension period as measured by:
  - Discontinuation rates
  - Treatment-emergent adverse events
  - Laboratory assessments, including lipid profile and glycosylated hemoglobin (HbA1c)
  - Vital signs
  - Electrocardiograms (ECGs)
  - Electrophysiology assessments.
- To evaluate the safety of duloxetine 60 mg BID for up to 65 weeks exposure with regard to the progression of diabetic complications, as measured by the Michigan Neuropathy Screening Instrument (MNSI) (neuropathy progression) (Feldman et al. 1994), electrophysiology assessments, microalbumin/creatinine ratio (nephropathy progression), and an ophthalmologic exam (retinopathy progression).
- To assess the impact of treatment with duloxetine 60 mg BID and routine care over the extension period of the study on patient-reported health outcomes, as measured by the SF-36, EQ-5D, and Resource Utilization Questionnaire (Resource Utilization measures are only obtained for Study Group A).
- To assess the efficacy of duloxetine 60 mg QD and duloxetine 60 mg BID versus placebo over a 12-week acute therapy period as measured by dynamic allodynia.

6.1.5.2.1.2 Design

HMAVa was to be a multicenter, parallel group, double-blind, randomized, placebo-controlled study. The acute treatment period was to last for thirteen weeks, followed by a one-year, open-label extension period.

6.1.5.2.1.3 Study Population

Inclusion Criteria

Patients would be eligible only if they met **all** of the following criteria:

1. Male or female outpatients at least 18 years of age.
2. Presents with pain due to bilateral peripheral neuropathy caused by Type I or Type II diabetes mellitus. "Pain must begin in the feet, with relatively symmetrical onset. Daily pain should be present for at least 6 months. The diagnosis must be confirmed by a score of at least 3 on the MNSI."
3. All females must test negative for a serum pregnancy test at Visit 1. Females of child-bearing potential (not surgically sterilized and between menarche and 1 year postmenopause) must agree to utilize medically acceptable and reliable means of birth control as determined by the investigator during the study and for 1 month following the last dose of the study. Examples of reliable methods include use of oral contraceptives or Depo-Provera® Contraceptive Injection (medroxyprogesterone

acetate suspension, Pharmacia & Upjohn), abstinence, partner with vasectomy, diaphragms with contraceptive jelly, cervical caps with contraceptive jelly, condoms with contraceptive foam, or intrauterine devices. Women who are pregnant or breast-feeding may not participate in the study.

4. Stable glycemic control as assessed by a physician investigator and a glycosylated hemoglobin (HbA_{1c}) ≤12% before randomization.
5. Mean score of at least 4 on the 24-hour average pain severity assessment; the mean is determined by averaging the daily scores from the 24-hour average pain assessment (Question #1) in the patient diary from Visit 2 to Visit 3.
6. Full completion of the daily diaries for at least 80% of the days between Visit 2 and Visit 3.
7. Educational level and degree of understanding such that they can communicate intelligibly with the investigator and study coordinator.
8. Judged to be reliable and agree to keep all appointments for clinic visits, tests, and procedures required by the protocol.

Exclusion Criteria

Patients were to be excluded if they met any of the following criteria:

1. Investigator site personnel were directly affiliated with the study, or if they were immediate family of investigator site personnel directly affiliated with the study. Immediate family was defined as "a spouse, parent, child, or sibling, whether biological or legally adopted."
2. Were employed by Lilly (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly sponsored clinical trials, but are not permitted to participate at a Lilly facility. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
3. Had received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry (Visit 1).
4. Current (≤1 year) DSM-IV Axis I diagnosis of major depressive disorder (MDD), dysthymia, generalized anxiety disorder, alcohol or eating disorders as determined by the MINI or a previous diagnosis.
5. DSM-IV diagnosis of mania, bipolar disorder, or psychosis determined either by patient history or by diagnosis using specific MINI modules.
6. Serious or unstable cardiovascular, hepatic, renal, respiratory, or hematologic illness, symptomatic peripheral vascular disease, or other medical condition (including unstable hypertension and not clinically euthyroid) or psychological conditions that in the opinion of investigator would compromise participation or be likely to lead to hospitalization during the course of the study.
7. At Visit 1, ALT >1.5 times upper limit of normal (ULN), based on Lilly reference ranges.
8. Prior renal transplant, current renal dialysis, or serum creatinine laboratory value >1.5 times ULN, based on Lilly reference ranges at Visit 1.
9. Historical exposure to drugs known to cause neuropathy (for example, vincristine), or a history of a medical condition, including pernicious anemia and hypothyroidism, that could have been responsible for neuropathy.

10. Pain that cannot be clearly differentiated from or conditions that interfere with the assessment of the diabetic neuropathy pain. Examples of painful conditions that could be confused with diabetic neuropathy pain included peripheral vascular disease (ischemic pain); neurological disorders unrelated to diabetic neuropathy (for example, phantom limb pain from amputation); skin condition in the area of the neuropathy that could alter sensation (for example, plantar ulcer); other painful conditions, (for example, arthritis).
11. Patients who have previously completed or withdrawn from this study or have been previously treated with duloxetine. (Note: Patients that have been previously screened for a duloxetine study other than this study and never received study drug will be eligible for this study if they meet all current entry criteria).
12. Patients taking excluded medications that cannot be stopped at Visit 1.
13. Treatment with a MAOI or fluoxetine within 30 days of Visit 3.
14. History of substance abuse or dependence within the past year, excluding nicotine and caffeine.
15. A positive urine drug screen for any substances of abuse or excluded medication. **Note:** If the patient had a positive drug screen at Visit 1 for an excluded medication that may not have had an adequate washout period, a retest was to be performed at Visit 2. If the retest was still positive for the parent compound, the patient was to be excluded.
16. Frequent and/or severe allergic reactions with multiple medications.

6.1.5.2.2 HMAVa Treatments

During the double-blind acute period (Study Period II), subjects were to receive one of three treatments: duloxetine 60 mg QD, duloxetine 60 mg BID, or placebo. During the open-label extension period (Study Period III), subjects were to receive either duloxetine 60 mg BID or "routine care."

6.1.5.2.3 HMAVa Efficacy Variables

The primary efficacy outcome measure was to be the change in the weekly mean of the 24-hour average pain scores (by 11-point Likert scale), recorded by the patient in their study diary.

The following secondary measures were also to be collected:

- **Pain Severity for worst pain and night pain** as measured by an 11-point Likert scale was completed daily by the patient in a diary. This is an ordinal scale with scores from 0 (no pain) to 10 (worst possible pain).
- The **Clinical Global Impression of Severity (CGI-Severity)** as administered by a physician investigator overseeing the clinical care of the patient in the presence of the patient. The CGI-Severity evaluates the severity of illness at the time of assessment. The score ranges from 1 (normal) to 7 (most severe illness).
- The **Patient Global Impression of Improvement (PGI-Improvement)** was to be completed by the patient to measure the degree of improvement at the time of assessment. The score ranges from 1 (normal) to 7 (most severe illness).

- The **Brief Pain Inventory (severity scales)** was to be completed by the patients to measure the severity of pain. The severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine).
- **Sensory Portion of the Short Form McGill** Pain Questionnaire was to be completed by the patient. This instrument consists of 11 pain descriptors, each of them scored from 0 (none) to 3 (severe).
- The 17-item **Hamilton Depression Rating Scale (HAMD17),** a widely used observational rating measure of depression symptom severity. This scale was to be administered by a Lilly approved rater. The HAMD17 was used to assess the severity of depression symptoms during the course of therapy. The HAMD17 total score ranges from 0 (not at all depressed) to 52 (severely depressed).
- **Dynamic Allodynia measure**. Dynamic allodynia was to be assessed by the clinician using a brush stroke (to the same body location at baseline and endpoint) to elicit from the patient the pain severity. The score ranges from 0 (no pain) to 3 (severe pain) scale.
- **Health Outcome Measures**

6.1.5.2.4 Analysis Plan

All analyses were to be conducted on an intent-to-treat basis (data was to be analyzed by the treatment groups to which patients were randomly assigned, even if the patient does not take the assigned treatment, does not receive the correct treatment, or does not comply with the protocol).

Treatment effects were to be evaluated based on a two-sided significance level of 0.05, and interaction effects at 0.10. No adjustments for multiple comparisons were to be made. No justification was to be made for any of the pairwise comparisons, "given that the interests of the study are to evaluate each individual duloxetine dose versus placebo in terms of efficacy."

All analysis of variance (ANOVA) models to be used to analyze continuous efficacy variables were to contain the terms of treatment, investigator, and treatment-by-investigator interaction (unless otherwise stated). The interaction was to be tested at the significance level of 0.10. When the interaction is not statistically significant, treatment effect was to be tested using the ANOVA model without the interaction term. Similar logic was to be applied to analysis of covariance (ANCOVA) models (which in general would refer to the ANOVA model with baseline values added as a covariate). Type II sum-of-squares for the least- squares means was to be used for the statistical comparison using ANOVA or ANCOVA.

When a total score was to be calculated from individual items, it would be considered missing if any of the individual items are missing. When an average score was to be computed from individual items, it would be calculated from non-missing values.

The evaluation of efficacy (in the double-blind acute therapy phase) was to focus on the time period that duloxetine would be used at its full dosage (before tapering). For all analyses for the acute therapy phase, 'baseline' would refer to the last non-missing

observation at or before the randomization visit (Visit 3), and 'endpoint' would refer to the last non-missing observation in the acute therapy phase (at full dosage: Visit 4 to Visit 10). The phrase "last visit of the acute therapy phase" would refer to a patient's latest visit at or before Visit 10.

For analyses by 'investigator sites' sites having less than 12 randomized patients (each of whom would need to have at least one non-missing value for baseline-to-endpoint change on the primary efficacy measure, 24-hour average pain), were to be pooled within a country, and considered a single site. If the pooled site still had fewer than 12 randomized patients, these patients were to be pooled with the smallest remaining site. This pooling procedure was to continue until every site used in the analysis has at least 12 patients.

Changes to the proposed analyses made prior to unblinding the data, would not necessitate a formal protocol amendment (with the exception changes to the primary efficacy analysis).

6.1.5.2.4.1 Analysis Plan, Primary Efficacy Measure

The primary efficacy measure was to be the weekly mean score of the 24-hour average pain severity, computed from diary scores. The primary efficacy analysis would assess the difference in the baseline-to-endpoint change on the 24-hour average pain score, between the duloxetine 60 mg BID group and the placebo group, during the acute therapy phase, is zero (after accounting for differences in baseline scores). The analysis would utilize an ANCOVA model, with the terms of treatment, investigator, treatment-by-investigator interaction, and baseline scores. The treatment-by-investigator interaction was to be tested at a significance level of 0.10. If the interaction were not statistically significant, treatment effect would be evaluated using the model without the interaction term. The distribution of the residuals was also to be checked. If assumptions of normality and homogeneity were violated, rank-transformed change scores were to be analyzed using an ANOVA model with the terms of treatment and investigator.

The 'baseline' 24-hour average pain score was to be the average of the (24-hour average pain) diary scores collected between Visit 2 and Visit 3. If there were less than three diary entries (less than three non-missing values), the baseline score was to be set as missing. Diaries were to be collected during each clinic visit to calculate weekly mean scores.

6.1.5.2.4.2 Analysis Plan, Secondary Efficacy Measures

Treatment group difference on the 24-hour average pain score, between duloxetine 60 mg QD and placebo was to be evaluated using a pairwise contrast from the ANCOVA model described above.

Other secondary efficacy measures in the acute therapy phase were to include the following (listed based on the frequency of data collection during the study):

- Weekly mean score of the 24-hour worst pain severity on the 11- point Likert scale (24-hour worst pain)

- Weekly mean score of the average night pain severity on the 11-point Likert scale (night pain score)
- Monthly Brief Pain Inventory (BPI): Severity (4 items: worst, least, average, and current), and Interference 7 items: general activity, mood, walking ability, normal work, relations to others, sleep, and enjoyment of life)
- Monthly CGI-Severity and PGI-Improvement scores
- HAMD17 total score at the randomization visit and at the last visit of the acute therapy phase
- The sensory portion of Short-Form McGill Pain Questionnaire (SF-MPQ): assessment at the randomization visit and at the last visit of the acute therapy phase (the sensory component consists of 11 pain descriptors: throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, splitting)
- Dynamic allodynia (measuring the response to the touch of brush) assessment at the randomization visit and at the last visit of the acute therapy phase.

6.1.5.2.4.3 Sample Size Calculation

Approximately 330 patients in total were to be enrolled, or 110 into each of the three treatment groups (duloxetine 60 mg QD, duloxetine 60 mg BID, and placebo). The sponsor's assumptions were:

- A treatment group difference of -1.20 points (in the baseline-to-endpoint mean change, on the weekly mean of the 24-hour average pain severity between duloxetine 60 mg BID and placebo treatment groups)
- A common standard deviation of 2.2
- A discontinuation rate of 35%
- Using a two-sided significance test with α=0.05 (at $\geq$90% power)

6.1.5.2.4.4 Missing Data

All efficacy analyses (examined in this review) were to utilize data obtained during the 'acute therapy phase,' the time interval in which the randomized treatment was to be administered: from Study Visit 2 through Visit 14. The primary efficacy analysis was to be performed on the set of all randomized patients with a baseline score and at least one post-baseline score. 'Baseline' would refer to the last non-missing observation at or before Visit 2. 'Endpoint' would be the last non-missing observation from Visit 3 through Visit 14.

Patients were to complete diary pain assessments ("worst" "least") daily, but efficacy analyses were to be conducted using weekly means. The baseline values (for each diary pain assessment) were to be the average of the last three non-missing diary scores before the randomization visit (Visit 2). Pain diary scores for each of the weekly post-baseline visits, was to be the average of all scores recorded since the last weekly visit, up to seven daily scores for each diary parameter. If less than three daily observations were recorded since the last visit (out of seven possible), the score for that week (for that parameter) would be considered missing.

6.1.5.2.5 Detailed Schedule of Study Events

HMAVa Schedule of Evaluations

Description	Study Period I / Screening (3 weeks)			Study Period II / Double-blind Acute (13 weeks)								
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**SP Early D/C**
Week	**-3 to -2**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**13**	
Clinical Assessments												
Medical Hx/Consent	X											
BP, HR, VSS	X	X	X	X	X	X	X	X	X	X	X	X
PEx			X									
12 Lead ECG	X					X		X		X	X	X
NCV Study			X							X		X
AEs, Hypoglycemic Events	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments												
Clinical Chemistry	X		X			X		X		X	X	X
Serum Pregnancy Test	X											
UDScreen	X	X										
Heme, Thyroid, CR Ratio	X											
Lipids			X							X	X	X
HbA1c	X									X	X	X
Efficacy Assessments												
Randomization			X								X	
Diary Activity, Questionnaires		X	X	X	X	X	X	X	X	X		X

Source: Clinical

6.1.5.2.6 Concomitant Medications

In general, concomitant medications with primarily central nervous system activity are not allowed in the acute phase. The detailed listing appears in Appendix 3.

6.1.5.2.7 Protocol Amendments, Changes in Study Conduct

6.1.5.2.7.1 Protocol Amendments

The protocol was amended April 1, 2003 after approximately two-thirds of the subjects had enrolled. The changes and their rationale were summarized by the Applicant as follows:

- Clarification of the fasting period prior to laboratory assessments to avoid changing a patient's routine maintenance of their blood sugar.
- Correction on the use of diuretics during the study. All patients will be allowed to utilize diuretics as a concomitant medication during the study.
- Clarification of the wording regarding the term "routine care" to prevent any confusion.
- Correction to the Concomitant Medication Table. Study Periods I and II are combined in the first two columns. Footnote 'd' was removed as it was not applicable. NSAIDs are combined with other analgesics in the analgesic category. Sedating antihistamines are added. Narcotics, Paracetamol® (acetaminophen), and Other are added as categories.

- Clarification on the exclusion for patients who are hyperthyroid or hypothyroid is included. Patients who are stable and clinically euthyroid are allowed in the study.

6.1.5.2.7.2 Changes in Study Conduct

6.1.5.2.7.3 Changes in Planned Analyses

Changes made before data lock:

- To meet the normality assumption, square root transformation as recommended by — . was applied to the Peroneal CMAP electrophysiology measure instead of using rank transformed change scores in the analysis. Other electrophysiology measures were treated as normal as recommended by —
- The protocol specified log-rank test and Wilcoxon test to compare the Kaplan-Meier time to event curves. In this report, stratified log-rank tests, controlled for investigator, were conducted to replace Wilcoxon test in order to better control variation among sites.
- A-wave was added to the electrophysiology assessment. Categorical analysis of electrophysiology assessment was added.
- Weekly data, rather than visit data, was used to define sustained response to be consistent with the primary measure.
- Changes were made to the two regression models used to perform the path analysis. Additional baselines were added to both models.

Change made after data lock:

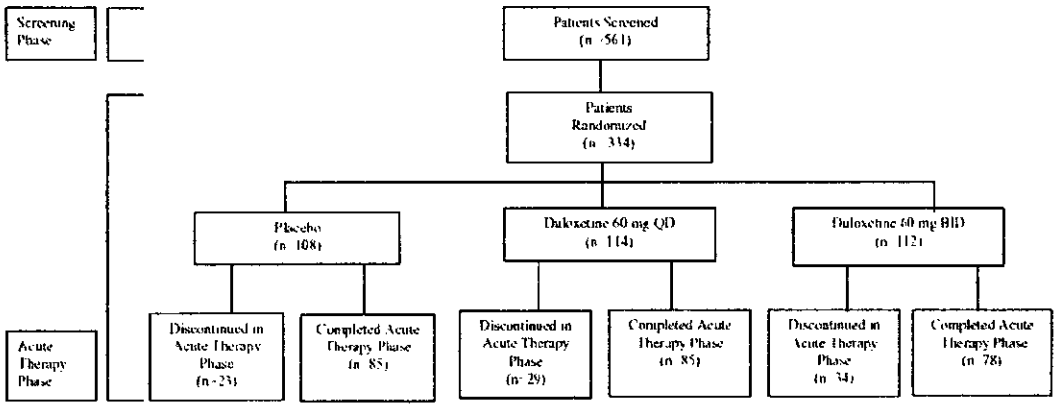
- To explore the possible reasons that caused the treatment-by investigator interaction seen in the primary and some secondary efficacy analyses, the mean change analysis of 24-hour average pain score was conducted by investigator (POOLINV) and a bar graph for the mean change by investigator was created. "It was found that the investigator 004 caused the treatment-by-investigator interaction." Subsequently, the mean change analyses for these efficacy analyses were rerun with investigator 004 excluded.

6.1.5.2.8 Study Conduct

6.1.5.2.8.1 Subject Disposition

The figure below summarizes patient disposition during the screening and acute therapy phases. Five hundred sixty-one patients entered the screening phase. Of these patients, 334 patients met entry criteria and were randomly assigned to one of three treatment groups: placebo, duloxetine 60 mg once daily (QD), or duloxetine 60 mg twice daily (BID). As in HMAW, the number of patients that discontinued during the acute therapy phase, 86 (25.7%), was not unusually high. A total of 248 (74.3%) patients completed the acute therapy phase (85 [79.0%] placebo-treated, 85 [75.0%] duloxetine 60 mg QD-treated, and 78 [70.0%] duloxetine 60 mg BID treated).

HMAVa Patient Disposition (per Applicant)



Source: Applicant Diagram HMAVa.10.1

6.1.5.2.8.2 Reasons for Discontinuation

The table below prepared by Lilly, shows reasons for discontinuation during the acute therapy phase (Visit 4 to Visit 10). They report that a statistically significant difference between placebo and duloxetine 60 mg BID was observed in number of patients who discontinued due to adverse events (p = 0.025). The discontinuation rate due to perceived lack of efficacy was highest in the placebo group.

HMAVa-Acute Reasons for Discontinuation – Per Applicant

Primary Reason	Placebo	DLX60QD	DLX60BID	Total
Completed Visit 10	85 (79%)	85 (75%)	78 (70%)	248 (74%)
Adverse Event	8 (7.4%)	17 (15%)	20 (19%)	45 (13%)
p vs. Placebo		0.091	0.025	0.056
Lack of Efficacy	5 (4.6%)	1 (0.88%)	3 (2.7%)	9 (2.7%)
Personal Conflict/Pt. Decision	1 (0.93%)	2 (1.8%)	4 (3.6%)	7 (2.1%)
Withdrawal of Consent	3 (2.8%)	3 (2.6%)	1 (0.89%)	7 (2.1%)
Protocol Violation	1 (0.93%)	2 (1.8%)	3 (2.7%)	6 (1.8%)
Lost to Follow-up	3 (2.8%)	2 (1.8%)	0	5 (1.5%)
Entry Criteria Not Met	1 (0.93%)	1 (0.88%)	2 (1.8%)	4 (1.2%)
Physician Decision	1 (0.93%)	1 (0.88%)	0	2 (0.60%)
Clin. Significant Lab Value	0	0	1 (0.89%)	1 (0.30%)

Source: Modified from Applicant Table HMAVa.10.1
DLX60QD vs. DLX60BID, all pairwise comparisons, p>0.37

Patients that received duloxetine 60 mg QD were twice as likely as the placebo-treated patients to discontinue due to an adverse event. Those that received duloxetine 60 mg BID were nearly three times as likely (compared to the placebo patients) to discontinue due to an adverse event.

6.1.5.2.8.3 Protocol Deviations and Violations

The table below summarizes significant protocol violations. Relatively few patients (6 of 334, or 1.8%) discontinued during the acute therapy phase because of protocol violations. Protocol violations appeared to be random in nature, and roughly equally distributed across treatment arms. Most protocol violations originated from the same few clinical sites (26 sites contributed patients, but sites 004, 003, 011 and 402 accounted for over 60% of the protocol violations). No changes in the analysis plan were made due to protocol violations. These violations appear unlikely to have materially affected the study results, or the ability to draw meaningful conclusions from them.

HMAVa Protocol Deviations/Violations

	Total
Inadequate informed consent	35
Drug accountability issue	21
Entry criteria error	15
Lab issues	18
Visit schedule inadherence	89
SAE Procedures not followed	4
Excluded medication use	20
Significant diary errors	10

Source: Compiled from Tables HMAVa.10.3 and HMAVA.10.3, and data listings (Appendix 6.2.3)

Baseline 24-hour Average Pain Scores Not Meeting Inclusion Criteria

Baseline	Placebo	60 mg QD	60 mg BID	Total
2.67	1	0	0	1
3.623	1	0	0	1
3.83	0	1	0	1
3.86	0	1	0	1

6.1.5.2.9 Datasets Analyzed

All analyses were conducted on an intent-to-treat (ITT) basis. All randomly assigned patients with at least one post-baseline follow-up were included in Lilly's efficacy analyses. All randomized patients were included in all safety analyses.

6.1.5.2.10 Patient Demographics/Group Comparability

HMAVa-Acute patient demographics, and disease (diabetes and neuropathy) characteristics are reported in the following two tables. Patients were roughly evenly distributed across treatment conditions, by ethnicity, age and gender. The ratio of Type I to Type II diabetics was similar between treatment groups, as was the time since diagnosis with diabetes, and since diagnosis with DPN. Baseline Michigan Neuropathy Scale scores appear to have been slightly lower, on average, for the duloxetine-treated patients (means = 5.49 and 5.55 for DLX60QD and DLX60BID, respectively), than for placebo-treated patients (mean = 5.86).

HMAVa Patient Demographics

Characteristic	Placebo n =108	DLX60QD n =114	DLX60BID n =112	All n=334
Ethnicity				
African Descent	5 (4.6)	3 (2.6)	3 (2.7)	11 (3.3)
Western Asian	0	1 (0.9)	1 (0.9)	2 (0.6)
Caucasian	86 (79.6)	90 (78.9)	85 (75.9)	261 (78.1)
East/Southeast Asian	0	1 (0.9)	1 (0.9)	2 (0.6)
Hispanic	17 (15.7)	16 (14.0)	21 (18.8)	54 (16.2)
Other	0	3 (2.6)	1 (0.9)	4 (1.2)
Chi-square (p=0.774)				
Mean Age	60.81	59.71	61.46	60.65
Median Age	61.83	58.51	60.70	60.81
Age Range	27.6 – 79.7	31.7 – 83.1	39.2 – 84.3	27.6 – 84.3
ANOVA (p=0.395)				
Female : Male	39 : 69	40 : 74	51 : 61	130 : 204
Chi-square (p=0.215)				

Source: Applicant Tables HMAVa.11.1 and ISS dataset DIABDEMO.XPT

HMAVa Baseline Diabetes Mellitus and DPN Characteristics

Characteristic	Placebo n=108	DLX60QD n=114	DLX60BID n=112	All n=334
Type I DM	11 (10.2)	10 (8.8)	9 (8.0)	30 (9.0)
Type II DM	97 (89.8)	104 (91.2)	103 (92.0)	304 (91.0)
Chi-square (p=0.862)				
DM Duration				
Mean Duration	11.08	9.74	9.88	10.22
Median Duration	9.11	6.35	6.65	7.13
Duration Range	0.49 -43.24	0.08 -43.34	0.19–52.37	0.08–52.37
ANOVA (p=0.459)				
DPN Duration				
Mean Duration	3.53	3.59	4.38	3.83
Median Duration	2.73	2.31	2.32	2.33
Duration Range	0.04*–17.33	0.04–19.35	0.04–37.10	0.04*–37.10
ANOVA (p=0.308)				
Baseline 24-Hour Average Pain				
Mean Pain	5.85	6.09	6.19	6.05
Median Pain	5.71	5.84	6.00	5.78
Range Pain	2.60*–10.00	3.83*–10.00	4.00–10.00	2.60*–10.00
ANOVA (p=0.216)				
Michigan Neuropathy Scale				
Mean	5.86	5.49	5.55	5.63
Median	6.00	5.50	5.75	6.00
Range	3.00*–9.00	3.00–8.50	3.00–8.00	3.00*–9.00
ANOVA (p=0.143)				

* Apparent protocol violations, discussed in Section 6.1

Source: Applicant Tables HMAVa 11.1 and 11.2 and dataset DIABDEMO.XPT

Neuropathy severity, as assessed by baseline testing of nerve conduction velocities was also approximately similar, on average, between treatment groups.

6.1.5.2.11 Treatment Compliance

During Study Periods II and III (on-treatment), compliance for each visit interval was defined as taking between 80% and 120% of the study medication prescribed for that interval. The protocol required investigative sites to "counsel patients on the importance of study drug compliance and drug accountability," and to repeat this counseling for patients who demonstrated noncompliance. Investigators were allowed to discontinue patients who were "consistently out of the compliance range." Compliance rates did not differ between treatment groups.

6.1.5.2.12 Excluded Patients

HMAVa patients excluded from primary efficacy analysis
(Missing post-baseline data, for 24-hour average pain score)

HMAVa Patients Excluded From Efficacy Analyses

Patient (Investigator)	Treatment	Baseline
0507 (005)	Placebo	8.00
1107 (011)	DLX60QD	4.00
1301 (013)	DLX60QD	3.86
1705 (107)	DLX60QD	4.63
1923 (109)	Placebo	6.29
2102 (021)	DLX60QD	8.14
3046 (030)	DLX60BID	4.38

Source: Applicant Table HMAVa.16.2.4

6.1.5.2.13 HMAVa Applicant's Primary Analysis

The pre-specified primary efficacy evaluation was the comparison (between the duloxetine 60 mg BID treated and the placebo groups) of the change from baseline to endpoint, in weekly mean of the '24-hour average pain' score. A pairwise contrast from an analysis of covariance (ANCOVA) model (with terms for treatment, investigator, treatment-by-investigator interaction, and baseline scores) was employed. The weekly means were calculated by averaging the daily '24-hour average pain' scores, for each week in which three or more daily diary ratings were available. Otherwise ($\leq$2 daily ratings for that week), that weekly mean score was considered missing. Where weekly values required for analysis were missing, imputation was by LOCF.

Both duloxetine doses were statistically significantly superior to placebo ($p< 0.001$). Sixty-mg BID was not (statistically significantly) better than 60-mg QD, but the baseline-to-endpoint changes were "in the right direction." These results are summarized in the table that follows.

HMAVa, Primary Efficacy Analysis, with Comparison (LOCF to BOCF)
24-Hour Average Pain Score, Change from Baseline to Endpoint (All Randomized)

		Baseline		Endpoint		Change		Pairwise p-values	
	n	Mean	Median	Mean	Median	Mean	Median	DLX60BID	DLX60QD
Placebo	106	5.85	5.7	4.50	4.9	-1.35	-0.9	<0.001	<0.001
DLX60QD	110	6.12	5.9	3.58	3.1	-2.54	-2.3	0.705	
DLX60BID	111	6.21	6.0	3.32	3.0	-2.89	-3.0	**LOCF**	
Placebo	108	5.85	5.7	4.49	4.9	-1.36	-0.2	0.026	0.006
DLX60QD	114	6.09	5.8	3.92	3.8	-2.17	-1.7	0.629	
DLX60BID	112	6.19	6.0	3.95	4.0	-2.25	-2.0	**BOCF**	

Source: Modified from Applicant Table HMAVa.11.9 and response to request (8/27/04)

6.1.5.2.13.1 Applicant's Additional Analyses of Primary Measure (All LOCF)

'Response' rate at endpoint for 24-hour average pain score (LOCF)

'Response' had been predefined as a 30% reduction from baseline in the 24-hour average pain score, and 'response at endpoint' had been predefined as a 30% reduction from baseline to endpoint (in the 24-hour average pain score). Using the pre-specified LOCF analysis, the proportion of responders at endpoint was statistically significantly greater for both duloxetine treatment arms, compared with placebo. Seventy seven (69.4%) patients treated with duloxetine 60-mg BID and 69 (62.7%) patients treated with duloxetine 60-mg QD achieved response at endpoint compared with 44 (41.5%) patients treated with placebo. Once again, 60-mg BID did not differ (statistically significantly) from 60-mg QD, but the treatment effect appeared to be in "the right direction." These results are presented in the table below.

HMAVa, Applicant's LOCF Analysis, Response Rate at Endpoint
(Response = 24-Hour Average Pain Score Reduced ≥ 30%, Baseline->Endpoint)

				Fisher's Exact (p-values)	
Treatment	N	n	% Response	vs. Placebo	vs. DLX 60QD
Placebo	106	44	41.51		
DLX60QD	110	69	62.73	0.003	
DLX60BID	111	77	69.37	<0.001	0.322

Source: Applicant Table HMAVa.11.13 Overall p<0.001

'Sustained response' rate for 24-hour average pain score (LOCF)

'Sustained response' had been defined as a 30% reduction from baseline to endpoint in the 24-hour average pain score, with a 30% reduction from baseline at any weekly visit at least 2 weeks prior to the final last, which then remains at least 20% below baseline, for all remaining weeks until endpoint. Using the pre-specified LOCF analysis, both dosing regimens, duloxetine 60 mg BID (p<0.001) and duloxetine 60 mg QD (p=0.004), were (statistically significantly) superior to placebo, at achieving 'sustained response.' Sixty nine (62.2%) patients in the duloxetine 60 mg BID group, and 59 (53.6%) in the duloxetine 60 mg QD group, achieved sustained response, compared with 36 (34.0%) placebo-treated patients. And again, although the proportion of 'sustained responders" was greater with 60-mg BID than with 60-mg QD, the difference in treatment effect between the groups was not statistically significant. The following table summarizes these findings.

HMAVa, Applicant's LOCF Analysis
Sustained Response Rate at Study Endpoint

				Fisher's Exact (p-values)	
Treatment	N	n	% Response	vs. Placebo	vs. DLX 60QD
Placebo	106	36	33.96		
DLX60QD	110	59	53.64	0.004	
DLX60BID	111	69	62.16	<0.001	0.221

Source: Applicant Table HMAVa.11.14 Overall p<0.001

Statistically significant treatment-group differences between placebo and both duloxetine 60 mg BID and 60 mg QD were observed beginning 1 week after randomization (Visit 4) and continuing through the acute phase. There were no significant differences in pairwise comparison between duloxetine 60 mg QD and 60 mg BID. Both duloxetine 60 mg BID and 60 mg QD were statistically superior to placebo at all recorded visits.

6.1.5.2.14 Reviewer Analyses (Primary Outcome Measure - BOCF Analyses)

All efficacy analyses performed by the applicant utilized a last-observation-carried-forward scheme for imputation of missing data. The section above compared the results obtained with the two imputation methods, LOCF and BOCF.

Using the pre-specified criteria for "clinical response" of $\geq$ 30% reduction in the 24-hour average pain score from baseline to endpoint, and the baseline observation carried forward imputation method for missing data, 38% of the placebo-treated patients, 54% of the duloxetine 60-mg QD treated patients, and 56% of the duloxetine 60-mg BID patients were classified as responders.

Similar analyses were performed by the Division for Study HMAVa as were performed for Study HMAW: fraction of patients achieving a specified degree of improvement, percent of responders at each week, percent of sustained responders, and first week of clinical response for those identified as sustained responders.

Response Rate Frequency

The table below contains the breakdown of the percentage of patients who reported a particular amount of decrease in pain score from baseline. The previously agreed criterion for clinical response is identified by the grey shading, and the results utilizing the two imputation methods are listed.

HMAVa BOCF, 'Response Rate' Frequency, as Required % Change, (in 24-Hour Average Pain Score, Baseline-to-Endpoint) Increases

	Pain Score Change From Baseline	Placebo n = 106 (%)	DLX60QD n = 110 (%)	DLX60BID n = 111 (%)
	Any increase	18 (17.0)	10 (9.1)	5 (4.5)
	No change	27 (25.5)	25 (22.7)	35 (31.5)
	> 0 % decrease	61 (57.5)	75 (68.2)	71 (64.0)
	≥ 10 % decrease	50 (47.2)	73 (66.4)	65 (58.6)
	≥ 20 % decrease	44 (41.5)	66 (60.0)	64 (57.7)
LOCF →	≥ 30 % decrease*	*44 (41.5)*	*69 (62.7)*	*77 (69.4)*
BOCF→	≥ 30 % decrease	40 (37.7)	60 (54.5)	62 (55.9)
	≥ 40 % decrease	32 (30.2)	53 (48.2)	53 (47.7)
	≥ 50 % decrease	28 (26.4)	44 (40.0)	46 (41.4)
	≥ 60 % decrease	24 (22.6)	34 (30.9)	37 (33.3)
	≥ 70 % decrease	18 (17.0)	25 (22.7)	28 (25.2)
	≥ 80 % decrease	9 (8.5)	15 (13.6)	19 (17.1)
	≥ 90 % decrease	2 (1.9)	11 (10.0)	8 (7.2)
	= 100 % decrease	1 (0.9)	8 (7.3)	7 (6.3)

*LOCF row from Applicant's analysis. All other rows use BOCF

The figure below is a graphical representation of part of the data in the table, specifically the percentages for responses of > 0% decrease to 100 % decrease.

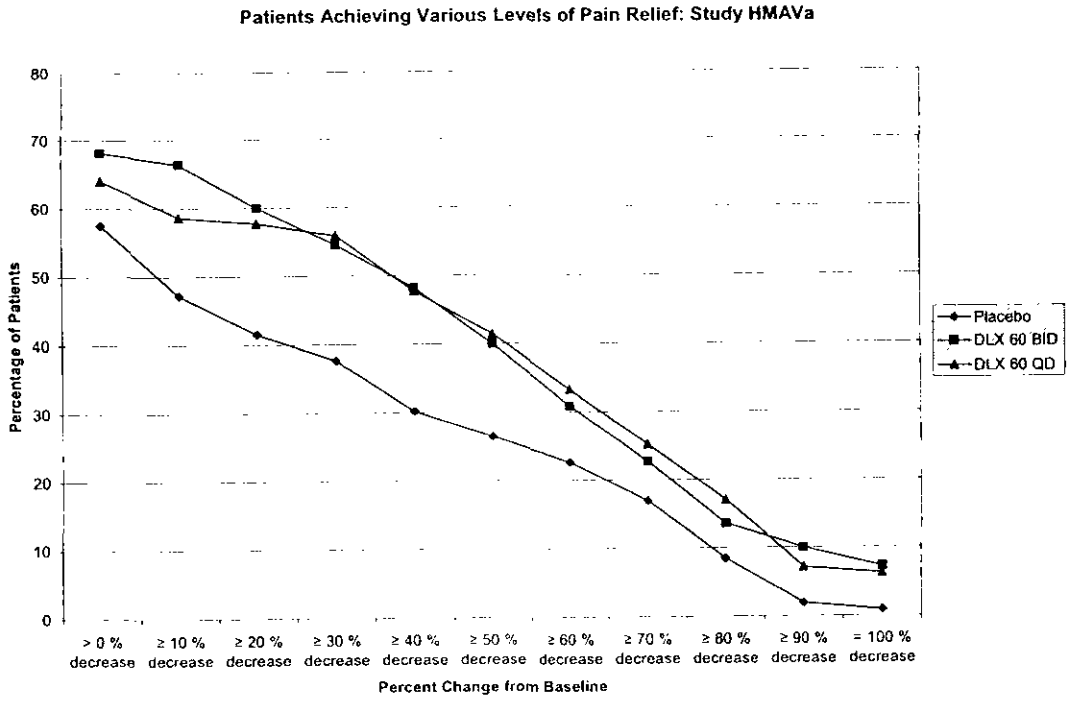


Table and Diagram: Modified from Applicant response to clinical reviewer request (8/27/04)

The table and graph above demonstrate that as more stringent criteria for 'clinical response' are applied, such as a ≥40% reduction (in 24-hour average pain score from baseline to endpoint), or a ≥50% reduction, the response rates decrease, but for all treatment groups. The relative differences between treatment groups are preserved. The response rates in the two duloxetine arms, 60-mg QD and 60-mg BID, remain nearly identical, and 50% or more higher than for the placebo arm (using response thresholds between 20% and 60%).

Response Rate by Week

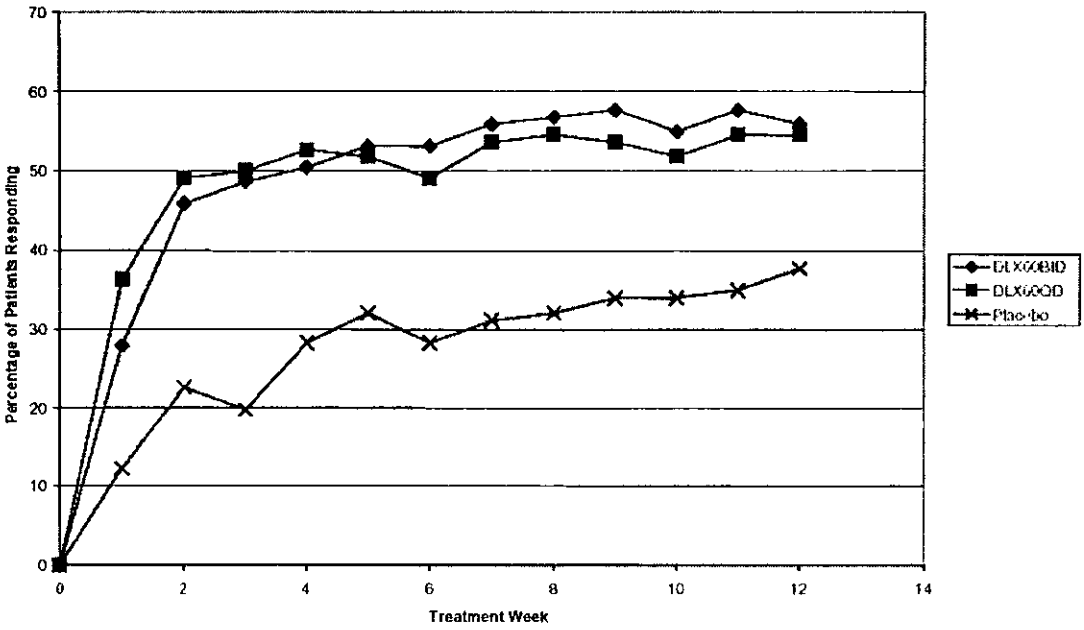
The table below contains the percent of patients who were classified as responders, using the pre-specified criteria for "clinical response" of ≥ 30% reduction in the 24-hour average pain score from baseline to endpoint, and the baseline observation carried forward imputation method for missing data. The grey-shaded row identifies the results obtained by the two different imputation methods for missing data.

HMAVa BOCF, Response Rate by Week

	Treatment Week	**Placebo** n = 106 (%)	**DLX60QD** n = 110 (%)	**DLX60BID** n = 111 (%)
	1	13 (12.3)	40 (36.4)	31 (27.9)
	2	24 (22.6)	54 (49.1)	51 (45.9)
	3	21 (19.8)	55 (50.0)	54 (48.6)
	4	30 (28.3)	58 (52.7)	56 (50.5)
	5	34 (32.1)	57 (51.8)	59 (53.2)
	6	30 (28.3)	54 (49.1)	59 (53.2)
	7	33 (31.1)	59 (53.6)	62 (55.9)
	8	34 (32.1)	60 (54.6)	63 (56.8)
	9	36 (34.0)	59 (53.6)	64 (57.7)
	10	36 (34.0)	57 (51.8)	61 (55.0)
	11	37 (34.9)	60 (54.6)	64 (57.7)
FDA→	12 (BOCF)	40 (37.7)	60 (54.6)	62 (55.9)
Lilly→	12 (LOCF)*	*44 (41.5)*	*69 (62.7)*	*77 (69.4)*

* LOCF row from Applicant's analysis. All other rows use BOCF

The figure below is a graphical representation of the data in the table above:



Source: Table and Diagram modified from Lilly response to request (7/27/08)

The table and figure demonstrate that at each week, the duloxetine treatment arms had a higher percentage of patients classified as clinical responders, compared to placebo. It is also apparent that the difference between the 60-mg QD treatment group and the 60-mg BID treatment group was not significant.

Sustained Responders

In order to asses the durability of the response, a sustained response was identified as one of the secondary endpoints. A "sustained response" was defined as a $\geq$ 30% reduction from baseline to endpoint in the 24-hour average pain severity, at study completion, with a $\geq$ 30% reduction from baseline at a visit other than the last visit, and at least $\geq$ 20% reduction maintained at every study visit between the first visit at which the patient achieves "clinical response" and study endpoint.

The table below lists the percentage of patients that were classified as having a "sustained response" at the different weeks during the study. The grey-shaded row identifies the results obtained by the two different imputation methods for missing data.

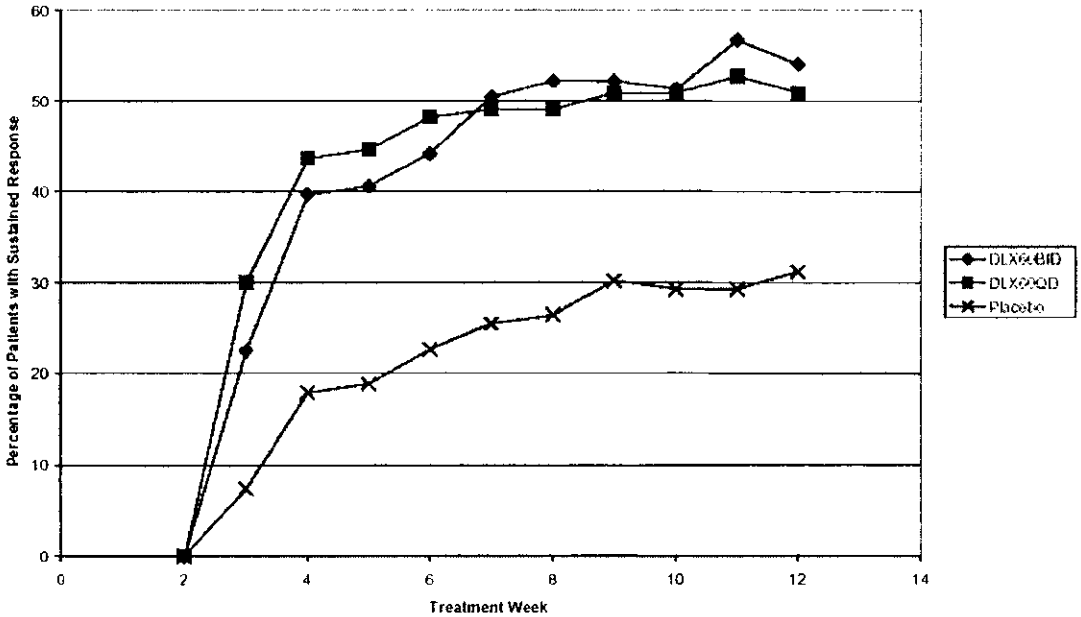
HMAVa BOCF, 'Sustained Response' Rate by Week

Treatment Week	Placebo n = 106 (%)	DLX60QD n = 110 (%)	DLX60BID n = 111 (%)
1	N/A	N/A	N/A
2	N/A	N/A	N/A
3	8 (7.6)	33 (30.0)	25 (22.5)
4	19 (17.9)	48 (43.6)	44 (39.6)
5	20 (18.9)	49 (44.6)	45 (40.5)
6	24 (22.6)	53 (48.2)	49 (44.1)
7	27 (25.5)	54 (49.1)	56 (50.5)
8	28 (26.4)	54 (49.1)	58 (52.3)
9	32 (30.2)	56 (50.9)	58 (52.3)
10	31 (29.3)	56 (50.9)	57 (51.4)
11	31 (29.3)	58 (52.7)	63 (56.8)
FDA→ 12 (BOCF)	33 (31.1)	56 (50.9)	60 (54.1)
Lilly → 12 (LOCF)*	*36 (34.0)*	*59 (53.6)*	*69 (62.2)*

*LOCF row from Applicant's analysis. All other rows use BOCF

The figure below is a graphical representation of the data in the table.

HMAVa Sustained Response Rate by Week (BOCF)



Source: Table and Diagram modified from Lilly response to request (7/27/08)

The table and diagram illustrate that in addition to having a higher percentage of patients classified as responders, the duloxetine treatment groups also had greater durability of response.

First week of clinical response (sustained responders)

The first week that a clinical response was achieved was identified for those patients that were identified as "sustained responders" at the end of the study. The table below tabulates the results, utilizing the BOCF imputation method for missing data. Since all sustained responders, by definition, would have needed to achieve at least a 30% reduction by Week 10, the rows for Weeks 11 and 12 are denoted as "not applicable" (NA).

HMAVa, First Week 'Clinical Response' Achieved, Sustained Responders at Week-12 (BOCF)

Treatment Week	Placebo N=33 (%)	Duloxetine 60 mg QD N=56 (%)	Duloxetine 60 mg BID N=60 (%)
1	8 (24.2)	30 (53.6)	19 (31.7)
2	8 (24.2)	15 (26.8)	19 (31.7)
3	4 (12.1)	3 (5.4)	6 (10.0)
4	5 (15.2)	3 (5.4)	5 (8.3)
5	3 (9.1)	1 (1.8)	6 (10.0)
6	0 (0.0)	0 (0.0)	3 (5.0)
7	3 (9.1)	3 (5.4)	0 (0.0)
8	0 (0.0)	1 (1.8)	1 (1.7)
9	2 (6.1)	0 (0.0)	1 (1.7)
10	0 (0.0)	0 (0.0)	0 (0.0)
11	N/A	N/A	N/A
12	N/A	N/A	N/A

Source: Applicant response, page 13 (8/27/04)

The table shows that a higher percentage of "sustained responder" patients in the duloxetine-treated arms achieved their first clinical response early in the study, compared to the placebo group.

Overall Conclusions

These four additional analyses, fraction of patients achieving a specified degree of improvement, percent of responders at each week, percent of sustained responders, and first week of clinical response for those identified as sustained responders, all had results that were consistent with what was found in Study HMAW.

6.1.5.2.15 Applicant's Secondary Efficacy Results

Twenty-four-hour average pain, worst pain, and night pain scores were obtained from the patient diaries, transcribed at each visit. The weekly means of these variables were calculated using week-long intervals (regardless of the length of the visit interval). Lilly's secondary efficacy analyses included:

- Analysis of the baseline-to-endpoint change in 24-hour worst pain score, night pain score, BPI: Severity and Interference, CGI-Severity, HAMD17 total score, sensory portion of the Short form McGill pain questionnaire (F-MPQ) total score of sensory component, and dynamic allodynia using an ANCOVA model (referred to hereafter as "mean change analysis").

- Repeated measures analysis of all baseline and post-baseline data in the acute therapy phase (by Visit 10) for 24-hour average pain score, 24-hour worst pain score, night pain score, BPI: Severity and Interference, CGI-Severity, and HAMD17 total score.
- Mean change analysis of all post-baseline data and last non-missing score (defined as endpoint) for Patient's Global Impression of Improvement (PGI-Improvement).
- Analysis of response rate and sustained response rate for 24-hour average pain severity using a Fisher's exact test.
- Analysis of treatment-associated change in each of the pain descriptors in SFMPQ sensory component using a Fisher's exact test.
- Analysis of the shift of the distribution of the reported pain types by SF-MPQ: endpoint versus baseline.
- Comparison of Kaplan-Meier survival curves between treatment groups of time to first 30% reduction in average pain severity and time to sustained response using a log-rank test.

6.1.5.2.16 HMAVa Discussion

Using BOCF instead of LOCF duloxetine treatment effect at the two higher doses is still present, although p-values increase slightly. 'Response rate' and 'sustained response rate' at endpoint, decrease (compared to those from the LOCF analysis), but for all treatment groups, including placebo, the overall conclusions are not affected.

- Both 60 mg BID and 60 mg QD are more effective than placebo.
- 60 mg BID does not appear to be more effective than 60 mg QD
- For both doses, efficacy generally begins within about one week of initiating treatment (response rates rise, and plateau by the second, or third treatment week).
- By the end of two weeks of treatment.
- For patients achieving sustained response (by Week 12)
  - Over 80% of 60-mg QD treated patients have done so within two weeks.
  - Over 63% of the 60-mg BID treated patients have done so within two weeks.
  - All but one 60-mg QD patient had their sustained-response by (the end of) the seventh week, as had 90% of the 60-mg BID patients.
- The higher dose does not appear to hasten time to response either.

6.1.6 Efficacy Conclusions

Duloxetine efficacy for the treatment of pain caused by diabetic peripheral neuropathy (as measured by reduction in diary-recorded ratings of "average pain over last 24-hours") has been established in both Lilly efficacy trials: HMAW and HMAVa. HMAW employed fixed duloxetine doses of 20-mg QD, 60-mg QD and 60-mg BID. HMAVa employed only the 60-mg QD and 60-mg BID doses, but was otherwise nearly identical to HMAW.

Sixty milligrams QD and sixty milligrams BID appear to exhibit approximately equal efficacy. Pain score reductions were not greater, on average, at the higher dose, nor was 'time to response' decreased. Patients treated at the higher dose (120 mg/day) did not appear more likely to attain 'clinical response' or 'sustained response.' There is no data,

then, demonstrating that doses above 60-mg QD confer additional benefit. Still, it is possible that higher doses could be beneficial for some patients.

Overall, dosing at 20-mg QD did not appear to be more effective than placebo. Doses below 60-mg per day (but above 20-mg per day) were not evaluated. Dose-ranging was not sufficient for determination of a minimum effective dose

Dosing at 20-mg QD did was not more effective than placebo, as assessed by primary, and most secondary outcome measures. Dose-ranging was not sufficient for determination of a minimum effective dose. Doses below 60-mg per day (but above 20-mg per day) were not evaluated. Duloxetine efficacy for DPN pain does not appear to differ between patient subpopulations based upon diabetes type (I or II), or disease duration.

Subgroup Analysis for Primary Efficacy Measure
(Baseline to Endpoint, LOCF, HMAW + HMAVa)

Subgroup	N	Therapy	n	Within Subgroup p-value [a]	Therapy by Subgroup p-value [b]
Age					0.911
< 65	443	Placebo	144	<0.001	
		Duloxetine	299		
≥ 65	216	Placebo	73	<0.001	
		Duloxetine	143		
Gender					0.755
Female	260	Placebo	91	<0.001	
		Duloxetine	169		
Male	399	Placebo	126	<0.001	
		Duloxetine	273		
Race					0.861
Caucasian	515	Placebo	169	<0.001	
		Duloxetine	346		
Other	144	Placebo	48	<0.026	
		Duloxetine	96		

[a] Chi square [b] Type II sum of squares ANOVA
Change in 24-Hour Average Pain Score Source: Applicant Table ISE 8.1

Subgroup Analysis for Primary Efficacy Measure
(Baseline to Endpoint, LOCF, HMAW + HMAVa)

Subgroup	N	Therapy	n	Within Subgroup p-value [a]	Therapy by Subgroup p-value [a]
DM type					0.860
Type I	66	Placebo	22	0.082	
		Duloxetine	44		
Type II	593	Placebo	195	<0.001	
		Duloxetine	398		
DPN Duration					0.983
≤ 2 yrs	272	Placebo	88	<0.001	
		Duloxetine	184		
> 2 yrs	387	Placebo	129	<0.001	
		Duloxetine	258		

[a] Chi square [b] Type II sum of squares ANOVA
Change in 24-Hour Average Pain Score Source: Applicant Table ISE 8.2

7 INTEGRATED REVIEW OF SAFETY

7.1 Brief Statement of Findings

NDA 21-733 contained data from three studies in DPN patients (37 clinical studies in total). The 120-Day Safety Update (submitted 7/01/04), added safety data from DPN open-label Study HMBT-Extension, as well as from three clinical pharmacology studies, and one SUI trial.

Exposure

Lilly reports that (as of 03/01/2004) 8604 patients have been exposed to duloxetine in the development programs for MDD, DUI, DN, and fibromyalgia, 7545 in Lilly trials and 1059 in [redacted] trials. The three NDAs, 21-427, 21-733 [redacted] account for 8447 of these exposures (and all 2867 placebo exposures).

Lilly's 'overall integrated safety database' contains data for 8454 subjects, who received duloxetine in clinical trials across all indications (diabetic peripheral neuropathy (DPN), major depressive disorder (MDD), stress urinary incontinence (SUI), and fibromyalgia). Duloxetine trials for diabetic peripheral neuropathy enrolled a total of 1240 patients, 1074 of whom received at least one dose of duloxetine. Of these, 484 patients have been exposed to duloxetine for at least six months, and 220 patients for at least one year. All of the six month and one-year exposures have been at the 120-mg/day dose. Lilly has met ICH guidelines for patient exposure (numbers, dose and duration) for the DPN indication, then.

Deaths

Lilly reports a total of 29 deaths in duloxetine trial participants, as of 07/01/04. Fourteen of these deaths were in DPN patients; 12 duloxetine-treated and two placebo-treated. Fourteen deaths were in MDD or SUI patients, nine had received duloxetine, three had received imipramine and two had received placebo. One death was in a (duloxetine-treated) clinical pharmacology subject. The overall mortality rate in duloxetine-treated DPN patients was 1.1% (12/1074), while in duloxetine-treated MDD/SUI patients it was ≈ 0.1% (9/≈7373). Deaths in the DPN population were most frequently classified as cardiac-related. This is consistent with known cause(s) of death in diabetic patients with peripheral neuropathy. There does not appear to be a clear association between the use of duloxetine and death.

Serious adverse events (SAEs)

Myocardial infarction, congestive heart failure, chest pain, cellulitis and skin ulcer were the most common SAEs in DPN patients. The overall number of SAEs in the controlled DPN trials was similar between duloxetine-treated patients (2.3%) and placebo-treated patients (2.1%). In the updated 'long-term safety database' (HMAW-Extension to 52-weeks + HMBT to 52-weeks) there were 77 SAEs in 671 patients treated with duloxetine 120-mg/day (11.5%). The 115 'routine-care' treated patients (no duloxetine) in HMAW-Extension experienced 22 SAEs (19.1%). The types of SAEs experienced were similar between long-term duloxetine-treated and routine-care treated patients. Duloxetine treatment did not appear to increase patients' risk of SAEs likely to be considered diabetes-related (i.e., DKA and severe hypoglycemic episodes, symptomatic hypoglycemic episodes, diabetic cellulitis, etc.).

Common (non-serious) AEs (DPN patients)
Patients treated with duloxetine more frequently reported a number of gastrointestinal (GI) and CNS related adverse events, than those treated with placebo (in the controlled trials) or 'routine-care' (in the open-label trials). The most common non-serious AEs were CNS-related (somnolence, dizziness, headache, insomnia, and fatigue) and GI-related (nausea, decreased appetite (including 'anorexia') constipation, dry mouth, diarrhea). The incidence of common AEs appears clearly dose-related.

AEs of interest (DPN patients)
The open-label, long-term exposure (6-months to 15-months) data from the DPN studies, suggest no association between duloxetine use and increased rates of the most common 'diabetic complications,' over the therapy duration studied. In addition to the 12 week placebo-controlled trials, Lilly utilized a 'routine-care' control arm in long-term study HMAW-Extension, in which patients did not receive duloxetine, but adhered to the same study visit and assessment schedule. The ability to draw conclusions about duloxetine effects on diabetes, and its progression, in the setting of actual 'long-term' use (years to decades), should not be overestimated, however.

Laboratory values (DPN patients)
The placebo-controlled data as well as the open-label, long-term exposure (6-months to 1-year) data suggest that duloxetine treatment (at 60 to 120-mg per day) may be associated with small increases in fasting serum glucose (baseline-to-endpoint, mean increase ≈ 5-10 mg/dL). This glucose finding, even if non-spurious, is likely of minimal clinical significance, however, because hemoglobin A1c values were unchanged over the same time periods. There was also no difference in fasting glucose baseline-to-maximum values. (Fasting glucose and hemoglobin A1c were not obtained as frequently in the MDD or SUI patients, to allow for similar evaluation.) Duloxetine's effect on serum transaminases, already documented in the approved labeling, was observed in the DPN population with similar incidence and magnitude (elevations to two or three times baseline in < 2% of patients, resolving with drug discontinuation).

Renal function assessment (microalbumin/creatinine ratio changes) indicates no differential progression of (or development of) renal disease in duloxetine-treated patients, compared to placebo-treated and to routine-care treated patients. The same appears true for retinopathy, although ophthalmologic evaluation was not as frequent, or as thorough as that for renal function (not all patients had both pre and post treatment ophthalmologic examination results).

Vital signs, weight, and ECGs (DPN patients)
Weight loss occurred more frequently in the duloxetine treated patients, in a dose-dependent manner (duloxetine-treated, mean ≈ 1.1 kg. vs. ≈ 0.2 kg. for placebo, over 12-13 weeks). Duloxetine did not appear to have any clinically significant effects on cardiac conduction, as assessed by 12-lead ECG. Duloxetine's effect on blood pressure is described in the approved labeling, which notes that blood pressure should be monitored throughout treatment. There were increases in resting diastolic blood pressure (≈ 2 mm Hg), in the duloxetine-treated DPN patients, compared with those treated with placebo. This finding appears to be dose-related, but is unlikely to be of clinical significance.

Neuropathy progression did not appear to differ between treatment groups either.

7.2 Approach to Safety Review/Methods

7.2.1 Methods and Findings

The objective of this safety review was to ascertain and elucidate all duloxetine clinical effects, and their ramifications for its safe use. Data from all Lilly duloxetine exposures was examined, with particular attention to the DPN patients, and to their similarities to, and differences from, duloxetine-treated MDD and SUI patients. The primary safety database (DPN trial duloxetine exposures) was reviewed for deaths, serious adverse events study dropouts (however classified), and common adverse events. Review was performed 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.

Labeling approved for the MDD indication cites the following as the major safety concerns associated with duloxetine:

- Duloxetine increases the risk of elevation of serum transaminase levels. In the dataset of all placebo-controlled trials (for all indications) reviewed for the MDD application, 1% (39/3732) of duloxetine-treated patients experienced ALT elevations to three times the upper limit of normal (or greater), compared to 0.2% (6/2568) of placebo-treated patients. This effect appears to be dose related. In placebo-controlled studies using a fixed dose design, there was evidence of a dose-response relationship for ALT and AST elevation of > 3 times the upper limit of normal and > 5 times the upper limit of normal, respectively.
- Duloxetine treatment was associated with mean increases in resting blood pressure, also in a dose-dependent fashion. (Note: These increases were ≈ 1-2 mm Hg.)
- Duloxetine is rapidly hydrolyzed to naphthol in acidic media. In the approved labeling, caution is advised in using duloxetine in patients with conditions that may slow gastric emptying. Gastroparesis, not uncommon in long-standing diabetic patients, is one such condition.
- Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in patients with ESRD and severe renal impairment (creatinine clearance <30 mL/min). For this reason, duloxetine is not recommended for patients with ESRD
- The most commonly observed adverse events in duloxetine-treated MDD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating. Nausea (duloxetine 1.4%, placebo 0.1%) was the only common adverse event reported as a reason for treatment (study) discontinuation, and considered to be drug-related.
- Duloxetine causes mydriasis and is therefore contraindicated in patients with uncontrolled narrow angle glaucoma
- Duloxetine has the potential to be involved in CYP1A2 and CYP2D6-mediated drug-drug interactions.

The safety findings in the DPN population were of primary interest for this review, although not only because NDA 21-733 is an application for duloxetine use in this population. The DPN patients were older, and had more concomitant disease at baseline (than patients in the MDD and SUI trials). The DPN trials included patients with the entire range of complications of long-

standing diabetes, whereas the MDD trials enrolled, for the most part, medically healthy patients. This could make them more vulnerable to drug toxicity adverse (and more likely to exhibit adverse drug effects). Also, on average, the DPN-trial patients received considerably higher duloxetine doses, for longer durations, than those in the other trials.

In the clinical trials, adverse events were elicited by open-ended questions. Lilly coded adverse event terms to the preferred terms using the MedDRA thesaurus (Versions 3.0, 4.0, 5.0, 6.0, 6.1) and counted patients who were enrolled in both acute phase and open-label extensions only once for all AE summaries.

Death narratives and CRFs for all DPN study subjects who died were reviewed individually. In addition, I reviewed the CRFs, narrative summaries, data sets, and study reports for a subset of SAEs, select AEs that led to premature study withdrawal, and AE preferred terms that were suggestive of AEs of interest.

To evaluate the accuracy of adverse event (AE) coding procedures, I compared investigator verbatim terms with the corresponding preferred terms assigned by Lilly, for a select sample of patients in all trials. For selected events (e.g. anorexia, decreased appetite, 'liver abnormalities' including abnormal values for liver function laboratory testing, ECG abnormalities), I reviewed the coding of a sample of those events in more detail by examining the CRFs, electronic data, narrative summaries, and study report listings, to determine if the coded terms accurately reflected the described events. I limited the sample to adverse events that led to dropout in DPN trials.

Based on this audit, the Applicant's preferred terms appeared generally appropriate, with several exceptions. Hepatic enzyme increases, for instance were coded to multiple terms ('Alanine aminotransferase increased,' 'Aspartate aminotransferase increased,' 'Gamma-glutamyltransferase increased,' and 'Hepatic enzyme increased'). Likewise, acute myocardial infarctions were variously coded as 'acute myocardial infarction' and also 'myocardial infarction.' Depending on the specific tabulation, the number of patients (and adverse events) affected changes, but was always less than eight. These findings (separation of events that should have been classified and tabulated together) have no bearing on the overall safety conclusions.

Lilly's adverse event risk calculations were also reviewed, as well as laboratory and vital sign data analyses, checking for internal consistency. Due to the formatting of the datasets submitted, however, additional detailed analyses of group changes in laboratory, vital sign and ECG data, were not possible.

7.2.2 Materials Utilized in the Review

7.2.2.1 Primary Source Data

Lilly's Integrated Summary of Safety (ISS) included data from 37 studies completed as of 10/01/03, the database lock date. Three of these studies were in the DPN population. The 120-Day Safety Update, submitted 07/01/04, added (DPN) safety data from patients enrolled in the 24-week open-label HMBT-Extension, as well as data from three clinical pharmacology studies and one Phase 3 SUI trial. The revised/corrected datasets Lilly provided (5/4/04 and 5/11/04) were utilized. All safety data submitted was utilized. (For tables referencing the 'long-term

safety database,' the HMBT-Extension data in the 120-Day Safety Update are reported separately.)

Table 7.1: 'Primary Safety Database'
Studies HMAW (+ Extension), HMAVa, HMBT to 28 Weeks

↓ Type / Trial →	HMAW	HMAVa	HMBT
Acute - Efficacy	HMAW-Acute	HMAVa-Acute	- - - - -
	(N = 457)	(N = 334)	
Duration	12-weeks	12-wks + 1-wk taper	
Treatment Arms (n)	- DLX 60 mg BID (113) - DLX 60 mg QD (114) - DLX 20 mg QD (115) - Placebo (115)	- DLX 60 mg BID (112) - DLX 60 mg QD (114) - Placebo (108)	- - - - -
	↓ ↓	↓ ↓	
Long-Term Safety	HMAW-Extension	HMAVa-Extension	HMBT
	(N = 337)	(N = 223*)	(N = 449)
Duration	52-weeks	52-weeks	28-weeks
Treatment Arms (n)	- DLX60BID (222) - 'routine care' (115)	- DLX60BID** - 'routine care'	- DLX60BID (334) - DLX120QD (115)
Status	Complete	Ongoing, no data	Complete
			↓ ↓
Long-Term Safety			HMBT-Extension
			(N = 87)*
Duration			24-weeks
Treatment Arms (n)			- DLX60BID (66)* - DLX120QD (21)*
Status			120-Day Update

* HMAVa-Extension and HMBT-Extension are ongoing (still accruing patients), as of 03/01/04
** HMAVa-Extension patients unable to tolerate DLX60BID may ↓ to DLX60QD, and continue in the trial
Source: Clinical reviewer

In order to facilitate analysis and reporting, Lilly grouped data into three discrete databases according to treatment indication and study design; the 'primary safety database,' the 'placebo-controlled secondary safety database' and the 'overall safety database.'

Primary Safety Database

The '**primary safety database**' includes duloxetine-treated patients from DPN studies (HMAW-Acute and Extension, HMAVa-Acute, and HMBT to 28-weeks). The 'primary safety database' includes data on all 1,074 patients from these studies. Of these, 484 patients were exposed to duloxetine for at least 6 months, and 158 patients were exposed for at least 1 year. The primary safety database was locked as of 10/1/03, and is the focus of this safety review. The sponsor has subdivided the primary safety database into four groups:

- Three-month placebo controlled patients ('placebo-controlled database')
- Twelve-month routine care-controlled ('routine care-controlled database'). The routine care-controlled database consists of data from the 52-week extension phase of Study HMAW (After completing the acute phase of Study HMAW, patients were rerandomized to receive either duloxetine 60 mg twice daily or routine care). Routine care was defined as "therapies

that the investigator and the patient believe permit the optimal benefit to the patient, including medicinal and non-medicinal treatments."

- Long-term exposure, up to 15 months exposure ('long-term database'). The long- term database consists of all duloxetine long-term exposures from Study HMAW (only patients randomized to duloxetine in the extension phase), and Study HMBT (up to 28 weeks). For patients in Study HMAW who were randomized to duloxetine in both the acute and extension phases, data from both study phases were included in this database. No statistical comparisons were made in this database; only summaries presented.
- All DPN duloxetine exposures ('Primary safety database' or 'all DPN database')

The basic design of the placebo controlled studies was described in the efficacy review. Study HMBT, a 28-week open-label safety study is described below in Section 7.2.2.1.

Placebo-Controlled Secondary Safety Database
The '**placebo-controlled secondary safety database**' includes information from all 6770 patients in all of the placebo-controlled duloxetine studies for indications other than DPN. A total of 3939 patients were randomly assigned to duloxetine treatment, and 2831 patients were randomly assigned to placebo treatment, in the placebo-controlled secondary safety database. Data from all duloxetine arms of these studies were pooled to form the duloxetine group, and data from all the placebo arms were pooled to form the placebo group.

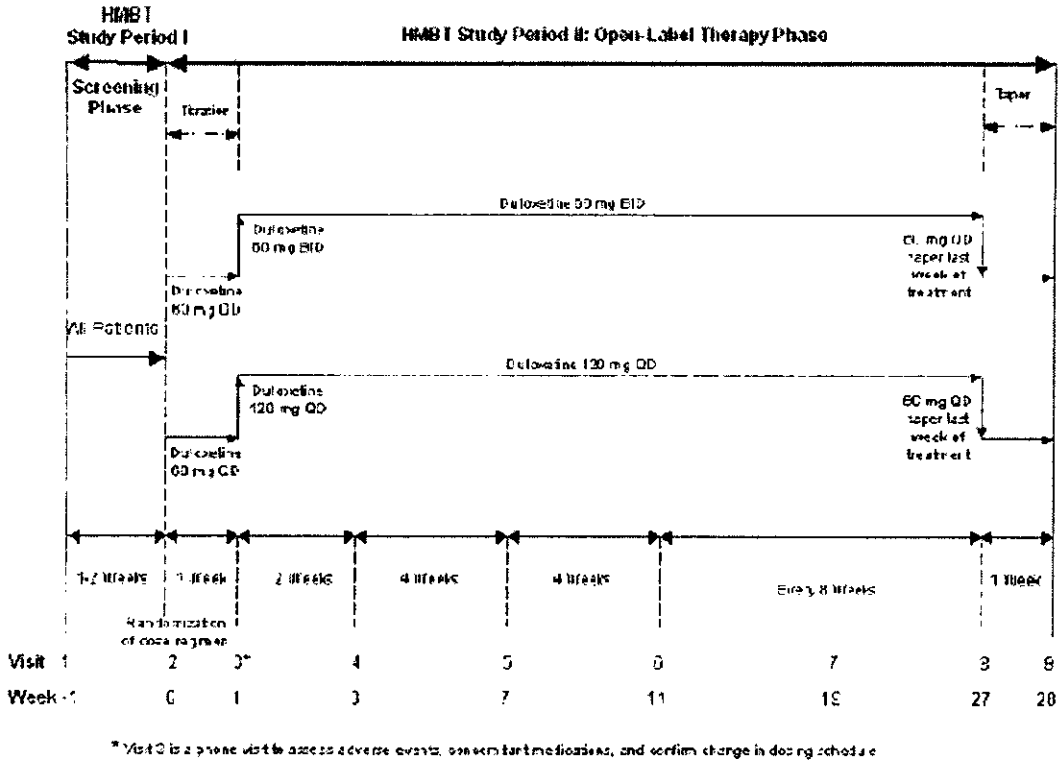
Overall Safety Database
Safety information from the '**overall safety database**' includes information from all 8454 patients treated with duloxetine in DPN, major depressive disorder (MDD), stress urinary incontinence (SUI), and fibromyalgia clinical studies.

Additional sources of safety data
Except for the five patient deaths (Section 7.4) safety data come from studies performed in Japan by — was not pooled with any of the Lilly data, nor reported in this review.

7.2.2.1.1 Study HMBT, Open-Label Safety Study

HMBT (conducted in Argentina, Australia, Brazil, Canada, Chile, and Taiwan) was a 28-week open-label, safety study (with a 24-week extension phase offered at a subset of clinical sites) in which all patients received duloxetine 120-mg/day (either as 60-mg BID or 120-mg QD, randomized 3:1). Patient selection criteria and safety assessments were nearly identical to those in HMAW and HMAVa. All patients received duloxetine 60-mg QD during their first and last treatment weeks. Four-hundred and forty-nine (449) patients enrolled in HMBT, and 285 completed 28 weeks of treatment. Of the 334 patients randomized to 60 mg BID, 213 completed the study, and of the 115 patients randomized to 120 mg QD, 72 completed the study. Eighty-seven (87) subjects opted for the extension phase, which was only conducted at sites in Canada. The study design is illustrated in the figure below.

HMBT Study Plan



* Visit 3 is a phone visit to assess adverse events, concomitant medications, and confirm change in dosing schedule

As in HMAW and HMAVa, many medications with primarily central nervous system (CNS) activity were not allowed in Study Period II, Lilly summarized and analyzed data from the 27 weeks preceding final treatment week taper. In all analyses, "baseline" was defined as the last non-missing observation of Visit 1 and Visit 2, and "endpoint" was defined as the last non-missing post-baseline observation at or before Visit 8 (treatment week 27).

7.3 Findings from DNDP and DRUDP Safety Reviews

In addition to NDA 21-733 for the DPN indication (in the Division of Anesthetic, Critical Care, and Addiction Drug Products), Lilly has submitted marketing applications for duloxetine for major depressive disorder (NDA 21-427 in the Division of Neuropharmacological Drug Products-DNDP), and for stress urinary incontinence (NDA

Duloxetine was approved for MDD on 07/23/04. DNDP labeling identifies the following safety issues:

- elevation of serum transaminase levels
- increases in blood pressure
- commonly-reported AEs of nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating
- potential for hydrolysis to naphthol in patients with conditions that may slow gastric emptying. No specific events related to this were identified as such patients were not studied.
- mydriasis
- potential drug-drug interactions with CYP1A2 and CYP2D6 inhibitors

Review by DRUDP identified a concern regarding cardiac conduction. The approved labeling for MDD does not indicate an effect of duloxetine on cardiac conduction.

DNDP Proposed Label, Review Cycle Two
Common and Drug-Related Adverse Events in the Placebo-Controlled MDD Safety Database (Occurrence Rate of ≥5% and at Least 2X Placebo)

Adverse Event	Placebo N=723		Duloxetine 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	15	(2.1)	67	(6.5)
Sweating Increased	11	(1.5)	56	(5.4)

Source: DNDP clinical/safety review (review cycle 2)

7.4 Safety Findings from Clinical Studies

7.4.1 Description of Patient Exposure

Lilly states that over 11,000 subjects have participated in duloxetine clinical trials "excluding clinical pharmacology and ongoing studies," with 8454 of these subjects randomized to receive duloxetine. Across all indications, 8447 clinical trial subjects received at least one

dose of duloxetine. All subjects in all studies received immediate release (IR) formulations. (Subjects in the earliest clinical pharmacology studies received an alternate formulation.) My tabulation of subject exposure to duloxetine by treatment indication, and trial type is shown below.

Subjects Exposed to DLX, Controlled and Uncontrolled Trials

Indication	Controlled Placebo	Controlled Duloxetine	Uncontrolled Duloxetine	Total Duloxetine
DPN	223	568	671	1074
MDD+SUI+PK*	2823	3939	≈7373*	≈7373*
ALL	3046	4507	≈3940	8447

* Totals of MDD/SUI trials combined with clinical pharmacology studies
Source: Clinical reviewer

To facilitate analysis and reporting Lilly defined several safety databases. The **'primary safety database'** contains data from all (N=1074) patients exposed to duloxetine in DPN studies (table below). Among the DPN patients, 484 had ≥ 6 months of exposure to duloxetine, and 158 had ≥ 12 months of exposure to duloxetine, as of 03/01/04. Lilly calculates that the primary safety database contains the equivalent of 509.9 patient-years of exposure. Data from DPN trial participants that received placebo (only) are not included in the primary safety database. Lilly's tabulation of DPN patient exposure, by dose appears below.

'Primary Safety Database' DLX Exposures in Lilly DPN Trials

	20 mg/d	60 mg/d	120 mg/d	Placebo	Routine Care
HMAVa - Acute	---	114	112	108	---
HMAW - Acute	115	114	113	115	
HMAW - Extension	---	---	222*	---	115
HMBT – 6 month data	---	---	449	---	---
Subtotal	115	228	731(896)*	223	115
Total DLX = 1074*					

*In the HMAW Extension Phase, 222 patients received DLX 120 mg/day
- 165 of these had been treated with DLX in the HMAW Acute Phase
- 57 were new exposures (received Placebo in Acute Phase, then DLX in Extension)

Source: Modified from Applicant Table 2.5.5.1

The '**placebo-controlled primary safety database**,' a subset of the 'primary safety database' contains data from all 568 patients exposed to duloxetine during placebo-controlled DPN trials (The Acute Phases of HMAW and HMAVa). Where exposure-by-duration tables refer to the 'placebo-controlled primary safety database' each patient's total duration of exposure is tabulated, including, if applicable, exposure during the HMAW open-label extension.

The '**placebo-controlled secondary safety database**' contains data from all 'non-DPN' controlled duloxetine studies. This database, also referred to as the 'secondary integrated safety database' contains data from 6755 patients randomized to receive either duloxetine or placebo; 3932 of these patients were exposed to duloxetine, and 2823 were exposed to placebo (over five hundred of the placebo-treated subjects subsequently enrolled in open-label extension studies where they did receive duloxetine).

7.4.1.1 Duration of Exposure

As of 10/01/03 8447 patients have received duloxetine during clinical trials across all indications (8554 randomized). The mean exposure duration was 138.5 days (3202.4 patient-years). In the 'secondary integrated database' (controlled MDD and SUI trials only) mean exposure duration was 91.0 days (978.9 patient-years). In the 'overall exposures' DPN database the 1074 patients received duloxetine (as of 10/01/03, and also as of 03/01/04). The mean exposure duration in DPN patients was 173.4 days (509.9 patient-years), as of 03/01/04. Table 7.1 summarizes exposure by indication.

Exposure Duration
All DPN Trials (03/01/04) vs. Controlled MDD and SUI Trials (10/01/04))

Duration	DPN Controlled Duloxetine [N=568]	DPN All Duloxetine [N=1074]	MDD/SUI Controlled Duloxetine [N=3939]	ALL ALL* Duloxetine [N=8447]
0 days	0	1 (0.1)	14 (0.4)	33 (0.4)
> 0	568 (100)	1073 (99.9)	3918 (99.6)	8414 (99.6)
≥ 7 days	561 (98.8)	997 (92.8)	3808 (96.8)	8027 (95.0)
≥ 30 days	482 (84.9)	899 (83.7)	3244 (82.5)	6824 (80.8)
≥ 60 days	458 (80.6)	839 (78.1)	2179 (55.4)	5253 (62.2)
≥ 90 days	177 (31.2)	684 (63.7)	1366 (34.7)	3987 (47.2)
≥ 120 days		--	1099 (28.0)	3273 (38.7)
≥ 180 days		484 (45.1)	911 (23.2)	2752 (32.6)
≥ 360 days		220 (20.5)	136 (3.5)	1003 (11.9)

Source: Modified from Applicant Tables ISS.6.4.1, ISS.6.1.4, ISS.APP.20.3 and datasets
PCPSDB = placebo-controlled primary safety database
PSDB = primary safety database, all patients who received DLX in HMAW, HMAVa and HMBT
* ALL: All subjects exposed to duloxetine

The table above appears to show that a greater proportion of the DPN patients were treated for at least six months, and one year, than of the MDD and SUI patients. Exposures in four open-label studies are not included, however; HMBC, HMBY and HMAU for MDD and SBAY for SUI. The total number of subjects enrolled in these trials was less than 20% of the total patients enrolled in the control MDD/SUI trials. Two of these MDD trials were less than 16-weeks duration. My tabulation of (additional) exposure from all four trials shows that less than 200 patients have been treated for six months or longer, and less than 100 treated for one year or longer. Overall, the basic conclusions based upon the MDD/SUI exposures in controlled trials still hold true. The DPN patients were treated for longer, on average than the MDD/SUI patients. Only about 23% of the MDD/SUI patients were treated for six months or more; less than 5% were treated for one year or longer. The DPN patients were treated for longer, on average than the MDD/SUI patients (Over 50% of all DPN exposures have been for six months or longer).

The tables below show dose-by-duration for the DPN population, and for the pooled MDD/SUI populations, respectively. As with Table 7.1, all MDD/SUI exposure tabulations incorporate exposures in controlled trials only.

Duloxetine Dose-by-Duration (through 03/01/04)
All DPN Exposures (Controlled and Uncontrolled Trials)

Duration	DLX20QD N=65	DLX60QD N=176	DLX60BID* N=718	DLX120QD* N=115	TOTAL N=1074
0	0	0	1 (0.1)	0	1 (0.1)
>0	65 (100)	176 (100)	717 (99.9)	115 (100)	1073 (99.9)
≥7	62 (95.4)	158 (89.8)	676 (94.2)	101 (87.8)	997 (92.8)
≥30	54 (83.1)	141 (80.1)	615 (85.7)	89 (77.4)	899 (83.7)
≥60	47 (72.3)	133 (75.6)	575 (80.1)	84 (73.0)	839 (78.1)
≥90	9 (13.8)	82 (46.6)	514 (71.6)	79 (68.7)	684 (63.7)
≥120	--	--	437 (60.9)	77 (67.0)	514 (47.9)
≥180	NA	NA	410 (57.1)	74 (64.3)	484 (45.1)
≥360	NA	NA	202 (28.1)	18 (15.7)	220 (20.5)
Mean			208.18	170.31	173.42
Median			195.0	196.0	99.0
Maximum	141	138	531	395	531
Patient – Years			409.23	53.62	509.94

* Duloxetine 60-mg BID and duloxetine 120-mg QD provide the same total daily dose
'Primary safety DB' (All duloxetine exposures, HMAW with Extension, HMAVa, HMBT) plus HMBT-Extension
Source: Clinical reviewer, computed from datasets PATINFO.XPT (ISS) and from Applicant Table ISS.6.4.1

Duloxetine (Daily) Dose-by-Duration (10/01/03) MDD/SUI Exposures Controlled Trials

Duration	≤20 MG N=800	30 MG N=166	40 MG N=391	60 MG N=392	80 MG N=1738	≥120 MG N=452	TOTAL* N=3939
0 days	7 (0.9)	1 (0.6)	2 (0.5)	0 (0.0)	1 (0.1)	0 (0.0)	11 (0.3)
> 0	793 (99.1)	165 (99.4)	389 (99.5)	392 (100.0)	1737 (99.9)	452 (100.0)	3928 (99.7)
≥ 7 days	787 (98.4)	162 (97.6)	383 (98.0)	386 (98.5)	1720 (99.0)	445 (98.5)	3883 (98.6)
≥ 30 days	655 (81.9)	105 (63.3)	332 (84.9)	311 (79.3)	1474 (84.8)	385 (85.2)	3262 (82.8)
≥ 60 days	461 (57.6)	6 (3.6)	145 (37.1)	257 (65.6)	1200 (69.0)	237 (52.4)	2306 (58.5)
≥ 90 days	226 (28.2)	0 (0.0)	35 (9.0)	2 (0.5)	605 (34.8)	160 (35.4)	1028 (26.1)
≥ 180 days	135 (16.9)	0 (0.0)	0 (0.0)	1 (0.3)	313 (18.0)	131 (29.0)	580 (14.7)
≥ 360 days	78 (9.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	78 (2.0)
Mean	105.18	35.89	58.06	51.78	101.09	109.57	90.98
Median	69.00	42.00	56.00	63.00	84.00	64.00	66.00
Maximum	436	68	159	181	336	271	436
Pt. - Years	228.65	16.21	61.83	55.58	481.04	135.59	978.90

Source: Modified from Applicant Table APP.20.3, datasets and response to reviewer request (8/27/04)
* TOTAL: All subjects exposed to duloxetine in placebo-controlled trials for MDD and SUI

The DPN patients were treated at higher doses, on average than the MDD/SUI patients. Over 50% of all DPN exposures have been at the 120-mg daily dose, while less than 20% of the MDD/SUI controlled exposures (and none of the uncontrolled) have been at or above 120-mg per day.

Looking at subpopulations within the DPN patients:
In the 'placebo-controlled primary safety database,' or all patients enrolled in placebo-controlled DPN trials:

Dose-by-Duration Placebo-Controlled DPN Trials*

Duration	DLX20QD [N=115]	DLX60QD [N=228]	DLX60BID [N=225]
> 0	115 (100)	228 (100)	225 (100)
≥ 7 days	114 (99.1)	226 (99.1)	221 (98.2)
≥ 30 days	105 (91.3)	193 (84.6)	184 (81.8)
≥ 60 days	97 (84.3)	189 (82.9)	172 (76.4)
≥ 90 days *	5 (4.3)	92 (40.4)	80 (35.6)

*Includes exposure in open-label extension Source: ISS.6.1.4

The 'long-term primary safety database' includes data from HMBT (to 28-weeks) and from HMAW-Extension. The acute-phase data for Study HMAW were also included for those patients that received duloxetine in the acute phase of Study HMAW. HMBT patients all received duloxetine 120-mg daily. HMAW-Extension patients received either duloxetine 120-mg daily, or 'routine care' for up to 52 weeks (in addition to 12-weeks of HMAW-Acute treatment).

Dose-by-Duration, at Proposed DPN Dosing
DPN (All Trials, 03/01/04), MDD/SUI (Controlled, 10/01/03), All Exposures (10/01/04)

Indication Trial Type Dose ↓ Duration	DPN All 60 mg/d [N=176]	MDD/SUI Controlled 60 mg/d [N=392]	ALL All 60 mg/d [N=1098]	DPN All 120 mg/d [N=833]	MDD/SUI Controlled 120 mg/d [N=1254]	ALL All ≥120 mg/d [N=1423]
0 days	0	0 (0.0)	1 (0.1)	1	0 (0.0)	10 (0.7)
> 0	176 (100)	392 (100.0)	1097 (99.9)	832 (99.9)	452 (100.0)	1413 (99.3)
≥ 7 days	158 (89.8)	386 (98.5)	1033 (94.1)	777 (93.3)	445 (98.5)	1335 (93.8)
≥ 30 days	141 (80.1)	311 (79.3)	846 (77.0)	704 (84.5)	385 (85.2)	1189 (83.6)
≥ 60 days	133 (75.6)	257 (65.6)	661 (60.2)	659 (79.1)	237 (52.4)	902 (63.4)
≥ 90 days	82 (46.6)	2 (0.5)	292 (26.6)	593 (71.2)	160 (35.4)	760 (53.4)
≥ 120 days		??	??	514 961.7)	??	??
≥ 180 days		1 (0.3)	126 (11.5)	484 (58.1)	131 (29.0)	615 (43.2)
≥ 360 days		0 (0.0)	0 (0.0)	220 926.4)	0 (0.0)	158 (11.1)

Source: Modified from Table ISS.6.1.4

7.4.1.2 Exposure Demographics

The overall exposures database includes data from all 8454 patients assigned to receive duloxetine during Lilly clinical studies (all indications), as of October 1, 2003. Of these, 8447 patients received at least one dose of duloxetine; 77.7% were women and 80.5% were white. Patients ranged in age from 18 to 89 years of age, with a mean of 49.3 years. Overall, there were 1094 (12.9%) patients who were at least 65 years old. One-thousand and seventy-four (1074) (12.7%) of duloxetine-treated patients were enrolled DPN studies. The rest of the patients had been enrolled in MDD or SUI trials.

One-thousand and seventy-four patients received duloxetine in DPN trials (both controlled and open-label), ranging in age from 20 to 89 (mean 60.1). Over 42% were women, and 357 (33.2%) were ≥ 65 years of age. The majority of patients were classified as being of Caucasian origin (69.3%); 10.9% were Hispanic, 8.3% 'Oriental', 6.6% East Asian, 3.7% 'African' including African-Americans, 0.9% 'Western Asian' and 0.2% Aboriginal.

Demographics of Patients in Controlled DPN Trials

	Placebo (N=223)	**Duloxetine** (N=568)	**Total*** (N=791)
Ethnicity			
African Descent	16 (7.2)	32 (5.6)	48 (6.1)
Western Asian	0	8 (1.4)	8 (1.0)
Caucasian	175 (78.5)	439 (77.3)	614 (77.6)
East/Southeast Asian	2 (0.9)	6 (1.1)	8 (1.0)
Hispanic	29 (13.0)	76 (13.4)	105 (13.3)
Other	1 (0.4)	7 (1.2)	8 (1.0)
Chi-square (p=0.437)			
Mean Age	60.61	60.27	60.37
Median Age	61.61	60.55	61.04
Age Range	23.9-80.6	22.4-88.8	22.4-88.8
Chi-square (p=0.728)			
Female	95 (42.6)	211 (37.1)	306 (38.7)
Male	128 (57.4)	357 (62.9)	485 (61.3)
Chi-square (p=0.157)			

Source: Applicant Table ISS.6.1.1 and ISS dataset DIABDEMO.XPT
* Includes only controlled DPN trials, HMAW and HMAVa, acute phase

Demographics of Patients in Long-Term DPN Trials

	RCCSDB Routine Care (N=115)	RCCSDB DLX60BID (N=222)	RCCSDB Total* (N=337)	LTSDB DLX120/day (N=671)
Ethnicity				
Aboriginal	---	---	---	2 (0.3)
African Descent	12 (10.4)	16 (7.2)	28 (8.3)	19 (2.8
Western Asian	0	4 (1.8)	4 (1.2)	6 (0.9)
Caucasian	86 (74.8)	174 (78.4)	260 (77.2)	435 (64.8)
East/Southeast Asian	2 (1.7)	3 (1.4)	5 (1.5)	67 (10.0)
Hispanic	13 (11.3)	24 (10.8)	37 (11.0)	59 (8.8)
Other	2 (1.7)	1 (0.5)	3 (0.9)	83 (12.4)
Chi-square			(p=0.461)	
Mean Age	58.90	60.22	59.77	60.00
Median Age	59.43	61.21	60.57	60.62
Age Range	22.42 – 84.37	23.92 – 88.82	22.42 – 88.82	20.83 – 88.82
Chi-square (p=0.315)				
Female	46 (40.0)	86 (38.7)	132 (39.2)	301 (44.9)
Male	69 (60.0)	136 (61.3)	205 (60.8)	370 (55.1)
Chi-square (p=0.906)				

Source: Applicant Table ISS.6.3.1 and ISS dataset DIABDEMO.XPT
* Includes HMAW-Extension

DM/DPN Characteristics, Patients in Controlled DPN Trials

PCPSDB	Placebo (N=223)	Duloxetine (N=568)	Total (N=791)
DPN Duration (years)			
Mean	3.79	3.77	3.78
Median	2.66	2.41	2.48
Range	0.02-19.89	(-0.31)-37.10	(-0.31)-37.10
Chi-square (p=0.983)			
DM Duration (years)			
Mean	11.27	10.64	10.82
Median	7.79	7.79	7.79
Range	0.49-66.49	0.08-52.37	0.08-66.49
Chi-square (p=0.343)			
Type I DM	22 (9.9)	61 (10.7)	83 (10.5)
Type II DM	201 (90.1)	507 (89.3)	708 (89.5)
Chi-square (p=0.718)			

Source: Applicant Table ISS.6.1.1 and ISS dataset DIABDEMO.XPT
* Includes only controlled DPN trials, HMAW and HMAVa, acute phases

7.4.2 Deaths

Lilly has identified 29 deaths in duloxetine clinical trial subjects, across all indications as of 8/15/04. Twenty-four of these deaths were in Lilly trial participants, and five were in studies conducted by [redacted] trials in Japan are described in Section 2). Fourteen of the deaths occurred in (Lilly) DPN trial patients; twelve of these had received duloxetine, two had received only placebo. Fourteen deaths occurred in MDD and SUI trial patients. None of the deaths in the MDD and SUI populations were assessed by the reviewers to be likely to be drug-related. One death, by suicide, was in a nineteen year old healthy volunteer enrolled in an inpatient clinical pharmacology study.

Deaths were more common in the duloxetine-treated DPN population (12/1074, 1.3%), and in the overall DPN population (14/1240, 1.1%), than in duloxetine-treated MDD and SUI trial participants (14/7373, ≈0.2%). This is not unexpected. The DPN patients were significantly older (than the other duloxetine-treated patients), and in many cases had longstanding diabetes (mean duration = 11.3 years, median=9.0 years). Treatment duration was also substantially longer, on average, for the DPN patients, providing more exposure time per patient.

Suicide occurred in five MDD patients; three duloxetine treated, one placebo treated, and one imipramine treated. The only 'non-MDD' suicide occurred in a healthy, nineteen year old volunteer, in a (high dose), inpatient clinical pharmacology study. No suicides were reported in the DPN population.

The table on the following page summarizes all deaths that occurred during duloxetine trials.

Deaths in All Duloxetine Trials — Included) as of 8/15/04

Indic.	Age/ Sex	Reported Cause of Death	Drug	Dose	Duration (days)
DPN	88/M	MI	DLX	60BID	353
DPN	56/M	Sepsis	DLX	60BID	212
DPN	75/F	Cardiac arrest, hypoxic brain injury	DLX	60BID	145
DPN	55/F	Septic shock	DLX	60BID	29
DPN	62/M	Acute MI	DLX	60BID	143
DPN	58/M	Acute MI	DLX	120QD	391
DPN	75/M	Peritonitis, pneumonia, colon CA, +/- sepsis	DLX	60BID	102
DPN	58/F	Vertebral column metastases	DLX	60BID	≈365
DPN	59/M	Lung cancer	DLX	120QD	343
DPN	73/M	Acute MI	DLX	60BID	122
DPN	61/M	Cardiac arrest (>30 days after study withdrawal because of renal insuffic.)	PBO	--	N/A
DPN	73/M	Accidental drowning	PBO	--	N/A
DPN	58/M	Acute MI (120-day Update)	DLX	120QD	391
DPN	68/M	'Lung Cancer' (120-day Update)	DLX	120QD	343
MDD	77/M	Cardio-respiratory arrest 4 days after patient stopped duloxetine	DLX	40BID	60
MDD	44/F	Noncardiogenic pulmonary edema	DLX	40BID	216
MDD	23/F	Suicide	DLX	60BID	82
MDD	44/M	Accident injury, cardiac arrest	DLX	40–60 BID	1
MDD	38/M	Completed suicide	DLX	60QD	16
SUI	58/F	Possible liver metastases	DLX	40BID	181
SUI	70/F	Cerebrovascular accident	DLX	40BID	52
MDD	60/F	Suicide	DLX	10QD	≈90
MDD	63/M	Suicide	DLX	40QD	≈210
SUI	38/F	MVA	PBO	---	222
MDD	52/F	Suicide	PBO	---	222
MDD	61/M	Suicide	IMIP	50–150/day	≈3
MDD	61/F	Pneumonia, apnea	IMIP	50–150/day	≈30
MDD	31/M	Acute heart failure	IMIP	50–150/day	≈90
PK	19/F	Suicide (120-day Update)	DLX	120-400/day	≈14

Source: Prepared by clinical reviewer (Applicant Tables 2.5.5.2, ISS.8.1.6, and 120-day update text)

7.4.2.1 Deaths, DPN trials

As of 08/15/04 Lilly identified 14 deaths in DPN trial patients; two of these deaths occurred in placebo-treated patients, an accidental drowning and a cardiac arrest. Of the 12 duloxetine-treated deaths, six appear to have been directly related to cardiac disease. Two were attributed to sepsis or septic shock, two to lung cancer, and one to "vertebral column metastases." Finally, one death is reported as due to peritonitis, pneumonia, colon cancer AND sepsis. None of these deaths seem to be attributable to duloxetine treatment (after review of the CRFs and narratives). All twelve duloxetine-treated DPN deaths, occurred during long-term open-label trials (mean time on treatment 245 days), hence, at the only dose used in those trials, 120-mg per day.

7.4.3 Serious Adverse Events

A total of 379 serious adverse events (SAEs) were reported by 271 (3.2%) of the 8447 patients exposed to duloxetine in Lilly clinical studies for DPN, MDD and SUI combined. Some patients had more than one event as part of the same incident, and some patients had more than one incident in which an SAE occurred. In all DPN studies combined, a total of 92 (8.6%) patients reported SAEs.

SAEs were more common overall in DPN patients than in patients with indications other than DPN. This was true for both duloxetine-treated and placebo-treated (or 'routine-care' treated) patients. This may possibly be explained by the fact that many of the patients in the DPN trials had long standing diabetes (mean 12.3 years, SD 9.3 years). The DPN trial patients were also considerably older, on average. Over 33% of the DPN patients were 65 years or older (mean 60.5 years, SD 10.8), while less than 6% of the MDD patients were (mean age MDD+SUI =46.7 years, SD 13.0). Many more of the DPN patients (proportionately) had long-term exposures (than the controlled non-DPN trials patients), as well. Forty-five percent (45%) of the DPN patients received duloxetine for ≥ 6 months, 21% ≥ 12 months. In the MDD/SUI population 23% of patients had exposures ≥ 6 months, and less than 5% had exposures ≥ 12 months.

Cardiac SAEs and cellulitis represent a much greater proportion of the total number of SAEs in the DPN patients than in the non-DPN patients. Overall, the distribution of SAEs within each patient population is largely consistent with their underlying illnesses. For instance, there are more SAEs consistent with the (older) age of the DPN patients, compared with the MDD/SUI patients (i.e., various malignancies, CVA). Likewise, SAEs like 'suicide attempt' (11 total) and 'suicidal ideation' (10 total) were not reported at in the DPN population.

The following table shows SAE incidence by treatment indication, and trial type.

Overview, Number (%) of Patients with ≥ One SAE

	Controlled + Uncontrolled **DPN Primary Safety DB [a] + 120-Update**	Placebo-Controlled **DPN PC Primary Safety DB [b]**	Placebo-Controlled **MDD/SUI PC Secondary Safety DB [c]**	Uncontrolled **MDD/SUI**	Controlled + Uncontrolled **All Overall Exp.**
Combined	**N = 1074**	**N = 791**	**N=6770**		**N = 8447**
SAE Total (All)	92 (8.6)	29 (3.7)	58 (0.9)	≈120	271 (3.2%)
Treatment					
Placebo	**NA**	**N = 223**	**N= 2831**		**NA**
		10 (4.5)	23 (0.8)		
All Duloxetine	**N = 1074**	**N = 568**	**N= 3939**	**≈120**	**N = 8447**
	83 (7.7)	19 (3.3)	35 (0.9)		271 (3.2)

Modified from Applicant Tables ISS.19.3.12, ISS.8.1.7, ISS.APP.19.3.12 and ISS.APP.19.3.13

[a] PSDB = Primary Safety Database = All duloxetine exposures in DPN trials, 120-Day Update included, this table

[b] PCPSDB = All DLX exposures in placebo-controlled DPN trials = acute phases of HMAW, HMAVa

[c] PCSSDB = Secondary placebo-controlled safety database

SAEs in DPN trials

In the placebo-controlled DPN trials, there were no notable differences between the placebo-treated patients and duloxetine-treated patients (all doses combined) in incidence or type of serious adverse events; 3.3% (19/568) of duloxetine-treated patients experienced SAEs as did 4.5% (10/223) of placebo-treated patients. No differences were apparent either, between the placebo-treated patients, and those treated with either of the two higher duloxetine doses, 60-mg QD (3.1% or 7 SAEs), or 60-mg BID (2.2% or 5 SAEs). The 115 patients treated with duloxetine 20-mg daily experienced a total of seven SAEs (6.1%).

The following table gives the breakdown, by study and by treatment, for SAEs in the DPN trials.

SAEs All Randomized Patients
Patients with One or More SAEs, All DPN Trials with 120-Day Safety Update

		Duloxetine		Placebo		Routine Care	
'Database Subdivision'	Duration	n/N	%	n/N	%	n/N	%
Placebo-controlled		19/568	3.3	10/223	4.5		
HMAW - Acute	12 weeks						
HMAVa - Acute	12 weeks						
Routine care-controlled		32/222	14.4			22/115	19.1
HMAW - Extension	52 weeks						
'Long-term'		77/671	11.5	NA		NA	
HMAW - Extension	52 weeks						
HMBT – All	28 weeks						

Source: Modified from Applicant NDA Tables 2.5.5.3, 2.5.5.4 and text in the 120-Day Safety Update

The higher rate of SAEs in the 'routine care-controlled' and 'long-term' databases, compared to the rate in the 'placebo-controlled primary safety database' is likely a reflection of the longer duration of treatment in HMBT (Acute + Extension = 52-weeks total) and HMAW-Extension (>52 weeks), than in HMAW-Acute and HMAVa-Acute (12-13 weeks).

Distribution of SAEs

Cardiovascular SAEs were most common. This is unsurprising given that many patients were older, and had long-standing diabetes. Many also had known cardiac disease. Myocardial infarction (plus 'acute myocardial infarction') was reported in 11 (0.9%) patients. There was also one case of 'unstable angina' and one of 'chest discomfort.' Additional terms used to describe events likely indicative of myocardial ischemia were 'coronary artery occlusion,' 'coronary artery stenosis,' and 'coronary artery disease' and 'coronary artery atherosclerosis' (one case of each).

The terms 'cellulitis,' 'diabetic foot ulcers' and 'skin ulcer' were reported in 9 patients (combined 0.8%). Otherwise, no single event was reported with a frequency of > 0.5%. Aside from myocardial infarction and cellulitis/skin ulcer, no single event or type of event was predominant. Most of the SAEs occurred in the longer-term trials, but there was no clear temporal pattern in the incidence or nature of the events. Table 7.12 below (with accompanying text) lists SAEs reported in the DPN studies.

Table 7.12 reports incidence rates, by system organ class, of individual SAEs. Some patients reported multiple SAEs, most often as part of one illness episode. For example patient HMAW-4802 was coded as having three SAEs all with the same onset date and time; 'myocardial infarction,' cardiac failure congestive,' and 'angina pectoris.' Patient HMAW-5254, a 43 year old male with a long history of ethanol abuse, and multiple baseline LFT abnormalities, had ten SAEs coded with the same onset date and time: five pertaining to individual laboratory test abnormalities (LFTs), plus 'jaundice,' 'ascites,' 'hepatosplenomegaly,' 'cholestasis,' and 'hepatic fibrosis.' (Patient HMAW-5254's records were carefully scrutinized by DNDP reviewers. His liver disease had actually improved while the on duloxetine, until another drinking binge. DNDP safety reviewers concluded that duloxetine did not appear to have caused the acute decompensation, but could not be ruled out.)

SAEs by System Organ Class (Several Patients Experienced > One SAE)
Placebo-Controlled Trials, 'Routine-Care Controlled Trial,' 'Long-Term' All DPN Trials

Population →	PCPSD	PCPSD	Routine	Control.	'Long-term'	All DPN
Treatment →	Duloxetine	Placebo	Duloxetine	Routine	Duloxetine	Duloxetine
	N=568	N=223	N=222	N=115	N=671	N=1074
↓System Organ Class↓	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood/Lymphatic	--	--	1 (0.5)	0	1 (0.1)	2 (0.2)
Cardiac	4 (0.7)	1 (0.4)	10 (4.5)	9 (7.8)	21 (3.1)	26 (2.4)
Gastrointestinal	1 (0.2)	1 (0.4)	5 (2.3)	2 (1.7)	7 (1.0)	9 (0.8)
General/Administrative	2 (0.4)	3 (1.3)	3 (1.4)	3 (2.6)	4 (0.6)	9 (0.8)
Hepatobiliary	--	--	2 (0.9)	0	3 (0.4)	3 (0.3)
Infections/Infestations	1 (0.2)	0	7 (3.2)	5 (4.3)	13 (1.9)	14 (1.3)
Injury, Poisoning, Proceds.	5 (0.9)	0	5 (2.3)	0	8 (1.2)	13 (1.2)
Investigations	1 (0.2)	0	2 (0.9)	0	3 (0.4)	4 (0.4)
Metabolism/Nutrition	2 (0.4)	1 (0.4)	1 (0.5)	1 (0.9)	6 (0.9)	8 (0.7)
Neoplasms	1 (0.2)	1 (0.4)	0	1 (0.9)	4 (0.6)	6 (0.6)
Nervous System	2 (0.4)	0	4 (1.8)	2 (1.7)	8 (1.2)	10 (0.9)
Psychiatric	--	--	1 (0.5)	0	1 (0.1)	1 (<0.1)
Renal and Urinary	1 (0.2)	0	0	2 (1.7)	2 (0.3)	3 (0.3)
Respiratory/Thoracic	0	1 (0.4)	0	3 (2.6)	3 (0.4)	4 (0.4)
Skin/Subcutaneous	0	1 (0.4)	1 (0.5)	2 (1.7)	4 (0.6)	5 (0.5)
Vascular	1 (0.2)	1 (0.4)	0	2 (1.7)	2 (0.3)	4 (0.4)

Placebo-controlled trials = HMAW and HMAVa, Routine-care-controlled = HMAW-Extension
Long-term = HMAW-Extension + HMBT-28 week data
Source: Modified from Applicant Tables 2.5.5.4, 6.1.8 and 6.1.9

Given the short duration (12-13 weeks) of the placebo-controlled trials, incidence rates within those trials, are not highly informative. Also, while SAE distribution, and incidence in the 'long-term safety database' roughly parallel the 'routine-care controlled' database, one-third of the 'long-term database' patients are the duloxetine-treated 'routine-care-controlled' patients. On the whole there do not appear to be any glaring differences between the routine-care controlled treatment arms. The 'long-term' incidences are expected to best predict real-world exposure.

The following table reports individual SAEs by preferred term.

All SAEs Reported in DPN Trials

SAEs Reported in ≥ 2 Patients	**92 (8.6%)**
Myocardial infarction	7 (0.7%)
Cardiac failure congestive	4 (0.4%)
Cellulitis	4 (0.4%)
Chest pain	4 (0.4%)
Skin ulcer	4 (0.4%)
Acute myocardial infarction	4 (0.4%)
Cerebrovascular accident	3 (0.3%)
Diarrhoea	3 (0.3%)
Hip fracture	3 (0.3%)
Urinary tract infection	3 (0.3%)
Vomiting	3 (0.3%)
Ankle fracture	2 (0.2%)
Atrial fibrillation	2 (0.2%)
Cerebral infarction	2 (0.2%)
Diabetes mellitus inadequate control	2 (0.2%)
Diabetic ketoacidosis	2 (0.2%)
Fall	2 (0.2%)
Myocardial ischaemia	2 (0.2%)
Orthostatic hypotension	2 (0.2%)

Reported SAEs (one patient each):

Abdominal pain, **Alanine aminotransferase increased**, Anaemia, Angina pectoris, Appendicitis, Ascites, **Aspartate aminotransferase increased**, Bacteraemia, Blood alkaline phosphatase increased, Blood bilirubin increased, Blood calcium increased, Cardiac arrest, Chest discomfort, Cholecystitis, Cholestasis, Chronic Back Pain, Colon cancer, Concussion, Convulsion, Coronary artery atherosclerosis, Coronary artery disease, Coronary artery occlusion, Coronary artery stenosis, Dehydration, Depression, Diabetic complication, Diabetic Foot Ulcers, Diverticulitis, Dizziness, Duodenal ulcer haemorrhage, Face injury, Fatigue, Femur fracture, Fracture displacement, **Gamma-glutamyltransferase increased**, Gastric ulcer, Gastritis, Gastrointestinal disorder, Haematocrit decreased, **Hepatic enzyme increased**, Hepatic fibrosis, Hepatic function abnormal, Hepatosplenomegaly, Hyperglycaemia, Hypertension, Jaundice, Ketoacidosis, Lacunar infarction, Lower limb fracture, Low Haemoglobin, Lung Cancer, Lung infection, Multiple Metastasis Column Vertebral, Migraine, Nephrotic syndrome, Neutropenia, Osteomyelitis, Pneumonia, Prostate cancer, Prostatic abscess, Reflux oesophagitis, Renal cell carcinoma stage unspecified, Renal impairment, Road traffic accident, Sepsis, Septic shock, Subacute Osteitis First Toe Left Foot, Subdural haematoma, Torn Rotator Cuff Right Shoulder, Transient ischaemic attack, Unstable Angina, Urinary retention

Review of the individual narratives and CRFs for all DPN SAEs did not uncover any events that appear to have been attributable to duloxetine therapy. As noted above, SAEs in the MDD and SUI populations were less frequent, and less likely to be cardiovascular in nature. Cardiovascular SAEs were not absent in those patients, however. There were a handful (<10) of cases where patients with depression, but no other known disease experienced myocardial infarctions. These patients ranged in age from the early forties to the late eighties. DNPD reviewers judged these events to be unrelated to study medication as well.

7.4.4 Study Dropouts

The total number of patients enrolled in DPN studies was 1240, 258 (20.8%) in South America, 803 (64.8%) in North America, 62 (5.0%) in Taiwan, and 117 (9.4%) in Australia. The total number treated with duloxetine was 1074. Placebo-controlled Studies HMAW and HMAVa enrolled 791 patients; 568 were randomized to duloxetine (20 mg QD, 60 mg QD, or 60 mg BID) and 223 to placebo. Of these, 337 patients continued into the open-label extension phase of Study HMAW. Open-label Study HMBT enrolled 449 patients, all of whom received 120-mg/day.

Lilly's classification of reasons for discontinuation failed to capture some discontinuations that were clearly due to laboratory abnormalities (and in at least two cases, adverse events). Twenty-three different disposition categories were possible, including "Other clinically significant laboratory value," "Personal conflict/Patient decision," "Physician decision," and "Sponsor decision." Examination of the CRFs and laboratory data for all patients assigned one of these disposition categories, revealed several obvious miscategorizations. CRFs were then requested for all patients assigned the "Physician decision" disposition (if they had been treated with duloxetine). Further review uncovered (at least) four patients inappropriately categorized by the investigator, and the Applicant as discontinuations due to 'physician decision' or 'other clinically significant laboratory value.' (See also Section 7.4.5)

HMBT-1708 categorized as a discontinuation for 'physician decision' at study Visit 7, comment field in data file states 'PATIENT WAS DISCONTINUED DUE TO ELEVATED LIVER FUNCTION TESTS' at Visit 7, treated with duloxetine 60-mg BID, ALT increased to 441, then **702**, AST > 350, Alkaline phosphatase > 175

HMAW-1229, discontinued from study for 'sponsor's decision' at Visit 14, treated with duloxetine 60-mg QD, GGT increased throughout study, discontinued at peak value (>100)

HMAVa-2613, discontinued for 'physician decision' at study Visit 9, treated with duloxetine 60-mg BID, GGT increased throughout study, patient discontinued at peak value (126)

Patient HMAW-1305, discontinued from study for 'sponsor's decision' at Visit 17, treated with duloxetine 60-mg BID in acute phase, AST and GGT increased throughout study, (both >100)

Patient HMBT-1503, categorized as a discontinuation due to 'patient decision/personal conflict' discontinued from the study after 184 days of treatment with duloxetine 120-mg QD. The patient's ALT, AST, and GGT mildly abnormal at baseline, increased during the study, peaking around study day 100 (GGT 1019, ALT 133, AST 80, alkaline phosphatase 348), before declining to about three times normal at discontinuation.

HMBT-3104 discontinued for 'physician decision' at study Visit 7, at Visit 7, treated with duloxetine 60-mg BID, total bilirubin elevated (peak) at last study visit.

HMAVa-0210, discontinued for 'physician decision' at study Visit 11 treated with duloxetine 60-mg BID, GGT increased throughout study, patient discontinued at peak value (64)

Patient HMAW-4013 (Extension phase), was categorized as discontinued due to "other clinically significant lab values" 43 days after beginning duloxetine 60-mg QD. The patient's final laboratory values showed a fasting glucose of 42.5 mmol/L (>700 mg/dL), and AEs of oral thrush, hyperglycemia and constipation.

Overall, there were very few patients that were clearly miscategorized, and they were scattered across trials and distributed between treatment groups. Most of Lilly's safety tables (incidence rates) would be unchanged, and where adverse event rates are altered slightly, the overall conclusions remain the same. Therefore, Lilly's classification, and adverse event tabulations are used throughout this review, with one exception. The Applicant's proposed label reports that patients were discontinued because of transaminase elevations. The first four patients listed above had no other laboratory findings or information recorded (on their CRFs) indicating why the physician, or sponsor decided study discontinuation was necessary. The label has been changed to include these four patients

Overall, adverse events were the most common reason for study discontinuation in Studies HMAW and HMAVa (as well as in open-label studies). Discontinuations due to adverse events were twice as common in the duloxetine-treated patients (14%) than in the placebo-treated patients (< 7%) in short-term placebo-controlled studies. A greater percentage of patients in the placebo groups discontinued due to lack of efficacy compared with the duloxetine groups (placebo 4.0%; duloxetine 1.6%). In the DPN long-term exposure database, 19.4% of subjects discontinued prematurely due to AEs, which is similar to the rate of premature discontinuation due to AEs in the overall, all-indications database (18.5%). In the routine care-controlled extension study, 14% of duloxetine-treated patients discontinued prematurely due to AEs, as compared to 10% of routine-care patients. Nausea (duloxetine 1.4%, placebo 0.1%) was the only common adverse event reported as reason for discontinuation and considered to be drug-related (discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Incidence of the most common adverse events leading to study drop-out in the placebo-controlled DPN trials, is presented in Table 7.14 below. Nausea, dizziness, somnolence, fatigue and hypersomnia were the most common AEs leading to study discontinuation during placebo-controlled trials. These AEs were also among the most commonly reported (as leading to discontinuation) in the overall DPN exposures database (Table 7.15 on the following page). These events, and their frequencies, are roughly similar to those reported during the MDD and SUI trials. Most of these events can reasonably be considered to be treatment-related.

Table 7.15, on the following page, lists AEs reported as reasons for discontinuation in two or more patients during the placebo-controlled trials.

Table 7.15: AEs Reported as Reason for Discontinuation in ≥ Two Patients in PCPSDB

Preferred term	Placebo N=223 (%)	DLX 20 mg/d N=115 (%)	DLX 60 mg/d N=228 (%)	DLX 120 mg/d N=225 (%)
Overall	16 (7.2)	5 (4.3)	32 (14.0)	42 (18.7)
Nausea	1 (0.4)	1 (0.9)	10 (4.4)	9 (4.0)
Dizziness	1 (0.4)	1 (0.9)	3 (1.3)	5 (2.2)
Somnolence	0	0	3 (1.3)	6 (2.7)
Fatigue	0	0	2 (0.9)	3 (1.3)
Hypersomnia	0	0	1 (0.4)	2 (0.9)
Insomnia	1 (0.4)	0	1 (0.4)	1 (0.4)
Confusional state	0	0	1 (0.4)	1 (0.4)
Headache	0	0	1 (0.4)	1 (0.4)
Lethargy	0	0	1 (0.4)	1 (0.4)
Tremor	0	0	1 (0.4)	1 (0.4)

Source: Modified from Applicant Tables ISS.6.1.13 and 2.5.5.6

The order of frequency of these adverse events closely parallels that for the longer-term exposures. Both tabulations are consistent with the overall commonly reported treatment-emergent adverse events incidence rates; the three most frequent of which are nausea, somnolence (+/- hypersomnia) and dizziness (Section 7.4.7).

Table 7.16: AEs Reported as Reason for Discontinuation
All DPN Trials (HMAW, HMAVa, HMBT-28 week lock)

Preferred term	N=1074 n (%)
Overall	219 (20.4)
Applicant Total	214 (19.9)
Nausea	34 (3.2)
Dizziness	18 (1.7)
Somnolence*	15 (1.4)
Fatigue	13 (1.2)
Vomiting	9 (0.8)
'LFT abnormality'	6 (0.6)
Diarrhea	5 (0.5)
Lethargy	5 (0.5)
Asthenia	4 (0.4)
Hypersomnia*	4 (0.4)
Acute MI	3 (0.3)
Confusional state	3 (0.3)
Constipation	3 (0.3)
Dry mouth	3 (0.3)
Erectile dysfunction	3 (0.3)
Hyperhidrosis	3 (0.3)
Hypertension	3 (0.3)
Insomnia	3 (0.3)
Tremor	3 (0.3)

Source: Modified from Applicant Table ISS.6.1.5

* Closely related terms; (somnolence and hypersomnia), (decreased appetite+ anorexia)

AEs leading to discontinuation in two patients (0.2%)
Atrial fibrillation, Balance disorder, Congestive heart failure, Cellulitis, Cerebral infarction, Colon cancer, Coronary artery disease, Depression, Dysgeusia, Dyspepsia, Dysuria, Headache, **Hepatic enzyme increased**, Libido decreased, Myocardial infarction, Nervousness, Orthostatic hypotension

AEs leading to discontinuation in one patient (0.1%)
Abdominal pain, Agitation, **ALT increased**, Ankle fracture, Anorexia, Aphthous stomatitis, Cardiac arrest, Cardiac failure, Carotid artery stenosis, Chest discomfort, Cholecystectomy, Contusion, Disorientation, Ejaculation failure, ECG QT prolonged, Femur fracture, Gait abnormal, Gastric disorder, GI disorder, Hepatitis, Hot flush, Jaundice, Loose stools, Lymphoma, Malaise, Migraine, Muscle twitching, Myocardial ischaemia, Nephrotic syndrome, Oesophageal stenosis acquired, Pain, Palpitations, Paraesthesia, Pollakiuria, Polymyalgia rheumatica, Pregnancy, Prostatic abscess, Rash Renal cell carcinoma stage unspecified, Rib fracture, Sepsis, Septic shock, Serotonin syndrome, Sinus disorder, Temporal arteritis, Urine flow decreased + Patient HMBT-1503 for 'Multiple adverse events'

The four readjudicated patients (with laboratory abnormalities, Section 7.4.4), combined with the two terms bolded above bring the total number of discontinuations due to 'LFT abnormalities' to six, or 0.6% of the 1074 patients. The overall percentage of discontinuations due to adverse events was 20.4% (219/1074).

7.4.5 Other Search Strategies

Lilly's categorization scheme for "reason for discontinuation" allowed for twenty-three unique choices. "Physician decision" was used in some cases where the accompanying summary notes indicated that the physician/investigator decided to discontinue the patient because of laboratory abnormalities or adverse events Likewise "personal conflict/patient decision" was also misused in several cases. In one instance, the accompanying text indicates that the patient decision was based on "multiple adverse events" including a hospitalization

For each study, the data were searched for patient dispositions in suspect categories. The findings are summarized below. For each patient identified the other data files from the study were examined, and summary notes, narratives and CRFs reviewed (All CRFs not already submitted, for all DPN patients categorized as discontinuations due to 'physician decision' were obtained from the Applicant).

Table 7.17: Patient Disposition Categories Audited

HMAVa Disposition	Total	Placebo n=108	DLX60QD n=114	DLX60BID n=112
Other Clin. Sig. Lab Values	1	0	0	1
Personal Conflict/ Pt. Decision	8	1	3	4
Physician Decision	4	2	1	1
Withdrawal of Informed Consent	10	4	4	2

Source: Clinical reviewer from HMAVa datasets PATINFO.XPT and SUMMARY.XPT

HMAW Disposition (Acute)	Total N=457	Placebo n=115	DLX20 n=115	DLX60QD n=114	DLX60BID n=113
Other Clin. Sig. Lab Values	1	0	0	1	0
Personal Conflict/ Pt. Decision	45	16	12	8	9
Physician Decision	7	1	1	3	2
Sponsor's Decision	6	1	1	3	1

Source: Clinical reviewer from HMAW datasets PATINFO.XPT and SUMMARY.XPT

HMBT Disposition	Total	DLX120QD n=115	DLX60BID n=335
Other Clin. Sig. Lab Values	2	0	2
Personal Conflict/ Pt. Decision	13	2	11
Physician Decision	9	2	7
Sponsor's Decision	1	0	1
Withdrawal of Informed Consent	5	2	3

Source: Clinical reviewer from HMBT datasets PATINFO.XPT and SUMMARY.XPT

Several patients (in addition to those listed in Section 7.4.4) had indeed been miscategorized, most notably HMBT-1503, categorized as a discontinuation due to 'Personal Conflict/ Patient Decision' after treatment with duloxetine 120-mg QD for 19 weeks (also discussed in Section 7.4.4). The patient's summary notes indicate that the 'patient decision' was because of 'multiple adverse events.' Patient HMBT-1503 had reported fifteen adverse events during their study participation, all non serious. These included increased tiredness, somnolence, lethargy, poor appetite, dry mouth, and dysuria. Basically patient HMBT-1503 reported many of the most

commonly reported adverse events, and then some. Exactly which adverse event, or combination prompted the decision is not clear.

The Applicant's reported incidence of 'discontinuation due to adverse events' has been revised upwards from 19.9% to 20.4%, but overall adverse event frequencies are essentially unchanged.

7.4.6 Safety Findings of Interest

7.4.6.1 Safety Findings of Interest: Hepatic

As noted in the approved labeling, duloxetine is associated with elevations in serum transaminases. Findings in the DPN population confirmed this association.

7.4.6.2 Safety Findings of Interest: Glucose Control

The incidence of diabetes-related adverse events, such as hyperglycemia and ketoacidosis, was of interest because of the patient population under study. In the placebo-treated patients, treatment-emergent adverse events (TEAEs) were more common [9 (4 %)] compared to the duloxetine-treated patients [8 (1.4%)]. The incidence of serious adverse events (SAEs) were comparable between the placebo-treated and duloxetine-treated patients [1 (0.4%) and 2 (0.4%), respectively].

The incidence of diabetes-related TEAEs in the routine-care patients was also higher than in the duloxetine-treated patients [8 (7%) and 7 (3.2%), respectively].There was one diabetes-related SAE reported in each treatment group.

The distribution of diabetes-related SAEs across both databases (placebo-controlled and routine-care) was as follows:

Placebo-controlled safety database		
	Placebo	Duloxetine
Ketoacidosis		1
Hyperglycemia	1	1
Routine-care controlled Safety Database		
	Routine-care	Duloxetine
Diabetic foot	1	
Diabetic ketoacidosis		1

Fasting Glucose Analysis

In the acute phases of Studies HMAW andHMAVa (placebo-controlled databases), the mean Baseline to Endpoint increase in fasting glucose for the placebo-treated patients was 6. 3 mg/dL; the mean increase in fasting glucose for the duloxetine-treated patients was 18 mg/dL. The patients treated with 20 mg/day of duloxetine are included in this group. The Baseline to Maximum change analysis identified a similar trend.

In the routine-care controlled database, the mean Baseline to Endpoint increase in fasting glucose for the duloxetine-treated patients was consistent with the other database, at 18.5 mg/dL. The routine-care controlled patients however, had a decrease in the mean Baseline to Endpoint

analysis of 10.1 mg/dL. The mean Baseline to Maximum changes did not change significantly for either group.

Hemoglobin A1c Analysis
In the acute phases of Studies HMAW and HMAVa (placebo-controlled databases), there were no significant differences in the mean change in hemoglobin A1c, from baseline to endpoint, between any dose of duloxetine and placebo.

In the routine-care controlled database (patients in the HMAW-extension, which compared 120 mg/day of duloxetine to "routine care"), the mean increase in hemoglobin A1c for duloxetine-treated patients was 0.51%, and 0.26% for the routine-care patients.

Analysis of potentially clinically meaningful glucose elevations
The percentage of patients with changes in fasting glucose levels > 100 mg/dL at anytime from baseline forward were not different between the duloxetin-treated, placebo-treated, and routine-care control patients.

In order to assess whether any patients may have experienced adverse events related to poor glucose control, the data listings for all patients who experienced any change from baseline that was greater than 100 mg/dL. In this group of patients, seven had at least one fasting glucose value > 500 mg/dL (Patient Nos. 0311, 1448, 3406, 3626, 4013, 4804, and 6214). All seven were in the HMAW-extension, and were receiving 120 mg/day of duloxetine. Each patient had demonstrated large fluctuations throughout the study. Most sustained elevations > 300 mg/dL from visit to visit, for a portion of the study. Only one patient (HMAW-1448) had a diabetes-related serious adverse event. According to the patient narrative and the case report form, the patient was often not compliant with the diabetic diet, and at times noncompliant with the medical treatment. This patient also had the highest recorded fasting glucose value (925 mg/dL) in the routine-care population database.

7.4.6.3 Electrophysiology/Nerve Conduction Measures

Nerve conduction studies were conducted in a subset of participants in Study HMAVa, in order to evaluate whether the pain relief provided by duloxetine was attributable to neurotoxicity. Electrophysiological assessments of the ulnar motor and sensory nerves, and peroneal motor nerve on the non-dominant side were performed at Visit 3, Visit 10 and Visit 20. Mean change analysis was performed for the following specific measures: Ulnar F-wave, Ulnar Distal Sensory Latency, Peroneal F-wave, and Peroneal CMAP. The analysis for Peroneal A-wave was not a mean change analysis, but rather a status change assessment, since the observation was a designation of either "present" or "absent."

There were no apparent changes in the mean change analyses for any of the measures assessed. There was a numerical increase in the status change of the Peroneal A-wave for the duloxetine-treated patients, which was of unknown clinical significance.

7.4.7 Common Adverse Events

Overall, of the 1074 DPN patients treated with duloxetine, 993 (92.5%) patients experienced TEAEs. Of the 791 enrolled patients in the 12-week placebo-controlled DPN trials, 87.7% of

duloxetine-treated patients (498) and 78.0% (174) of placebo-treated patients reported at least one treatment-emergent adverse event (TEAE).

Events reported with a frequency of ≥ 5.0% in duloxetine-treated patients ('overall exposures') were: nausea, somnolence, dizziness, insomnia, constipation, diarrhea, fatigue, dry mouth, hyperhidrosis, decreased appetite (7.4%), asthenia, anorexia (6.0%).

headache, constipation, dry mouth, fatigue, diarrhea, hyperhidrosis, insomnia, vomiting, asthenia, decreased appetite (7.4%), anorexia (6.0%), nasopharyngitis, cough, and arthralgia.

The most common events in the placebo-controlled trials were: nausea, somnolence, dizziness, insomnia, constipation, (decreased appetite + anorexia ≈ 10%), diarrhea, fatigue, dry mouth, hyperhidrosis, and asthenia. Dose-dependency was apparent for all of these, except for diarrhea.

The table below shows AEs reported by at least 2% of patients in the controlled studies (in any treatment arm). Most of the most commonly reported AEs seem to be dose related. Interestingly, while the incidence of 'constipation' increases as duloxetine dose does, for 'diarrhea' the inverse is seen; as duloxetine dose increases, the incidence of diarrhea decreases. Also, throughout the duloxetine clinical programs for both MDD and DPN, 'decreased appetite' and 'anorexia' were both reported relatively commonly. These AE terms were used exclusively of one another. Individual patients had one or the other, but not both. Review of the DPN CRFs shows that 'anorexia' seems to have been used to describe a more profound decrease in appetite (than 'decreased appetite'). Combining the two terms, as in Table 7.Z, shows that reduction in appetite occurs in over 16% of patients treated at the 60-mg BID dose. At each dose, the combined category would fall within the top six or seven most common adverse events, again in a dose related fashion.

TEAEs by Dose in Placebo-Controlled DPN Trials

		All	Placebo	Controlled	Studies
	PBO	DLX	DLX	DLX	DLX
		20QD	60QD	60BID	TOTAL
	N=223	N=115	N=228	N=225	N=568
Event [a]	%	%	%	%	%
Any Event					
Nausea	8.5	13.9	22.4	29.8	23.6
Somnolence*	4.5	7.0	14.5	20.9	15.5
Dizziness	6.3	6.1	13.6	16.9	13.4
Insomnia	6.7	8.7	8.3	12.9	10.2
Constipation	3.1	5.2	11.0	14.7	11.3
Diarrhea	5.8	13.0	11.4	6.7	9.9
Fatigue	4.9	1.7	10.1	12.0	9.2
Dry Mouth	3.6	5.2	7.0	11.6	8.5
Hyperhidrosis	1.8	6.1	6.1	8.4	7.0
Asthenia	1.3	1.7	3.9	8.0	5.1
(↓ Appetite+Anorexia)*	0.8	5.2	6.1	16.4	10.0
↓ Appetite	0.4	2.6	3.5	11.1	6.3
Anorexia	0.4	2.6	2.6	5.3	3.7
Pharyngeal pain	1.3	2.6	0.9	5.8	3.2
Myalgia	0.4	2.6	0.9	3.6	2.3
Erectile dysfunction	0.0	0.0	1.3	4.4	2.3
Tremor	0.0	0.0	0.9	4.9	2.3
Lethargy	0.0	0.0	2.2	2.2	1.8
Hypersomnia*	0.0	0.0	1.8	1.8	1.4
Urinary retention	0.0	0.0	2.2	1.3	1.4
Fall	0.0	1.7	1.8	0.0	1.1
Sleep disorder	0.0	0.0	1.8	0.9	1.1
Agitation	0.0	0.0	1.8	0.4	0.9

* Closely related terms; (somnolence and hypersomnia), (decreased appetite+ anorexia)
[a] TEAEs in placebo-controlled primary safety database for which DLX (any dose)>placebo
Source: Modified from Applicant Tables 2.5.5.7 and ISS.6.1.14

The AE terms 'decreased appetite' and 'anorexia,' both commonly reported as (non-serious) AEs, were coded exclusively of one another. Individual patients experienced one, or the other, but not both. Review of the DPN CRFs shows that 'anorexia' was used to describe a more profound decrease in appetite (than 'decreased appetite'). Combining the two terms for the commonly reported AE tabulations shows that reduction in appetite occurs in over 16% of patients treated at the 60-mg BID dose. The broader category would one of the six or seven most commonly reported events. Likewise, two other closely related events are reported separate from one another; 'somnolence' and 'hypersomnia.'

The following table reports the same treatment emergent AEs by SOC category.

Common TEAEs by System Organ Class, Controlled DPN Trials

Event [a]	Duloxetine n=568 (%)	Placebo n=223 (%)	Total n=791 (%)
Any Event	498 (87.7)	174 (78.0)	672 (85.0)
Gastrointestinal	282 (49.6)	52 (23.3)	334 (42.3)
Nervous System	241 (42.4)	45 (20.2)	286 (36.2)
General/Administration	136 (23.9)	35 (15.7)	171 (21.6)
Infections/Infestations	131 (23.1)	52 (23.3)	183 (23.1)
Psychiatric	101 (17.8)	24 (10.8)	125 (15.8)
Musculoskeletal/Conn. Tissue	98 (17.3)	43 (19.3)	141 (17.8)
Skin/Subcutaneous	82 (14.4)	30 (13.5)	112 (14.2)
Metabolism/Nutrition	79 (13.9)	20 (9.0)	99 (12.5)
Respiratory/Thoracic	62 (10.9)	21 (9.4)	83 (10.5)
Injury/Poisoning/Proc. Compl.	46 (8.1)	16 (7.2)	62 (7.8)
Renal/Urinary	50 (8.8)	8 (3.6)	58 (7.3)
Eye	43 (7.6)	13 (5.8)	56 (7.1)
Investigations	42 (7.4)	18 (8.1)	60 (7.6)
Reproductive/Breast	27 (4.8)	3 (1.3)	30 (3.8)
Surgical/Medical Procedures	24 (4.2)	8 (3.6)	32 (4.0)
Vascular	22 (3.9)	6 (2.7)	28 (3.5)
Cardiac	15 (2.6)	11 (4.9)	26 (3.3)
Ear/Labyrinth	12 (2.1)	4 (1.8)	16 (2.0)
Neoplasms	10 (1.8)	3 (1.3)	13 (1.6)
Immune System	3 (0.5)	4 (1.8)	7 (0.9)
Blood/Lymphatic	1 (0.2)	0	1 (0.1)

Source: Modified from Applicant Table 6.1.15

Common TEAEs During Long-Term Open-Label Study HMBT

Event [a]	60 BID n=334 %	120 QD n=115 %	Total N= %
Any Event			
Nausea	40.4	42.6	
Somnolence	33.5	36.5	
Dizziness	19.5	16.5	
Insomnia	11.1	7.8	
Constipation	12.3	8.7	
Diarrhea	9.6	11.3	
Fatigue	8.4	11.3	
Dry Mouth	14.7	13.9	
Hyperhidrosis	13.2	13.9	
↓ Appetite & Anorexia	18.6	18.2	Mutually exclusive
↓ Appetite	9.0	10.4	
Asthenia	10.8	6.1	
Anorexia	9.6	7.8	
Pharyngeal pain	1.8	2.6	
Myalgia	0.6	1.7	
Erectile dysfunct.	1.5	2.6	
Tremor	2.7	0.9	
Lethargy	3.6	2.6	
Hypersomnia	1.5	1.7	
Urinary retention	0.6	0.9	
Fall	0.9	1.7	
Sleep disorder	0.9	0.9	
Agitation	0.0	0.9	

[a] TEAEs in placebo-controlled primary safety database
Source: Applicant Table 2.5.5.9

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ON ORIGINAL

Common AEs in Long-Term' and Overall DPN Exposures

DPN Population →	Routine-Care-Controlled		'Long-Term'	ALL
	Duloxetine 120-mg/day N=222	Routine Care N=115	Duloxetine 120-mg/day N=671	Duloxetine All N=1074
Event [a]	%	%	%	%
Nausea	7.7	9.6	34.6	31.4
Somnolence*	6.8	13.0	29.8	23.9
Dizziness	9.0	11.3	18.9	16.9
Insomnia	3.2	4.3	11.8	10.2
Constipation	5.4	4.3	12.5	11.7
Diarrhea	5.0	5.2	11.0	10.5
Fatigue	9.0	9.6	11.3	11.0
Dry Mouth	5.4	5.2	14.5	11.6
Hyperhidrosis	0.0	0	0.0	10.4
(↓ Appetite+ Anorexia)*	2.3	0.0	16.4	13.4
↓ Appetite	1.4	0.0	8.9	7.4
Anorexia	0.9	0.0	7.5	6.0
Asthenia	3.6	0.9	8.5	7.5
Pharyngeal pain	0.0	0.0	2.4	2.9
Myalgia	0.5	1.7	1.6	1.7
Erectile dysfunct.	3.6	0.0	2.4	2.7
Tremor	2.7	0.0	3.0	2.8
Lethargy	0.0	0.9	2.5	2.3
Hypersomnia*	0.5	0.0	1.3	1.5
Urinary retention	0.0	0.0	0.7	1.0
Fall	5.4	2.6	2.8	2.1
Sleep disorder	0.9	0.0	1.3	1.2
Agitation	0.0	0.0	0.1	0.6

* Closely related terms; (somnolence and hypersomnia), (decreased appetite+ anorexia)

APPEARS THIS WAY
ON ORIGINAL

The table below demonstrates that incidence in the DPN population for many of the common TEAEs, was similar to that in the 'overall duloxetine exposures database' (15% of which actually was the DPN patients).

Common Adverse Events
PCPSDB, Overall Duloxetine Exposures Database

Preferred term	All DPN N=1074 (%)	Overall DLX N=8454 (%)
Overall		
Nausea	31.4	27.8
Somnolence	23.9	13.4
Dizziness	16.9	12.8
Insomnia	10.2	14.3
Constipation	11.7	12.1
Diarrhea	10.5	9.4
Fatigue	11.0	10.7
Dry mouth	11.6	15.1
Hyperhidrosis	10.4	7.5
Decreased appetite	7.4	4.8
Asthenia	7.5	3.5
Anorexia	6.0	4.2
Pharynx/larynx pain	2.9	2.0
Myalgia	1.7	1.6
Erectile dysfunction	2.7	1.3
Tremor	2.8	3.9
Lethargy	2.3	1.9
Hypersomnia	1.5	0.9
Urinary retention	1.0	0.0
Fall	2.1	0.7
Sleep disorder	1.2	1.5
Agitation	0.6	0.8

Source: Modified from Applicant Table ISS.6.4.5.

Treatment Emergent AEs, Long-Term DPN Trials

Event [a]	RCSDB DLX 60BID N=222 %	RCSDB Routine Care N=115 %	LTSDB DLX 120/Day N=671 %	Overall All Doses N=1074 %
Any Event				
Nausea	7.7	9.6	34.6	31.4
Somnolence	6.8	13.0	29.8	23.9
Dizziness	9.0	11.3	18.9	16.9
Insomnia	3.2	4.3	11.8	10.2
Constipation	5.4	4.3	12.5	11.7
Diarrhea	5.0	5.2	11.0	10.5
Fatigue	9.0	9.6	11.3	11.0
Dry Mouth	5.4	5.2	14.5	11.6
Hyperhidrosis	0.0	0.0	0.0	10.4
↓ Appetite	1.4	0.0	8.9	7.4
Asthenia	3.6	0.9	8.5	7.5
Anorexia	0.9	0.0	7.5	6.0
Pharyngeal pain	0.0	0.0	2.4	2.9
Myalgia	0.5	1.7	1.6	1.7
Erectile dysfunct.	3.6	0.0	2.4	2.7
Tremor	2.7	0.0	3.0	2.8
Lethargy	0.0	0.9	2.5	2.3
Hypersomnia	0.5	0.0	1.3	1.5
Urinary retention	0.0	0.0	0.7	1.0
Fall	5.4	2.6	2.8	2.1
Sleep disorder	0.9	0.0	1.3	1.2
Agitation	0.0	0.0	0.1	0.6

[a] TEAEs in placebo-controlled trials occurring in duloxetine-treated > placebo-treated
Source: Modified from Applicant Table 2.5.5.7

7.4.7.1 Eliciting adverse events data in the development program

The applicant's methods of eliciting adverse event data in clinical trials appear to have been adequate. Both checklists and open-ended questions were employed, at each study visit. Study visits occurred weekly for the 12-week efficacy trials. HMBT, and the open-label HMAW-Extension stipulated visits roughly every two weeks, initially, and then monthly.

7.4.7.2 Appropriateness of adverse event categorization and preferred terms

The Applicant coded adverse events using multiple versions of the MedDRA (3.0, 4.0, 5.0, 6.0, 6.1) dictionary (predominantly Version 6.1).

7.4.7.3 Incidence of common adverse events

Of the 791 enrolled patients in placebo-controlled DPN trials, 672 (85.0%) reported at least one TEAE. Overall, statistically significantly more duloxetine- treated patients experienced TEAEs compared with placebo- treated patients.

Lilly's "anticipated target dose" of duloxetine in the treatment of diabetic neuropathic pain (DNP) will be 60 mg/ day. Events reported by this group are presented in greater detail (severity, time course). Nine events were reported by at least 5% of patients (nausea, somnolence,

dizziness, insomnia, constipation, diarrhea, fatigue, dry mouth, and hyperhidrosis) in the 60 mg QD group.

7.4.7.4 Additional analyses and explorations

Analyses for time to event onset, and for adaptation were not possible, due to the structure and format of the datasets submitted.

7.4.8 Laboratory Findings

(Also see Section 7.4.7 Safety Findings of Interest)
There were small treatment group differences between placebo and duloxetine (all doses combined), for change from baseline to maximum value in ALT (+/- GGT) consistent with findings from the MDD patients. In the categorical analysis, the majority of patients (87.5% of duloxetine-treated patients and 88% of placebo-treated patients), ALT levels remained in the same category. The majority of patients (83.8% of duloxetine-treated patients and 85.7% of placebo- treated patients) experienced maximum ALT levels in the ≤1.5 times the upper limit of normal (ULN) range while on study drug.

The percentage of patients with shifts in ALKPH values was the same between groups. Almost all patients' (99.6% of duloxetine-treated patients and 99.5% of placebo-treated patients) ALKPH levels remained in the same category. Nearly all patients (99.5% of duloxetine-treated patients and 99.5% of placebo treated patients) experienced maximum ALKPH levels in the ≤ 2 times ULN range while on study drug. Likewise, for the majority of patients (99.8% of duloxetine-treated patients and 100% of placebo-treated patients), TBILI levels remained in the same category. Nearly all patients (99.8% of duloxetine-treated patients and 100% of placebo-treated patients) experienced maximum TBILI levels in the ≤ 1.5 times ULN range while on study drug.

7.4.9 Vital Signs

Duloxetine has been found to increase resting blood pressure, in previous DNDP safety reviews.

Duloxetine-treated patients experienced statistically significant mean decreases in weight compared with placebo-treated patients (mean change = -1.05 kg. versus 0.16 kg., respectively).

7.4.9.1 Overview of vital signs testing in the development program

Vital sign assessment during the duloxetine (DPN) development program was adequate.

7.4.9.2 Selection of studies and analyses for overall drug-control comparisons

7.4.9.3 Standard analyses and explorations of vital signs data

The table on the following page summarize the change from baseline to endpoint for vital signs and weight. Duloxetine-treated patients had significantly greater mean increases in sitting heart rate compared with placebo-treated patients (mean change =1.56 bpm versus -0.22 bpm, respectively). Placebo-treated patients experienced a statistically significantly mean decrease in sitting diastolic heart rate compared with duloxetine-treated patients (mean change = -1.72 mm Hg versus 0.30 mm Hg, respectively). These findings are consistent with inhibition of norepinephrine (NE) reuptake.

PCPSDB

Vital Signs and Weight, Change from Baseline to Endpoint

	n	Base line Mean	SD	Δ to Endpt. Mean	SD
Systolic BP					
Placebo	218	135.06	15.24	-2.49	15.45
DLX20QD	109	133.71	18.75	-1.24	17.03
DLX60QD	225	133.96	16.62	-1.88	15.04
DLX60BID	221	134.35	15.20	-1.97	16.11
All DLX	555	134.06	16.49	-1.79	15.85
Diastolic BP					
Placebo	218	77.67	8.78	-1.72	9.88
DLX20QD	109	76.47	9.67	0.41	8.30
DLX60QD	225	78.16	9.25	0.41	9.53
DLX60BID	221	77.22	9.05	0.14	8.86
All DLX	555	77.45	9.26	0.30	9.02
Pulse					
Placebo	218	75.78	9.53	-0.22	9.38
DLX20QD	109	74.79	9.66	1.06	10.58
DLX60QD	224	76.09	10.51	0.79	10.92
DLX60BID	221	76.63	9.59	2.58	10.97
All DLX	554	76.05	9.99	1.56	10.89
Weight					
Placebo	211	99.25	23.55	0.16	2.76
DLX20QD	102	99.37	18.39	-0.41	2.90
DLX60QD	218	100.08	22.77	-1.16	3.23
DLX60BID	217	97.91	22.86	-1.25	2.89
All DLX	537	97.93	22.14	-1.05	3.05

Source: Applicant Table ISS.6.1.18

7.4.9.3.1 Analyses focused on outliers or shifts from normal to abnormal

In the placebo-controlled primary database, three patients experienced SAEs involving hypertension (out of a total of 29 patients in the primary placebo controlled database that experienced an SAE). Two (0.9%) of the patients were from the placebo group and 1(0.2%) patient was from the duloxetine group.

In the routine care-controlled safety database, one patient (routine-care) experienced an SAE involving hypertension (out of a total of 54 that experienced an SAE).

Categorical (shift) analysis

Criteria used to define a 'treatment-emergent elevation' of blood pressure were as follows:

- systolic blood pressure elevation of = 140 mmHg with an increase = 10 mm Hg
- diastolic blood pressure elevation of = 90 mmHg with an increase = 10 mm Hg

Criteria for a 'sustained elevation' of blood pressure entail either of the following:

- treatment-emergent elevations of BP from baseline at two consecutive follow-up visits

- treatment-emergent elevations of BP from baseline at three consecutive follow-up visits

Three consecutive elevations of blood pressure are thought to represent a relatively specific but less sensitive definition of sustained elevation of blood pressure. In contrast, two consecutive elevations are felt to represent a less specific but more sensitive definition of the same.

A 'potentially clinically significant' blood pressure elevation will be defined as follows:
- sitting systolic blood pressure of = 180 mm Hg with an increase of = 20 mm Hg
sitting diastolic blood pressure of = 105 mm Hg with an increase of = 15 mm Hg

Mean SBP and DBP Change, Baseline to Endpoint

Population		Placebo	Duloxetine
PCPSDB	SBP	(-) 2.5	(-) 1.8
DLX 568	DBP	(-) 1.7	(+) 0.30
PBO 223	Sustained SBP ↑ at 2 visits	6.9%	7.4%
	Sustained DBP ↑ at 2 visits	0.5	2.2
	Sustained SBP ↑ at 3 visits	2.3	2.7
	Sustained DBP ↑ at 3 visits	0.0	0.7
RCCSDB	SBP	1.13	0.48
DLX 222	DBP	0.44	0.61
Routine 115	Sustained SBP ↑ at 2 visits	0.9	1.8
	Sustained DBP ↑ at 2 visits	0.0	0.5
	Sustained SBP ↑ at 3 visits	0.0	0.5
	Sustained DBP ↑ at 3 visits	0.0	0.0

Source: Modified from Applicant Tables ISS.9.2.1 to ISS.9.2.6

7.4.9.3.2 Marked outliers and dropouts for vital sign abnormalities

No patients in the placebo-controlled database discontinued due to hypertension.

There were no apparent differences in incidence of discontinuation as a result of treatment-emergent hypertension between the routine care and duloxetine cohorts in the long-term safety database. Hypertension was reported as a reason for discontinuation in 0.9% of both groups.

7.4.10 Electrocardiograms (ECGs)

The ECG testing in the duloxetine DPN program appears to have been adequate in light of preclinical findings and previous human findings. There was a relatively low suspicion for cardiac conduction effects at the proposed doses. The table below summarizes change from baseline to endpoint in ECG parameters.

7.4.10.1 Standard analyses and explorations of ECG data

7.4.10.1.1 Analyses focused on measures of central tendency

There were no differences between duloxetine-treated, and either placebo-treated, or 'routine care' treated patients, in the changes (from baseline to endpoint, and from baseline to maximum), of QTc(F) interval or QRS length.

7.4.10.1.2 Analyses focused on outliers or shifts from normal to abnormal

One duloxetine-treated patient (HMAVa-017-1704) had electrocardiogram QTcB prolongation (512 msec) reported as an adverse event. This patient had several confounding factors, specifically hypertension and according to the CRF "the possibility of left ventricular hypertrophy and ischemic disease." The patient had a prolonged QTcB at baseline (471 msec) and also demonstrated considerable off-drug variability (71 msec) during the trial. The patient was using diuretics (furosemide), possibly predisposing them to hypokalemia or hypomagnesemia.

One placebo and one duloxetine patient each had an increase in QTcF >60 msec from baseline. The duloxetine patient was a 60-year-old male whose 374 msec baseline QTcF increased to a maximum value of 438 msec. Both patients also had several confounding factors (history of CAD and LVH). Both were also taking diuretics, which may have predisposed them to electrolye imbalances.

The shift table below shows that proportion of patients with QTc increases to 30-60 msec above their baseline (either to study endpoint, or at any point during the study), did not differ between duloxetine-treated (all doses) and placebo-treated patients, in the placebo-controlled trials.

QTc Friederich Shift Table

Therapy	N (%)	Increase in QTc < 30 msec	Increase in QTc ≥ 30 to 60 msec	Increase in QTc ≥ 60	QTc ≥ 500 msec
		At Any Time	At Any Time	At Any Time	At Any Time
Placebo	207	194 (93.7)	12 (5.8)	1 (0.5)	0
Duloxetine	528	501 (94.9)	26 (4.9)	1 (0.5)	1 (0.2)
		At Endpoint	At Endpoint	At Endpoint	
Placebo	207	199 (96.1)	7 (3.4)	1 (0.5)	
Duloxetine	528	511 (96.8)	17 (3.2)	0	

7.4.11 Special Safety Studies

EMG testing is discussed above in Section 7.4.6.

Michigan Neuropathy Screening Instrument (MNSI) scores were obtained (for patients in the HMAW-Extension), at the beginning of the study (extension), and at the end, or at the last visit. The Table below shows that on average, scores were unchanged for both the duloxetine treated, and the 'routine care' treated (no duloxetine) patients.

Routine Care-Controlled DPN Patients, MNSI, Baseline → Endpoint

Treatment	n	Base line Mean	SD	End Point Mean	SD	Change Mean	Change SD
Routine	106	5.38	1.48	5.38	1.84	0.00	1.32
DULOX120/day	203	5.09	1.54	5.04	1.71	-0.05	1.37

Source: ISS.6.2.26

Retinopathy progression did not differ between duloxetine treated and routine care treated patients.

Routine Care-Controlled DPN Patients, Percent with Changes in Retinopathy

Variable	Routine		Duloxetine	
	N	n (%)	N	n (%)
Right Eye	46	3 (6.5%)	99	11 (11%)
Left Eye	46	4 (8.7%)	100	10 (10%)

Source: ISS.6.2.25

There were no suicides, or suicide attempts reported in the DPN trial patients. I reviewed all adverse events for events possibly suggestive of a suicide attempt (i.e., self-inflicted injuries), but found none.

7.4.12 Withdrawal Phenomena and/or Abuse Potential

Abuse Potential

CSS previously concluded (and recently restated) that duloxetine has no abuse potential.

The recently approved Cymbalta® label wording is:

Discontinuing Cymbalta (duloxetine hydrochloride)

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

7.4.13 Human Reproduction and Pregnancy Data

Women who were pregnant or breast-feeding were excluded from participating in all duloxetine clinical studies, as were women of childbearing potential not using a medically accepted means of contraception. Nonetheless, 30 pregnancies had been reported in clinical trial subjects, in women exposed to duloxetine at various doses, as of 10/01/03. All exposures were in the first trimester. Two pregnancies were ongoing, 4 women were lost to follow-up, 3 women elected to have therapeutic abortions, 1 woman experienced a spontaneous abortion (with other information available), 1 woman experienced a spontaneous abortion in the first trimester after a rock-climbing accident, and 2 women had ectopic pregnancies. Fourteen women delivered apparently normal babies at term. Three women delivered after premature rupture of membranes and/or preterm labor, with none of the three infants surviving. Of the reported outcomes, no reports of malformation were observed in any of these cases. It would be difficult to conclusions about the

effects of duloxetine exposure during pregnancy based upon so few exposures. The frequency of spontaneous abortion in the general population is at least 15% according to one review article (Kiely 1991). In all likelihood duloxetine played no role in the reported events. The MDD label classifies duloxetine as Pregnancy category C.

Known Pregnancy Exposures-All First Trimester

Pregnancy Outcome	N
Ectopic pregnancy	2
Spontaneous abortion	2
Therapeutic abortion (Elective TOP)	3
Lost to follow-up	4
Ongoing pregnancy	2
Preterm delivery with fetal demise	3
Normal term infant	14
Total	30

Modified from Applicant Table ISS.12.1.1

7.4.14 Assessment of Effect on Growth

Lilly has made Pediatric Written Requests for deferral of pediatric studies, for —
— DPN, MDD, — None of the duloxetine studies conducted to date enrolled pediatric subjects, and no height and weight data are provided.

7.4.15 Overdose Experience

In pre-marketing clinical trials, as of July, 2004, no cases of fatal acute overdose of duloxetine have been reported. Four non-fatal acute ingestions of duloxetine (300 to 1400 mg), alone or in combination with other drugs, have been reported. No overdoses were reported in the DPN studies. No change in the approved overdose section of labeling is warranted.

7.4.16 Postmarketing Experience

Lilly had not provided any post-marketing data, as of July 31, 2004. Duloxetine's first approval was in Mexico, in April of 2004. US approval for the MDD indication was granted 7/23/04.

7.5 Adequacy of Patient Exposure and Safety Assessments

7.5.1 Description of Primary Clinical Data Sources Demographics

The overall exposures database includes data from all 8454 patients assigned to receive duloxetine during a Lilly study (all indications), as of October 1, 2003. Of these, 8447 patients received at least one dose of duloxetine; 77.7% were women and 80.5% were white. Patients ranged in age from 18 to 89 years of age, with a mean of 49.3 years. Overall, there were 1094 (12.9%) patients who were at least 65 years old. One-thousand and seventy-four (1074, or 12.7%) of the patients in the overall safety database had enrolled in DPN trials.

Primary safety database

The 1074 patients that received duloxetine in DPN trial ranged in age from 20 to 89 (mean 60.1). By my tabulation, 42.3% were women, and 357 (33.2%) were ≥ 65 years of age. The majority of patients were classified as being of Caucasian origin (69.3%); 10.9% were Hispanic, 8.3%

'Oriental', 6.6% East Asian, 3.7% 'African' including African-Americans, 0.9% 'Western Asian' and 0.2% Aboriginal. There were no significant treatment group differences between the duloxetine-treated patients and either placebo-treated or routine care-treated patients, in breakdown by age, ethnic origin, or gender. Patients' ages ranged from 20.8 to 88.8 years with a mean age of 60.0 years. The majority of patients were Caucasian (77% in placebo-controlled trials, 65% in long-term trials) and male (61% in placebo-controlled trials, 55% in long-term trials).

'Origin' of Patients Exposed to DLX in Controlled DPN Trials

	Controlled DPN Trials		
Ethnicity	**Placebo** (N=223)	**Duloxetine** (N=568)	**Total*** (N=791)
African Descent	16 (7.2)	32 (5.6)	48 (6.1)
Western Asian	0	8 (1.4)	8 (1.0)
Caucasian	175 (78.5)	439 (77.3)	614 (77.6)
East/Southeast Asian	2 (0.9)	6 (1.1)	8 (1.0)
Hispanic	29 (13.0)	76 (13.4)	105 (13.3)
Other	1 (0.4)	7 (1.2)	8 (1.0)
Chi-square (p=0.437)			

Source: Applicant Table ISS.6.1.1 and ISS dataset DIABDEMO.XPT
* Includes only controlled DPN trials

Demographics, Patients Exposed to DLX in Controlled DPN Trials

Characteristic	**Placebo** (N=223)	**Duloxetine** (N=568)	**Total** (N=791)
Mean Age	60.61	60.27	60.37
Median Age	61.61	60.55	61.04
Age Range	23.9-80.6	22.4-88.8	22.4-88.8
Chi-square (p=0.728)			
Female	95 (42.6)	211 (37.1)	306 (38.7)
Male	128 (57.4)	357 (62.9)	485 (61.3)
Chi-square (p=0.157)			

Source: Applicant Table ISS.6.1.1 and ISS dataset DIABDEMO.XPT
* Includes only controlled DPN trials

Primary safety database (all DPN duloxetine exposures)

'Ethnic Origin' of Patients Exposed to Duloxetine in DPN Trials

Ethnicity	RCCSDB Routine Care (N=115)	RCCSDB DLX60BID (N=222)	RCCSDB Total (N=337)	LTSDB DLX120/day (N=671)
Aboriginal	---	---	---	2 (0.3)
African Descent	12 (10.4)	16 (7.2)	28 (8.3)	19 (2.8
Western Asian	0	4 (1.8)	4 (1.2)	6 (0.9)
Caucasian	86 (74.8)	174 (78.4)	260 (77.2)	435 (64.8)
East/Southeast Asian	2 (1.7)	3 (1.4)	5 (1.5)	67 (10.0)
Hispanic	13 (11.3)	24 (10.8)	37 (11.0)	59 (8.8)
Other	2 (1.7)	1 (0.5)	3 (0.9)	83 (12.4)
Chi-square			(p=0.461)	

Source: Applicant Table ISS.6.3.1 and ISS datasets SUMMARY.XPT and PATINFO.XPT

Demographics of Patients Exposed to Duloxetine in DPN Trials

Characteristic	RCCSDB Routine Care (N=115)	RCCSDB DLX60BID (N=222)	RCCSDB Total (N=337)	LTSDB DLX120/day (N=671)
Mean Age	58.90	60.22	59.77	60.00
Median Age	59.43	61.21	60.57	60.62
Age Range	22.42 – 84.37	23.92 – 88.82	22.42 – 88.82	20.83 – 88.82
Chi-square (p=0.315)				
Female	46 (40.0)	86 (38.7)	132 (39.2)	301 (44.9)
Male	69 (60.0)	136 (61.3)	205 (60.8)	370 (55.1)
Chi-square (p=0.906)				

Source: Applicant Table ISS.6.3.1 and ISS dataset DIABDEMO.XPT and SUMMARY.XPT

Secondary safety database (all placebo-controlled studies for indications other than DPN)
Patients' ages ranged from 18 to 89 years with a mean age of 47.8 years. The majority of patients were Caucasian (90.1%) and female (83.1%).

All DPN exposures safety database
Patients in the overall safety database were 81% Caucasian, and only 22% male. Overall they were younger than the DPN patients.

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'Origin' of Patients Exposed to Duloxetine in Lilly Trials

Ethnicity	Duloxetine (N=8454)
Aboriginal	2 (0.0)
African Descent	300 (3.5)
Western Asian	39 (0.5)
Caucasian	6806 (80.5)
East/Southeast Asian	117 (1.4)
Hispanic	915 (10.8)
Other	275 (3.3)

Source: Applicant Table ISS.8.1.1 and ISS datasets SUMMARY.XPT and PATINFO.XPT
* Includes all duloxetine exposures during Lilly clinical trials

Demographics,
Patients Exposed to Duloxetine in Lilly Trials

Ethnicity	Duloxetine (N=8454)
Mean Age	49.27
Median Age	49.14
Age Range	17.78 – 88.22
Female	6570 (77.7)
Male	1884 (22.3)

Source: Applicant Table ISS.8.1.1 and ISS datasets SUMMARY.XPT and PATINFO.XPT
* Includes all duloxetine exposures during Lilly clinical trials

DM/DPN Characteristics, Controlled DPN Trials

PCPSDB	Placebo (N=223)	Duloxetine (N=568)	Total (N=791)
DPN Duration (years)			
Mean	3.79	3.77	3.78
Median	2.66	2.41	2.48
Range	0.02-19.89	(-0.31)*-37.10	(-0.31)*-37.10
Chi-square (p=0.983)			
DM Duration (years)			
Mean	11.27	10.64	10.82
Median	7.79	7.79	7.79
Range	0.49*-66.49	0.08-52.37	0.08*-66.49
Chi-square (p=0.343)			
Type I DM	22 (9.9)	61 (10.7)	83 (10.5)
Type II DM	201 (90.1)	507 (89.3)	708 (89.5)
Chi-square (p=0.718)			

Source: Applicant Table ISS.6.1.1 and ISS dataset DIABDEMO.XPT
* Protocol violations discussed in Section 6.1

7.5.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.5.2.1 Postmarketing experience

The Applicant reports active marketing applications in — Although approved in Mexico, this past March, and in the USA last month, there have been no postmarketing reports.

7.5.3 Adequacy of Overall Clinical Experience

The overall exposure in the DPN population has been adequate, meeting ICH criteria, including at the 60 mg BID dose. There may be some limitations on generalizability, however given the fact that in clinical practice, many patients may be treated with combinations of drugs for their DPN pain, including opioids, anticonvulsants, and possibly even other antidepressant type medications (tricyclics).

7.5.4 Adequacy of Routine Clinical Testing

As noted previously, there were a handful of cases in which the recognition and reporting of abnormal laboratory results, by the Applicant was inadequate (transaminase abnormalities). Applicant efforts to monitor laboratory parameters, vital signs and ECGs, and efforts to elicit reports of abnormalities appear to have been adequate in both scope and frequency, on the whole, however.

7.5.5 Adequacy of Metabolic, Clearance, and Interaction Workup

Overall, the metabolic, clearance and interaction evaluation was adequate.

7.5.6 Adequacy of Evaluation for Potential Adverse Events

Recent DNDP and DRUDP safety reviews (of NDAs 21-427 - identified hepatotoxicity as the major "potentially problematic" duloxetine toxicity, based upon earlier

clinical trials (in which several thousand subjects had received the drug). Lilly's efforts to detect hepatic adverse events (and transaminase elevations), appear to have been adequate, on the whole. A handful of study discontinuations, apparently due to transaminase elevations, were misclassified, and tabulated, as due to "physician decision." None of these cases were classified as SAEs, or were reported as being symptomatic (as far as the CRFs indicate).

Assessment of possible cardiac conduction effects was adequate.

Evaluation for possible effects on the patients' underlying diabetes, and its potential complications also appears to have been adequate, as was assessment for progression of the underlying neuropathic process itself.

7.5.7 Additional Submissions, Including 120-Day Safety Update

NDA 21-733 (including the revised/corrected datasets submitted in May 2004) contained all primary data used in the preparation of this review, although DNDP safety reviews and memos have been quoted (liberally) throughout.

The 120-Day Safety Update included data from five studies completed between the cut-off date for the NDA submission (October 1, 2003), and the cut-off date for the 120-Day Update (February 2, 2004). (Expedited reporting has been in effect, and continues, for all SAEs and deaths, however; none have occurred subsequent to receipt of the Update).

The only additional DPN data comes from what Lilly calls a 24-week "extension phase" to the 28-week open-label safety study HMBT (see Section 7.2.2). Patients that "completed" HMBT (the first 28 weeks) were eligible to enter the 24-week "extension" during which they would continue their duloxetine regimen. All 449 subjects that enrolled in (the first part of) HMBT received duloxetine 120-mg per day; half were dosed 60-mg BID, and the other half 120-mg QD. Of the 334 patients randomized to 60 mg BID, 213 "completed" the study, and of the 115 patients randomized to 120 mg QD, 72 "completed" the study.

Sixty-six of the 60-mg BID, first phase completers enrolled in the extension, 57 of whom completed 24 more weeks. Twenty-one of the 120-mg QD first phase completers enrolled in the extension, and eighteen of these completed 24 more weeks of duloxetine.

HMBT and HMBT 'Extension' Enrollment and Disposition

	Duloxetine 60-mg BID	Duloxetine 120-mg QD
Enrolled in first part	334	115
Completed first part (28-weeks)	213	72
Continued to extension	66	21
Completed extension (24-weeks)	57	18

Two of these studies (SBAZ, SBCH) were clinical pharmacology studies, enrolling a total of less than one hundred subjects. No adverse events were reported. Study SBBL, for the SUI indication, was a double-blind, placebo-controlled, randomized study. In SBBL 306 women received one of three treatments (duloxetine 40 mg BID, duloxetine 60 mg BID, or placebo). In study SBCG 32 healthy volunteer females received duloxetine 40-mg BID, duloxetine 100-mg BID, or placebo, for 7 days, to assess safety and tolerability.

7.6 General Methodology

7.6.1 Pooling Data Across Studies to Estimate and Compare Incidence

For the different safety analyses, within the DPN population, data were pooled across studies into several databases:

- The two placebo-controlled trials were combine to create the 'placebo-controlled (primary) safety database.'
- Data from HMAW-Extension and HMBT-28 week lock, were pooled to create the 'long-term safety database.'
- Data from HMAW-Acute and HMAW-Extension, HMAVa, and HMBT-28 week lock, were pooled to form the 'overall DPN exposures' database.
- Data from the 120-Day Safety Update (HMBT-Extension, 24 weeks) were included for all tabulations of SAEs and deaths, as well as for all exposure and dose-by-duration tabulations.

All data, from all Lilly duloxetine trials (DPN, MDD, SUI, fibromyalgia, and clinical pharmacology studies) were pooled for the 'overall duloxetine exposures database' [redacted] clinical trials were not included).

Section 7.2 contains more complete descriptions of these databases.

7.6.2 Explorations for Predictive Factors

7.6.2.1 Explorations for dose dependency for adverse findings

Data from both placebo-controlled and noncontrolled show a clear dose-related increase in the most common duloxetine related adverse events (i.e., nausea, dizziness, somnolence).

7.6.2.2 Explorations for drug-demographic interactions

There were no apparent differences in duloxetine safety, between male and female patients. Older patients (≥65) experienced a greater incidence of SAEs than those younger. Overall, the number, and proportion of patients in the individual 'Non-Caucasian' categories were not sufficient to permit extensive comparison with the 'Caucasian' group. The number of African-Americans, and of patients classified as 'Hispanic' were not representative of the US population as a whole.

7.6.2.3 Explorations for drug-disease interactions

The incidence of observed adverse events does not appear to be related to baseline severity of underlying disease (either the neuropathy or diabetes mellitus).

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Efficacy at daily doses of 60-mg and 120-mg (for up to 12-weeks) was demonstrated in two placebo-controlled trials. For 'sustained responders' treatment response was usually evident within one to two weeks of duloxetine initiation (both 60-mg QD and 60-mg BID). Most 'sustained responders' (by treatment week 12), had achieved 'clinical response' by the end of the second or third treatment week. Efficacy, as assessed by magnitude of response, or response rate, did not appear to diminish once response was achieved.

The 120-mg dose was not demonstrably better than the 60-mg dose, by any of a number of measures (change in pain scores from baseline to study endpoint, response rate, sustained response rate, time to response). The 120-mg daily dose was, however, associated with increased rates of the most common drug-related adverse events (nausea, dizziness, somnolence, insomnia). There was no apparent increase in SAEs at the higher dose.

The 20-mg daily dose was not statistically significantly superior to placebo. Daily doses between above 20-mg but less than 60-mg were not studied. Duloxetine can be taken with or without food. The 120-mg daily dose can be taken as 120-mg QD or 60-mg BID.
Lilly provided abbreviated reports for three (non-DPN) duloxetine studies in which patients received up to 120-mg per day.

8.2 Special Populations

The studies conducted to assess use in special populations were adequate, with the possible exception of evaluation in hepatic and renal insufficiency. Renal insufficiency (across the continuum of severity) is actually quite common in older DPN patients

- Special dosing considerations based on coexisting states (e.g., **hepatic**, renal insufficiency)
- The racial breakdown, while not ideal, is acceptable.
- Pregnant and lactating women were excluded from all duloxetine trials.

8.3 Pediatrics

The Division has agreed that no pediatric studies are necessary for the duloxetine DPN indication. DPN does not occur in the pediatric population to any significant extent. All duloxetine marketing applications have been in compliance with the Pediatric Research Equity Act (PREA).

8.4 Advisory Committee Meeting

No advisory committee meetings were held pertaining to this application.

8.5 Literature Review

Lilly submitted thirty-one articles pertaining to diabetic peripheral neuropathy. They included:

- Preclinical findings in, and experimental models for studying neuropathic pain
- Reviews on the pharmacologic treatment of DPN using available products (mostly off-label)
- Clinical trial reports of studies using anticonvulsants, SSRIs, and/or tricyclic antidepressants
- Two articles reported on trials in which DPN patients received venlafaxine, the only FDA approved SNRI. Venlafaxine is approved for the treatment of depression, though.
- Measurement of pain, and of relief from pain
- One report on a trial evaluating an investigational (unapproved) drug
- Mechanisms of diabetic complications

None of the articles discussed, or reported on duloxetine administration, however, or provided any sort of safety data.

8.6 Postmarketing Risk Management Plan

Lilly has not submitted a postmarketing risk management plan.

8.7 Other Relevant Materials

All relevant materials are addressed elsewhere in this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

9.2 Recommendation on Regulatory Action

I recommend an approval action for NDA 21-733, duloxetine for the [redacted] associated with diabetic peripheral neuropathy.

9.3 Recommendation on Postmarketing Actions

Labeling
Placement of a Precautions statement describing the transaminase abnormalities and cases of severe liver injury associated with the combination of duloxetine use and ethanol abuse

Request that the sponsor provide close monitoring of the postmarketing experience of duloxetine with regard to liver AEs, including expedited reporting of all liver-related AEs during the postmarketing period.

(?) Quarterly summaries on all liver related AEs along with an estimate of drug usage for that quarter and an explanation of the method used to estimate drug usage. DNDP, along with the Office of Drug Safety, will review the submitted data

Hepatic Insufficiency: Observation and periodic monitoring of serum ALT, AST, ALP, GGT, and TBL for patients with pre-existing liver disease (chronic hepatitis B or C, alcoholic or non-alcoholic fatty liver disease with or without steatohepatitis, primary biliary cirrhosis or sclerosing cholangitis, α1-antitrypsin deficiency, hemochromatosis, Wilson's disease or other problems).

"Renal Insufficiency: Additional clinical studies?

9.3.1 Risk Management Activity

No specific postmarketing risk management activities, or restricted distribution schemes are indicated at this time. Duloxetine is expected to have minimal potential for abuse.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

9.4 Labeling Review

The Applicant's label proposes a [redacted] dose of 60 mg/day [redacted]

Treatment-Emergent Adverse Events Incidence in DPN Placebo-Controlled Trials[1]

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

Treatment-Emergent Adverse Events Incidence in DPN Placebo-Controlled Trials[1]

System Organ Class / Adverse Event	Percentage of Patients Reporting Event			
	Duloxetine 60 mg BID (N=225)	Duloxetine 60 mg QD (N=228)	Duloxetine 20 mg QD (N=115)	Placebo (N=223)
Cough	5	3	6	4
Pharyngolaryngeal pain	6	1	3	1
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis	8	6	6	2

[1] Events reported by at least 2% of patients treated with duloxetine and more often ~~with~~ than placebo. The following events were reported by at least 2% of patients treated with duloxetine for DPNand had an incidence equal to or less than placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.

[2]Male patients only

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