CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-733

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-733	Submission Date: 3/03/04 Review Date: 7/21/04
Submission Type; Code:	1 P; 505(b)(1)
Brand/Code Name:	Cymbalta
Generic Name:	Duloxetine HCl
Primary Reviewer:	David Lee, Ph.D.
Secondary Reviewer	Suresh Doddapaneni, Ph.D.
OCPB Division:	DPE 2
ORM Division:	Division of Anesthetic, Critical Care and Addiction Drug Products
Sponsor:	Eli Lilly and Company
Relevant IND(s):	I 37,071; I 38,838; — , I 62,536; —
Cross References	NDA 21-427 (for major depressive disorders (MDD)) NDA — (for stress urinary incontinence (SUI))
Formulation; Strength(s):	20, 30, — 60 mg capsule
Proposed Indication:	—
Proposed Dosage Regimen:	Cymbalta should be administered at a total dose of 60 mg/day given once a day, without regard to meals.

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1 Executive Summary

1.1 Recommendation

From Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) point of view, the information contained in the NDA is acceptable provided that:

a) A mutually satisfactory agreement can be reached between the Agency and Applicant regarding the text in the package insert; this agreement may include the

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b) Drug-drug interaction (duloxetine interaction with 1A2 and 2D6 inhibitors) and QT prolongation related deficiencies — — are adequately addressed. However, if deemed appropriate by the Reviewing Medical Division, —

1.2 Comments to the Medical Officer

Based on exposure–response (safety/efficacy) relationship information, modeling and simulations incorporating relevant patient demographic variables, the following dose adjustment proposal is provided (See Appendix 4.5 for further information). The existing data and modeling/simulation indicated that sub-population with the highest duloxetine exposure will be female elderly non-smokers.

1.

2. For hepatic impaired patients:

Duloxetine exposure (mean AUC) is approximately 5-fold higher in moderately impaired hepatic patients who took 20 mg capsule (exposure equivalent to approximately 150 mg daily dose). Therefore, the following recommendation is proposed in hepatic impaired patients :

3. For renal impaired patients:

Since duloxetine exposure is approximately doubled in end stage renal disease (ESRD) patients who took a 60 mg capsule (two major metabolites' exposures were 7-9-fold higher),

4. Concomitant Drugs:

Duloxetine exposure (mean AUC) is approximately 5.6-fold higher in patients who were taking fluvoxamine (100 mg/day multi-dosing) and duloxetine. Duloxetine exposure (mean AUC) is approximately 1.6-fold higher in patients who were taking paroxetine (a single 20 mg dose) and duloxetine.

1A2 inhibitors – Given the increase in duloxetine exposure in patients who are on concomitant drugs, which will inhibit CYP1A2 metabolism (e.g. fluvoxamine).

2D6 inhibitors – Given the possibility of increase in exposure in patients who are on concomitant drugs which will inhibit CYP2D6 metabolism (e.g. paroxetine),

These recommendations will greatly expand the utility of this important drug for treating neuropathic pain patients, including renally and/or hepatically impaired patients as well as certain drug interaction situations. These patient sub-populations are currently excluded in the label.

1.3 Phase IV Commitments

See above RECOMMENDATION section.

1.4 Background Information and Summary of CPB Findings

1.4.1 Background Information

Eli Lilly and Company has previously submitted to the Agency two NDAs to support the safety and efficacy of duloxetine for the treatments of major depressive disorders (MDD) and stress urinary incontinence (SUI). These NDAs were submitted, respectively, to the Division of Neuropharmacology Drug Products (NDA 21-427). To date, these NDAs include the original submissions, the 120-day updates, and any amendments and responses to specific regulatory questions from those divisions.

NDA 21-427 was approved on August 3, 2004

On 30 July 2003, the Applicant met with the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) to discuss the format of the NDA for duloxetine for the At that meeting, the Applicant and the Agency agreed that the Biopharmaceutics package would include all studies and relevant information available since the original submission, NDA 21-427.

The current CPB Review will address the newly submitted information in the NDA 21-733. Clinical and Biopharmaceutical information on duloxetine capsules can be found in the following reviews :

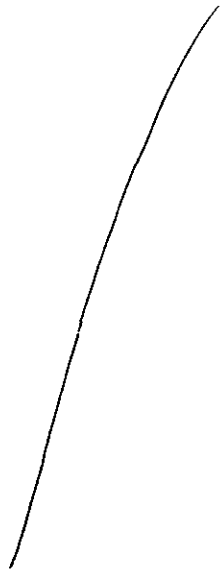
a) **New Drug Application Clinical Pharmacology and Biopharmaceutics Review, document signed date: 8/23/02; Reviewer: Dr. Ron Kavanagh. This review is for NDA 21-427;**

b) **New Drug Application – Response to Approvable Letter, Clinical Pharmacology and Biopharmaceutics Review. Submission date: 3/24/03; document signed date: 6/11/03; Reviewer: Dr. Ron Kavanagh. This review is for NDA 21-427;**

c) **New Drug Application - Amendment Clinical Pharmacology and Biopharmaceutics Review. Submission date: 12/22/03; document signed date: 5/10/04; Reviewer: Dr. Ron Kavanagh. This review is for NDA 21-427;**

1.4.2 CPB Findings in the Current NDA 21-733

The current submission includes information from the 120-day update to NDA 21-427,



Agency Request:

2. Clearly identify the new Clinical Pharmacology and Biopharmaceutics information submitted in NDA 21-733

Applicant's Response:

" The following lists documents in the NDA 21-733 (DNP) Table of Contents

CATEGORY: Metabolism Studies Using Hepatocytes, Microsomes, Etc.

1. ADME Report 91: Summary of In Vitro Metabolism of 14C-Duloxetine (LY248686) by Human, Rat, and Dog Microsomes and Liver Slices
2. ADME Report 105: In Vitro Interaction of Duloxetine with Human Cytochrome P450 CYP2C19

CATEGORY: Reports of Human PK Studies--Healthy Subject PK and Initial Tolerability Studies

1. F1J-LC-SBCH Synopsis: Safety and Tolerance of Duloxetine in Healthy Females at Supratherapeutic Doses Achieved by a Progressive 1- to 3-Day Titration
2. F1J-BD-SBCG Synopsis: Tolerability and Safety of 40 mg and 100 mg Duloxetine BID Given Over 7 Days in Healthy Female Subjects. A Randomised, Placebo-Controlled Double-Blind Trial

3. F1J-FW-SBAZ Report: Pharmacokinetic Study of Duloxetine in Japanese and Caucasian Subjects
4. SBAZ Datasets

CATEGORY: Reports of Human PK Studies--Intrinsic Factor PK Study Reports

1. F1J-LC-HMAX(a) Report Amendment Summary: Single-Dose Pharmacokinetics of Duloxetine in Patients with Cirrhosis Compared with Healthy Subjects
2. Pooled Population Pharmacokinetic Analysis for Studies: F1J-MC-HMAQ, F1JMC-HMAU, F1J-MC-HMAVa, F1J-MC-SAAW
3. Renal PK Datasets

CATEGORY: Reports of Human PD Studies--Other Studies--Key Japanese Studies Conducted by

1. F1J-JE-HMCU Report: LY248686 Phase I Repeated Dose Study (60 mg, 7 days)

CATEGORY: Assay and Validation Reports--Other Compounds

1. Method Report 01048VTJO_LI: Quantitation of Tolterodine and 5-Hydroxymethyl Tolterodine in Human Plasma Using Detection. This report was inadvertently omitted from the NDA 21-733 submission. Therefore, it is included in this amendment. "

Reviewer's Comments on Metabolism Studies Using Hepatocytes, Microsomes, Etc.:

Acceptable. No new information was submitted. ADME Report 91 provided the *in vitro* metabolism information of duloxetine. The major metabolic pathways are consistent with those previously identified in the *in vivo* studies in these species. The Applicant stated that the microsomal incubation data identified hydroxy metabolites and desmethyl metabolite of duloxetine and further stated that since these incubations lack the appropriate enzymes and cofactors for conjugation reactions, microsomes are not a good predictor of the in vivo metabolism. The metabolites identified after liver slice incubations of duloxetine are qualitatively similar to those observed in the *in vivo* studies. However, quantitatively, the metabolites in liver slice homogenates differ from the *in vivo* metabolites in their relative amounts based on the radiochemical profiles. ADME Report 105 provided duloxetine's ability to inhibit *S*-mephenytoin. In addition to 1A2 and 2D6, duloxetine was found to competitively inhibit the biotransformation of *S*-mephenytoin to 4'-hydroxymephenytoin, a marker activity for CYP2C19, yielding a Ki value of 7.1 μM.

Reviewer's Comment on Reports of Human PK Studies--Healthy Subject PK and Initial Tolerability Studies

For studies F1J-LC-SBCH and F1J-BD-SBCG, there are no clinical pharmacology and Biopharmaceutics data to review.
For Study F1J-FW-SBAZ, this study report was reviewed by Dr. R. Kavanagh (Submission Amendment to N21--427, 12/22/03).

Reviewer's Comment on Reports of Human PK Studies--Intrinsic Factor PK Study Reports

For the hepatic impairment Study F1J-LC-HMAX(a), the conclusion from this submission is same as that from the original data set submitted to Division of Neuropharmacological drug products. The only noted difference is that the predicted concentrations in the submission are lower than those concentrations in the original review.

Revised from :

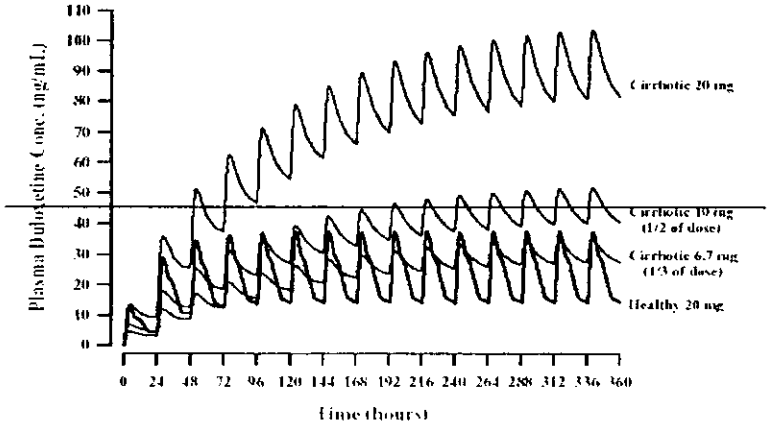


Figure HMAX.13.2. Simulations of duloxetine plasma concentration-time curves following QD administration of full (20 mg), half (10 mg), and one-third (6.7 mg) duloxetine dose for a typical cirrhotic subject compared to a 20 mg QD concentration profile for a typical healthy subject.

Revised to :

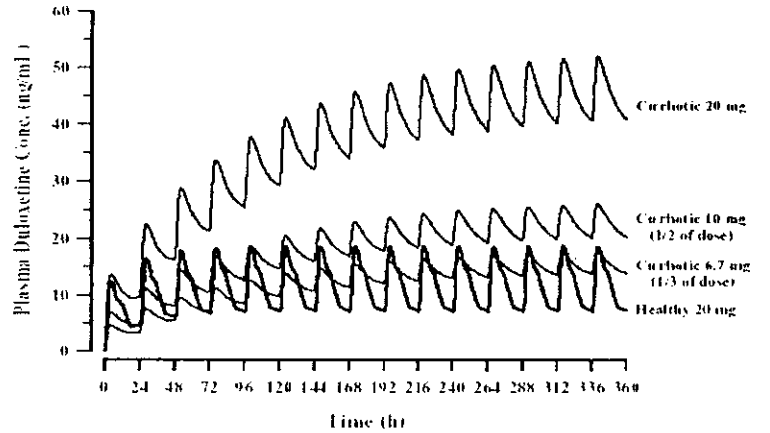


Figure HMAX.13.2. Simulations of duloxetine plasma concentration-time curves following QD administration of full (20 mg), half (10 mg), and one-third (6.7 mg) duloxetine dose for a typical cirrhotic subject compared to a 20 mg QD concentration profile for a typical healthy subject.

With respect to the pooled population analysis for renal impairment, Dr. He Sun (Pharmacometics Reviewer) commented that:

- Clearly, the prediction is low (biased) at higher concentration range, indicating a possible problem in structure model. Maybe a 2-compartment model is more appropriate for this data.

- Blood samples were collected within the initial 6 hours after dosing and are distributed within the initial 72 hours after starting the trial. Considering the t1/2 of the drug is about 12-16 hrs in normal health subject and maybe even longer in renally impaired and elderly, the blood sampling time-points appear to be collected not at optimal times. The impact of such a sampling schedule on CL/F estimate is unknown.

- The inclusion of covariates (Gender, smoking status, dose and age) in the model decreased inter-subject variability of CL/F from 64.8% to 54.3%, suggesting a large inherent inter-subject variability for the drug. However, inter-occasion and inter-study variability was not tested in the model building process.

- Renal function is confounded by age, and the ability of detecting renal function as a significant covariate for CL/F was influenced by the fact that the data were provided from multi-sources. Since age has been found to be a significant covariate for CL/F and the range of CLcr were for mild and moderate only, whether CL/F correlates with CLcr is not conclusive.

- The inter-subject and intra-subject variability of CL/F is large. Although the influence of mild and moderate renal function impairments on CL/F is unknown, dose adjustment for mild and moderate renal function alone is not needed.

Reviewer's Comment on Reports of Human PD Studies--Other Studies--Key Japanese Studies (Conducted by

For Study F1J-JE-HMCU, this study report was reviewed by Dr. R. Kavanagh (Submission Amendment to N21--427, 12/22/03).

Reviewer's Comment on Assay and Validation Reports--Other Compounds

Acceptable. The results indicate that the presence of duloxetine (100 ng/mL) does not interfere with the quantitation of tolterodine and 5-hydroxymethyl tolterodine for the human plasma assay. This method validation report is used in support of Study F1J-FW-SBAS Report (Duloxetine / tolerodine interaction study)

1.4.3 Overall Clinical Pharmacology Findings from the original NDA 21-427 CPB Review (Dr. R. Kavanagh)

How is duloxetine eliminated and what is its metabolic profile?

Duloxetine is extensively metabolized with over 80% of the dose recovered as metabolites. Approximately 70% of the dose is recovered in the urine almost exclusively as metabolites. The major primary metabolites include, hydroxy-duloxetine with hydroxylation at the 4, 5, or 6 positions, N-desmethyl-duloxetine, and dihydrodiol-duloxetine. The various hydroxides are secondarily metabolized via conjugation, or to a 5,6 catechol which is then conjugated. The various hydroxy metabolites are formed by CYP1A2 and CYP2D6 and account for around 2/3's – 4/5/'s of duloxetine's elimination. Whereas, the N-demethylation probably occurs via CYP2C11. The dihydrodiol is probably formed via hydrolysis of an epoxide intermediate, possibly via epoxide hydrolase, and is then conjugated. The formation of a potentially reactive expoxide intermediate is supported by the finding of some cysteine conjugates.

* **Are there any formulation issues with duloxetine?**

Duloxetine is acid labile, and acid hydrolysis of the ether linkage produces a thienyl-alcohol and 1-napthol. 50% of the dose is hydrolyzed to napthol in 1 hour at pH 1.2, which is achieved under fasting conditions. At pH 2 there's approximately 10% degradation in 1 hour, and at pH 4, 10% degrades in 63 hours. 1- Naphthol is extremely toxic and produces cramping, abdominal pain, nausea and vomiting. Severe systemic effects include nephritis, cystitis, liver damage, convulsions and acute intravascular hemolysis in individuals with RBC glucose-6-phosphate deficiency. Consequently, duloxetine is formulated as encapsulated enteric-coated pellets to avoid hydrolysis secondary to gastric acids. Whether concurrent ethanol ingestion or a potent acid inhibitor such as a proton-pump inhibitor might speed up dissolution of the enteric coating in the stomach was not examined. The risk of increased dissolution with increased pH would obviously be counterbalanced by decreased degradation, but the timing of the proton pump inhibitor dose relative to duloxetine dosing may alter the net effect and cannot be predicted.

Risk Management – Labeling should advise that the pellets should be swallowed whole and should not be crushed or chewed. Use with proton pump inhibitors should be avoided. The sponsor should be asked to provide *in vitro* dissolution data in an acidified ethanolic solution.

* **Has a biowaiver been requested?**

The sponsor requests a biowaiver for the 30 mg [redacted]. In assessing this request the following conclusions were made:

Three 20 mg capsules (lowest to-be-marketed strength) are bioequivalent to the 60 mg capsule (highest to-be-marketed strength).

The 20 mg, 30 mg [redacted], and 60 mg capsules are encapsulated beaded formulations that only differ by the number of beads and are thus compositionally proportional

Dissolution of 3 x 20 mg capsules are similar to one 60 mg capsule, and the dissolution performance of the 30 mg [redacted] capsules are similar to the 20 mg capsule strength.

A biowaiver is granted for the 30 mg [redacted] capsule strengths.

* **Does duloxetine exhibit linear kinetics?**

No. Upon multiple dosing the degree of accumulation of duloxetine is greater than predicted by single dose kinetics and the half-life is several hours longer. Based upon *in vitro* enzyme kinetic parameters this nonlinearity appears to be related to total duloxetine concentrations being in the range of 1/10 to 4/10's of the Km for CYP2D6.

* **Does duloxetine exhibit time invariant kinetics?**

Although half-life is prolonged slightly due to nonlinearity and will change slightly based upon the concentrations achieved, there is no *in vivo* evidence of auto-inhibition or auto-induction.

* **What are duloxetine's apparent pharmacokinetic parameters and secondary pharmacokinetic metrics?**

Apparent clearance (Cl/F) is high at around 1.1 L/ hr x kg^{-1} (i.e. > 90 L/hour), and apparent volume (V/F) is also high with means around 20 – 25 L/kg, (range 10 - >80 L/kg). Mean half-lives are around 12 – 14 hours, Tlag is around 2 hours, Tmax is around 6 hours, and mean steady-state Cmaxs are around 90 ng/ml with dosages of 60 mg qAM and 55 ng/ml with dosages of 40 mg BID, although these values are quite variable and means vary drastically between studies.

* **What is duloxetine's protein binding and the effects of changes in protein binding?**

Duloxetine is highly protein bound to both albumin and α_1-acid glycoprotein, with over 90% protein binding to both. Over a number of experiments protein binding tended to average around 96% with CVs of around 1.5%. Thus, there was quite a range of free fractions in normals ranging over 10 fold. There will be some changes in total plasma concentration profiles but there should not be any significant clinical consequences.

* **What is the bioavailability of duloxetine?**

Based on radiolabeled mass balance studies, 80% or more of the dose is absorbed. However, the nonlinearity and protein binding confound the quantification and although the systemic bioavailability is low, due to confounding factors it has not been, and may not be possible to accurately quantify.

* **What is the BCS Catergory?**

BCS categorization is not applicable to an enteric-coated formulation.

* **Is there an effect of gender on duloxetine pharmacokinetics?**

Women have higher exposures than men and exposures are on average 2 fold higher. This greater exposure cannot be explained simply on the basis of weight, nor can it be normalized to body size or mass, but is probably largely due to lower expression of CYP1A2 in women, with a possible contribution from the higher protein binding (lower free fraction) in women. In several phase I studies women had a higher incidence of adverse effects compared with men.

* **Do duloxetine's pharmacokinetics change with age?**

There is a decrease in clearance with age. Clearance decreases by approximately 1/3 from 25 years of age to 50 years of age, and decreases by another 1/3 from 50 to 75 years of age. This translates into about a 1% decrease in clearance with each year of age. Currently there is no evidence suggesting a need for initial dosage adjustment in the elderly.

* **Are duloxetine's pharmacokinetics different in children?**

Duloxetine's pharmacokinetics have not been studied in children.

* **Are there pharmacokinetic or pharmacodynamic differences by race or ethnicity?**

There was no difference in duloxetine pharmacokinetics between Caucasians and Hispanics. There were either insufficient numbers of subjects with different ethnic backgrounds or limitations in study designs that prevented finding any differences by race or ethnicity. Inspection of the data did not reveal any striking differences between Caucasian 2D6 extensive metabolizers and 'Blacks'.

In studies conducted in the Far East in Chinese and Malays, (Studies HMBB and SBAG), inspection of the data reveals a mixed picture. With single doses Cmaxs and AUCs are approximately half of those in Caucasians, Blacks and Hispanics receiving doses, (40 mg SD - (Study HMBB). Whereas with multiple dosing exposures are similar (study SBAG).

Since duloxetine is CYP2D6 substrate and especially since there's nonlinearity we would expect to find ethnic differences if studies were properly designed, as CYP2D6 poor metabolizers are found in 6-10% of the Caucasian population, approximately 2% of 'Blacks' and in 1% of Asians. In addition, there appears to be a common allellic variant in Asians that results in higher clearances and lower exposures on average. This might explain the low duloxetine exposures seen in study HMBB. Currently there is no evidence suggesting a need for initial dosage adjustment.

* **What is the effect of renal insufficiency on duloxetine?**

In subjects with end-stage renal failure on hemodialysis Tlag and Tmax were similar, however mean Cmax, was approximately 2 fold higher as compared to controls after a single

60mg dose of duloxetine. In addition, AUCt and AUC∞ were both approximately 2 fold higher, with Cl/F and V/F both decreased by approximately half, thus half-life was relatively unchanged. The decreased clearance is likely due to the inhibition of CYP2D6 due to non-dialyzable endogenous compounds. As expected, hemodialysis did not remove duloxetine from the body to any clinically significant degree.

The exposure to the primary circulating metabolites of 4-Hydroxy-Duloxetine Glucuronide and 5-Hydroxy, 6-Methoxy-Duloxetine Sulfate were approximately 7 – 9 fold higher than normals with half-lives extended ~2 fold. As expected hemodialysis did eliminate significant amounts of these metabolites. Several other glucuronide conjugates were also detected circulating at low levels in plasma in ESRD.

Population pharmacokinetics failed to find a significant covariance of duloxetine's kinetic parameters with estimated creatinine clearances above 40 ml/min

There was also a higher incidence of duloxetine's common side effects in ESRD as compared to controls. There was also an increase in blood pressure in the ESRD patients, especially in those with a history of hypertension. In addition, there was a single individual who had a coagulation problem that required surgical intervention, this could be related to inhibition of platelet serotonin reuptake and may be a risk in ESRD with indwelling catheters.

Risk Management – — Risks in severe renal insufficiency are unknown (Clcr < 30 ml/min); due the lack of safety information in this group . —

* **What is the effect of hepatic insufficiency on duloxetine?**

Mean duloxetine Cmaxs after single doses were similar in cirrhotics with moderate hepatic insufficiency (Child-Pugh Scores 7-8) and controls, however the upper 90% confidence limit on the geometric mean ratio was almost 2 fold. When AUC∞ is compared the upper limit of the 90% confidence limit on the geometric mean ratio is >11 fold higher in cirrhotics. On average clearance decreases by 80%, and half-life increases over 3 fold. Tlag was shorter in cirrhotics, even in the face of discontinuance of laxatives, and Tmax was significantly delayed (~4 hours). These delays are at least partly due to delayed elimination.

In contrast, concentrations and exposures to the 4-hydroxy-duloxetine glucuronide and 5-hydroxy, 6-methoxy-duloxetine sulfate tend to be decreased in most cirrhotics. The above findings indicate that metabolism through CYP1A2 and CYP2D6 is diminished. This means that duloxetine must be eliminated via an alternative pathway. Thus even if the duloxetine dose is decreased to produce equivalent duloxetine exposures to non-cirrhotics, on average at least 6 times as much epoxide and other metabolites are being formed as compared to normals. This is especially problematic in cirrhotics and other subjects with hepatic insufficiency where they don't have any reserve capacity and even a small degree of hepatotoxicity due to an epoxide could have dire consequences.

Risk Management – Duloxetine should not be administered to patients with mild, moderate, or severe hepatic insufficiency.

* **Is there any diurnal variation in duloxetine's kinetics?**

Three different studies (HMAO, HMBN, and SBAA) show a consistent pattern of diurnal variation regardless of the formulation studied, although all 3 studies used enteric-coated products. In each study there is a delay in Tlag and Tmax of about 3 hours, a decrease in Cmax and AUC by 40% and a 1/3 increase in Cl/F. These differences may be due in part to delayed gastric emptying. Delays in gastric emptying raises the potential concern that the enteric coating may not remain intact for a sufficient time period resulting in possible formation of naphthol. This issue has not been addressed by the sponsor.

Risk Management – The stability of duloxetine's enteric coating in acidic medium should be examined *in vitro* for a duration of at least 6 hours.

* **What is the effect of tobacco use on duloxetine pharmacokinetics?**

Overall the effect of smoking is to decrease duloxetine exposures on average 30%, presumably due to induction of CYP1A2. In some subjects induction might result in subtherapeutic duloxetine dosing, thus dosage may need to be titrated.

* **What is the effect of food on duloxetine bioavailability and pharmacokinetics?**

When given with a high caloric, high fat meal, there was a delay in Tlag and Tmax, (about 4 hours) for 2 different clinical trial formulations without any changes in other pharmacokinetic metrics. A delay in Tlag and in Tmax with food is common with enteric-coated encapsulated pellets and is expected. However, this delay should not effect the efficacy, as the mean change in exposures did not change in a consistent manner or by a large percentage. However, we don't know if this delay, presumably due to a delay in gastric emptying, will allow any duloxetine to be degraded to naphthol. Consequently, as with any EC encapsulated pellet formulation, until additional data is available, opening the capsules and sprinkling the contents on food should be discouraged. Administration of duloxetine either 2 hours before or after meals in studies SAAY and HMBN does not appear to have major effects on either Tlag or Tmax. Since food delays gastric emptying by several hours and since we don't know how long the enteric coating is stable in gastric juices the risk of acid hydrolysis in unknown.

Risk Management – As with diurnal variability, the stability of duloxetine's enteric coating in acidic medium should be examined *in vitro* for a duration of at least 6 hours, and until additional data is available, opening the capsules and sprinkling the contents on food or taking with food should be discouraged.

* **What other dietary considerations are there with duloxetine?**

A number of dietary factors are known to induce CYP1A2 and are thus expected to increase the clearance of duloxetine and decrease exposure. These factors include:

Charcoal Broiled and Fried Meats and Fish
Cruciferous Vegetables (e.g. broccoli, cabbage, brussel sprouts)

Polyaromatic hydrocarbons and tryptophan pyrolysis products have been implicated as the potential inducing agents in these foods.

The clinical implications of diets heavy in these substances would be similar to the implications of chronic tobacco use, where a certain subpopulation might lose clinical efficacy.

* **Are there any interactions with drugs that might effect GI absorption?**

Neither famotidine nor Mylanta® (51 mEq) effected the absorption of duloxetine. However, maximum labeled doses of antacids may be higher and doses up to 200 mEq have been suggested in peptic ulcer disease. In contrast, activated charcoal significantly reduced absorption with ~1/3 decreases in mean Cmax and AUC. Thus charcoal may be useful in overdose situations. However, some subjects had minimal decreases in duloxetine absorption with charcoal administration.

Drugs that effect gastric motility such as antidiarrheals, or cathartics were not examined but might effect absorption rate with duloxetine.

Risk Management – As with diurnal variability, the stability of duloxetine's enteric coating in acidic medium should be examined *in vitro* for a duration of at least 6 hours. Labeling regarding antacids should be modified.

* **Are there any effects of diseases that might effect GI absorption of duloxetine?**

The effect of diseases that slow gastric emptying, such as diabetic gastroparesis, is unknown, but again raises the issue of prolonged exposure to gastric juices and the stability of the enteric coating.

Diseases that increase gastric emptying are clearly expected to decrease both lag time and Tmax, although the rate of absorption in the intestines is not expected to be drastically effected.

Risk Management – Same as item above regarding testing in acidic media and modifying labeling.

* **Are there any pharmacokinetic interactions via CYP1A2?**

In vitro studies suggest that duloxetine is unlikely to be a competitive inhibitor or inducer of CYP1A2, plus duloxetine did not inhibit theophylline metabolism by CYP1A2 *in vivo*.

The effect of other agents that induce or inhibit CYP1A2 on duloxetine pharmacokinetics was not examined. However, the clinical effects of induction due to drugs would be the same as for tobacco. The effects of inhibition will be discussed later.

* **Are there any pharmacokinetic interactions via CYP2D6?**

Duloxetine exposures were increased by low doses (20 mg qd) of paroxetine, a CYP2D6 inhibitor, by 1.6 fold on average with an upper 90% CI of 2 fold. The degree of increase in exposure would be expected to be even greater with clinical dosages and in CYP2D6 EMs with low CYP1A2 activity.

Duloxetine itself is also a moderate CYP2D6 inhibitor and will inhibit the metabolism of other compounds with less affinity for CYP2D6 than duloxetine has. For example, when duloxetine was administered at the maximum therapeutic dose (60 mg BID) with a single 50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold.

Risk Management – Labeling should advise that

* **Are there any pharmacokinetic interactions via CYP2C11?**

Temazepam decreased the exposure to desmethyl-duloxetine by 30% suggesting that inhibition of CYP2C11 may effect exposure to this metabolite. However, there was no effect on parent duloxetine kinetics as this is a relatively minor pathway.

* **Are there any pharmacokinetic interactions via glucuronidation?**

Coadministration of lorazepam did not effect duloxetine pharmacokinetics, however duloxetine did result in a slightly faster absorption and 16% greater Cmax for lorazepam. Whether this is due to an effect on glucuronidation, or some other effect can't be discerned.

* **Is duloxetine an enzyme inducer?**

Duloxetine did not induce either CYP1A2 or CYP 3A4 *in vitro*. The sponsor claims that these are the only isozymes that are readily inducible and were thus the only isozymes tested for inducibility. This is incorrect. In addition, to 1A2 and 3A4, 2C9, 2C19, 2E1, and 2A6 are also inducible. Glucuronidation is also inducible. Of the inducible P450s; 2C9, 2C19, and 2A6 metabolize drugs and 2E1 metabolizes ethanol. *In vivo* studies were not conducted for sufficient duration to see any effects of induction.

* **Are there any pharmacokinetic interactions with active transporters?**

The effect of transporter inhibitors or activators on duloxetine pharmacokinetics was not examined, nor was the effect of duloxetine on transporters specifically examined.

* **Are there any special concerns regarding drug interactions with duloxetine's metabolic profile?**

Duloxetine is extensively absorbed and metabolized, with the most important enzymes responsible for eliminating duloxetine being CYP1A2 and CYP2D6. CYP2D6 is polymorphically expressed, and both isozymes have a range of activity in people that do not covary with each other.

If either CYP1A2 or CYP26 is inhibited in an individual which a low baseline activity of the other enzyme, or if both enzymes are inhibited simultaneously the exposure to duloxetine may increase many fold. In addition, individuals with low baseline activities of both isozymes will also have much higher exposures. The main issue in both situations, is shunting of elimination to alternative pathways. This shunting will result in a many fold increase in exposure to the potentially reactive epoxide intermediate. This is will probably occur to a greater extent with drug interactions where there is near complete blockade of CYP1A2 and CYP2D6 as compared with the scenario with low baseline activities, which would still allow some duloxetine to be eliminated via these pathways.

Epoxide formation has been implicated as a risk for hepatotoxicity and teratogenicity. The risk of teratogenicity has also been shown to increase when multiple agents that form epoxides are co-administered and when inhibitors of epoxide hydrolase are also co-administered as they prevent the detoxification of the reactive epoxide.

Duloxetine is an antidepressant and depression commonly afflicts women of child bearing age. In addition, it appears that it may be able to claim a low incidence of sexual side effects. Consequently, it may be commonly used in patients in whom pregnancies may occur. In addition, duloxetine is likely to be prescribed to patients with bipolar illness. These patients are also at risk of increased sexual activity and pregnancy. They are commonly prescribed carbamazepine and valproic acid. Carbamazepine is also metabolized to an epoxide and valproic acid is a potent inhibitor of epoxide hydrolase.

Risk Management - Labeling should

* **Are there pharmacodynamic interactions with benzodiazepines?**

Duloxetine increased the degree of sedation seen with lorazepam.

* **Is there a pharmacodynamic interaction with ethanol?**

No evidence of a pharmacodynamic interaction with ethanol was seen, however, the study design may not have adequately stressed the test system.

* **Are there any other potentially significant pharmacodynamic effects or interactions?**

Since duloxetine inhibits serotonin reuptake, and from the *in vivo* pharmacodynamic information it appears that duloxetine may also inhibit norepinephrine reuptake. Thrombocytopenia and echymoses were reported in a phase I study. Inhibition of platelet serotonin may effect platelet aggregation, thus a pharmacodynamic effect on platelet aggregation should be considered a possibility.

A pharmacodynamic interaction of duloxetine with tryptophan, (high content in turkey), should also be considered a possibility. Headache, nausea, sweating and dizziness have been reported when tryptophan was administered to patients taking other SSRIs.

Risk Management

Labeling

— :ould be considered for duloxetine.

* **Are the to-be-marketed and clinical trial formulation bioequivalent?**

Yes.

APPEARS THIS WAY
ON ORIGINAL

2 QBR

QBR for this NDA will address only new information for this NDA. Extract from Dr. Ron Kavanagh's review in the previous pages of this review will provide the information that is normally contained in this section.

2.1.1 Exposure-response

2.1.1.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the pharmacological response or clinical endpoint.

There is no concentration-exposure relationship data. However, the P3 clinical trials assessed dose-response relationship. See Medical Officer's Review for efficacy findings. The following figures are from the Applicant's proposed package insert on the dose-response:

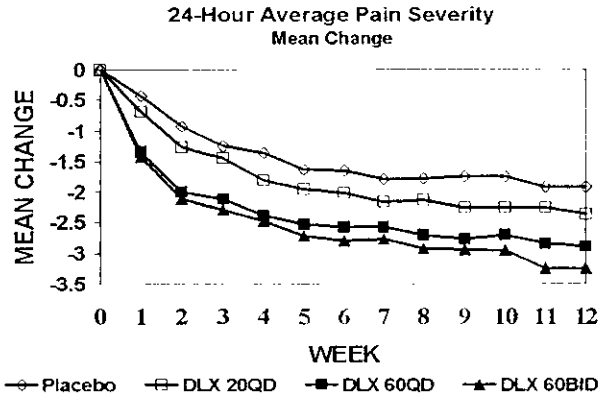


Figure 1. Mean Change in Average 24-Hour Pain - Study 1
(p<0.05 versus placebo for Cymbalta 60 mg QD and 60 mg BID at all time points)

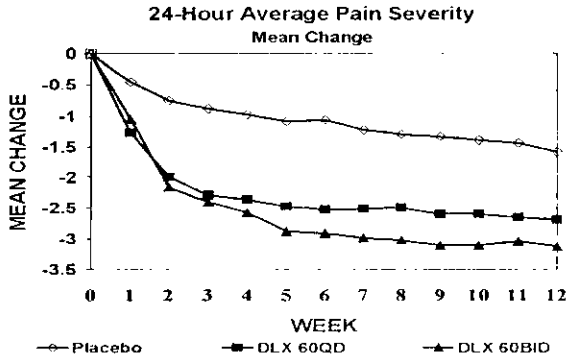


Figure 2. Mean Change in Average 24-Hour Pain - Study 2
(p<0.05 versus placebo for Cymbalta 60 mg QD and 60 mg BID at all time points)

In addition to above, based on exposure–response (safety/efficacy) relationship information, modeling and simulations incorporating relevant patient demographic variables, the following dose adjustment proposal is provided (See Appendix 4.5 for further information) :

- . This proposal offers a safe and simple dose regimen;
-
- For renal impaired patients
- Given the increase in exposure in patients who are on concomitant drugs which will inhibit CYP1A2 and CYP2D6 metabolism, such as SSRIs (e.g. fluvoxamine - 1A2 inhibitor; paroxetine - 2D6 inhibitor),

These recommendations will greatly expand the utility of this important drug for treating neuropathic pain patients, including renally impaired patients as well as certain drug interaction situations.

3 Detailed Labeling Recommendations

The approved package insert from NDA 21-426 will be used with appropriate modifications, if necessary. This package insert is appended to this review. Additional dosage adjustment recommendation is proposed as stated in the Recommendation section and Appendix 4.5.

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

16 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

4.3 Individual Study Review

4.3.1 ADME Report 91 : Summary of the In Vitro Metabolism of 14C-Duloxetine (LY248686) by Human, Rat, and Dog Microsomes and Liver Slices

Studies: 2000IV-HSL03, 2000IV-HSL05, 2000IV-DSL08, and 2000IV-RSL06

ADME Report 91 Report Amendment 01 October 2002

Reviewer's Comment: The Applicant's findings in this study report are adequate to describe the in vitro metabolism information. However, the results from this study do not provide any additional information that is already available; this study confirms that the major metabolic pathways are consistent with those previously reported in the in vivo studies.

Summary:

The in vitro metabolism of duloxetine was evaluated in humans, rat, and dog liver microsomes and slices. In addition to duloxetine, a total of 20 metabolites were identified by LC/MS method. The major metabolic pathways are consistent with those previously identified in the in vivo studies in the same species.

Duloxetine and 4 metabolites were found in the liver microsomes. Metabolites were identified as the 5-hydroxy (M12), 6-hydroxy (M13), 4-hydroxy (M14), and desmethyl (M23) metabolites of duloxetine. All four metabolites were observed in the rat microsomal samples. The 6-hydroxy (M13) metabolite was not observed in the human or dog microsomal incubations, 4-hydroxy (M14) duloxetine was not observed in the dog microsomal samples.

In human liver slice samples, 17 peaks (duloxetine and 16 metabolites) were identified by LC/MS. The largest peak in the radiochromatogram was duloxetine. Other prominent peaks observed corresponded to glucuronide conjugates of 5-hydroxy (M4), 4-hydroxy (M6), and 6-hydroxy (M8) duloxetine. In rat liver slice samples, 16 peaks (duloxetine and 15 metabolites) were identified by LC/MS; the largest peak in the radiochromatogram was duloxetine. The other large radiochemical peaks were identified as desmethyl (M23) duloxetine and two glucuronide conjugates of hydroxy duloxetine. The study report stated that the position of the conjugates of the hydroxy duloxetine metabolites could not be positively identified in this case due to chromatographic retention time shifts. In dog liver slice samples, 14 peaks (duloxetine and 13 metabolites) were identified by LC/MS; the largest peak in the radiochromatogram was the cysteinylhydroxy conjugate (M18) of duloxetine. Two other large radiochemical peaks were identified as duloxetine and a sulfate conjugate of hydroxy duloxetine (M22).

In conclusion, the microsomal incubation data identified hydroxy metabolites and desmethyl metabolite of duloxetine. The study report stated that since these incubations lack the appropriate enzymes and cofactors for conjugation reactions, microsomes are not a good

predictor of the in vivo metabolism. The metabolites identified after liver slice incubations of duloxetine are qualitatively similar to those observed in the in vivo studies. However, quantitatively, the metabolites in liver slice homogenates differ from the in vivo metabolites in their relative amounts based on the radiochemical profiles.

Methods

Preparation and Incubation of Microsomes

Following 10-, 20-, and 30-minute incubations at approximately 37°C, quenched incubations of 14C-duloxetine and microsomes were analyzed for metabolite formation by LC/MS. Incubation mixtures of 0.5 mL contained rat, dog, or human hepatic microsomes (0.25 mg/mL) in 100 mM sodium phosphate buffer (pH 7.4) containing 2 mMNADPH and 14C-duloxetine (10 µM). Reactions were quenched with an equal volume of cold acetonitrile (0.5 mL).

Preparation and Incubation of Liver Slices

Human liver tissue samples were received from [redacted] on wet ice. Dog liver was chilled in modified Sack's cold preservation buffer and rat liver tissue was chilled in normal saline (Monden and Fortner 1982) after excision, and all tissues were kept ice-cold before and during slice preparation. Slices were prepared under aseptic conditions in Sack's buffer using a [redacted] The slices were cut to a thickness of approximately 200 to 250 micrometers, were mounted in Teflon/titanium inserts (2 slices per insert), and were placed in 20-mL scintillation vials containing 1.7 mL of medium with or without drug. Slices were cultured in sterile [redacted] medium without phenol red or glutamine ([redacted]) which was supplemented with 10% fetal bovine serum ([redacted]), 50 µg/mL gentamicin, 0.05 µg/mL Fungizone_, and 350 µg/mL L-glutamine. Drug-containing media with a final drug concentration of 50 µM or 250 µM 14C-LY248686 were prepared from DMSO stock solutions. The DMSO concentration did not exceed 0.5% (v/v). Incubation vials were sealed with a cap having a hole for gas exchange, and were placed in a [redacted] incubator at 37°C. The vials were rotated at approximately 3 rpm under a humidified atmosphere of 95% O2/5% CO2. Control incubations without slices or without drug were conducted in each study. Samples were collected after 4 and 24 hours in culture. At these times, the slices were collected and weighed, the slices were sonicated in their medium, and the homogenates were quick-frozen on dry ice.

Homogenates were maintained in an ultracold freezer prior to analysis.

7-Ethoxycoumarin metabolism was used as a positive control to demonstrate the capacity of the liver slice preparations to retain integrated phase I and phase II metabolism (Barr et al. 1991). Liver slices were incubated with 50 µM 7-ethoxycoumarin for 3 hours after which the incubation was terminated by homogenization of the samples and rapid freezing on dry ice. Metabolite profiles of human, rat, and dog liver slices were comparable to those reported by Steemsa et al. (1994) confirming the ability of the slice preparations to carry out coupled

phase I and phase II metabolic reactions. Details regarding liver slice preparation and analysis are given in departmental method [illegible]

Table 1: Metabolites of Duloxetine Identified in Human, Rat, and Dog Liver Microsomes

Peak[a]	$[M+H]^+$	Proposed Metabolite Identification	Rat	Dog	Human
P	298	Duloxetine	X	X	X
M12	314	5-hydroxy duloxetine	X	X	X
M13	314	6-hydroxy duloxetine	X		
M14	314	4-hydroxy duloxetine	X		X
M23	284	Desmethyl duloxetine	X	X	X
[a] = The peak nomenclature is the same as that used in the in vivo studies.					

Table 2: Metabolites of Duloxetine Identified by LC/MS in 24-Hour Liver Slice Homogenates from Rat, Dog, Monkey, and Human

Proposed Metabolite Identification	Peak [a]	$[M+H]^+$	Rat	Dog	Human
Duloxetine (LY248686)	P	298	X	X	X
Dihydrodiol (isomer)	M2-A	332	X	X	X
Dihydrodiol (isomer)	M2	332		X	X
Glucuronide conjugate of 5-hydroxy, 6-methoxy	M3	520	X	X	X
Glucuronide conjugate of 5-hydroxy	M4	490	X	X	X
Glucuronide conjugate of dihydroxy (catechol) duloxetine	M5	506			X
Glucuronide conjugate of 4-hydroxy	M6	490	X	X	X
Sulfate conjugate of 5-hydroxy, 6-methoxy	M7	424			X
Glucuronide conjugate of 6-hydroxy	M8	490	X		X
Sulfate conjugate of 4-hydroxy	M11	394	X	X	X
5-hydroxy	M12	314	X	X	X
6-hydroxy	M13	314	X	X	X
4-hydroxy	M14	314	X	X	X
6-hydroxy, 5-methoxy or 5-hydroxy, 6-methoxy	M15 or M16				X
Cysteinylhydroxy	M18	435	X	X	X
Sulfate conjugate of hydroxy	M22	394	X	X	X
Desmethyl	M23	284	X	X	X
Thienyl Alcohol	M26	172	X		X
Glucuronide conjugate of N-hydroxy	M30	490	X		
Glucuronide conjugate of duloxetine carbamic acid	M31	535 $[M+NH_4]$	X	X	
[a] = The peak nomenclature is the same as that used in the in vivo studies.					

4.3.2 ADME Report 105: In Vitro Interaction of Duloxetine with Human Cytochrome P450 CYP2C19

Study 22-246-TC; conducted by — August 2003

Reviewer's Comment: The study report is adequate. In addition to 1A2 and 2D6, duloxetine was found to competitively inhibit the biotransformation of *S*-mephenytoin to 4'-hydroxymephenytoin, a marker activity for CYP2C19, yielding a Ki value of 7.1 μM.

Summary

The ability of duloxetine to inhibit the metabolism of the marker catalytic activity for CYP2C19 was examined. The untransformed data from inhibition studies were modeled using conventional enzyme inhibition relationships. Duloxetine was found to competitively inhibit the biotransformation of *S*-mephenytoin to 4'-hydroxymephenytoin, a marker activity for CYP2C19, yielding a Ki value of 7.1 μM.

In clinical studies, the mean steady state Cmax plasma concentration of duloxetine after 60-mg twice daily doses was 0.48 μM. The projected in vivo inhibition of the CYP2C19 mediated metabolism of *S*-mephenytoin was 6%.

In summary, duloxetine would not be predicted to cause significant inhibition of the metabolic clearance of drugs metabolized by CYP2C19. However, predictions concerning the amount of inhibition expected to be observed in vivo from this in vitro model cannot be definitively modeled without information as to the concentration of duloxetine at the active site of the enzyme.

4'-Hydroxylation of (*S*)-Mephenytoin (CYP2C19)

Incubation Conditions

Following 60-minute incubations at approximately 37 °C, quenched incubations of (*S*)-mephenytoin and microsomes, with or without the addition of LY248686, were analyzed for the formation of 4'-hydroxymephenytoin by — Incubation mixtures of approximately 500 μL contained human hepatic microsomes (0.1 mg/mL protein; see Materials) in 100 mM potassium phosphate buffer (pH 7.4), 1 mM NADPH, and (*S*)-mephenytoin (10, 25, 50, 100, or 250 μM) in the presence or absence of 10, 25, 50, or 75 μM LY248686 as inhibitor. The client requested the use of four concentrations of LY248686 plus no inhibitor, which is a deviation from the study plan calling for five concentrations of LY248686 plus no inhibitor. The use of five concentrations of inhibitor is routine for this type of study, and is considered acceptable to appropriately model the inhibition observed in this study. Formation of 4'-hydroxymephenytoin under these conditions is linear with respect to time and protein concentration.

Results

LY248686 was examined for its ability to inhibit form-selective catalytic activity associated with CYP2C19. (*S*)-Mephenytoin metabolism to 4'-hydroxymephenytoin has demonstrated

isoform-selective catalytic activity for human CYP2C19 (Rettie et al. 2000). The kinetics of formation of 4'-hydroxymephenytoin by the human microsomal mixture in the inhibition study with LY248686 yielded apparent Km and Vmax values of 43 ± 3 μM and 68 ± 2 pmol/min/mg protein, respectively. The inhibition of (*S*)-mephenytoin metabolism by LY248686 was found to best fit the competitive inhibition model, yielding an apparent Ki value of 7.1 ± 0.4 μM (Table 1).

Table 1: Inhibition of CYP2C19 Form-Selective Catalytic Activity In Vitro by LY248686

Form-Selective Catalytic Activity	Type of Inhibition	Apparent Ki
CYP2C19: (*S*)-Mephenytoin 4'-hydroxylation	competitive	7.1 ± 0.4 μM
(*S*)-Mephenytoin concentrations were 10, 25, 50, 100, and 250 μM. At each substrate concentration, either diluent or one of four concentrations of inhibitor was included. The concentrations of LY248686 used for the inhibition of 4'-hydroxymephenytoin formation were 10, 25, 50, and 75 μM. The apparent Ki value represents the parameter estimate ±standard error of the parameter estimate.		

4.3.3 Method Validation Report: Quantitation of Tolterodine and 5-Hydroxymethyl Tolterodine in Human Plasma Using
— — Detection (Project 01048VTJO_LI.DOC)

Study conducted by : — (Original Report Date: 24 July 2001)

Reviewer's Comment: The study report is acceptable. There are no review issues with this study report. The results indicate that the presence of duloxetine (100 ng/mL) does not interfere with the quantitation of tolterodine and 5-hydroxymethyl tolterodine for the human plasma assay. This method validation report is used in support of Study F1J-FW-SBAS Report (Duloxetine / tolerodine interaction study) —

Summary : An analytical method was developed by —
—, to quantitate tolterodine and 5-hydroxymethyl tolterodine in sodium heparinized human plasma samples. [2H6]Tolterodine was used as the internal standard (IS) for both analytes. Plasma samples (0.1 mL) were prepared using a —
— , procedure, to isolate the analytes and internal standard from human plasma. Sample extracts were analyzed by —
—. The lower limit of quantitation (LLQ) was
for both analytes. The calibration curves were fit by a weighted (1/x2) quadratic equation
— for each analyte. The coefficients of determination of the calibration curves ranged from — for both analytes. The overall mean extraction efficiency was — or tolterodine, and — for 5-hydroxymethyl tolterodine. Validation samples were prepared at tolterodine and 5-hydroxymethyl tolterodine concentrations of — ng/mL to determine the precision and accuracy of the human plasma assay. The intra-assay and inter-assay precision (relative standard deviation: RSD) results calculated from validation samples were — for both analytes at all concentrations. The intra-assay and inter-assay accuracy values (relative error: RE) calculated from validation samples ranged from — for both analytes at all concentrations. Tolterodine and 5-hydroxymethyl tolterodine were stable in human plasma after storage at room temperature for up to — (thawed from approximately –70 °C), after — freeze/thaw cycles at approximately -20 and -70 °C, and after storage for up to —
— at approximately -20 °C and -70 °C. Extracted human plasma validation and dilution QC samples demonstrated reliable results upon reinjection after storage for — at room temperature.

Standard Curve

Standard #	Final Conc. (ng/mL) each analyte	Volume (µL) x Standard Solution	µL Control Plasma Added	Final vol. (µL)
9				
8				
7				
6				
5				
4				
3				
2				
1				

Validation Control Samples

Validation Sample	Concentration (ng/mL)	Working Solution Added	Amount of Working Solution Added	Final Volume
VAL4				
VAL3				
VAL2				
VAL1				

QC Sample The plasma QC samples used during stability determinations were prepared. The QC samples were prepared in sodium heparinized human control plasma by adding the working solutions to a class "A" volumetric flask and diluting to the mark with control plasma as indicated in the following table:

Quality Control Sample	Concentration (ng/mL)	Working Solution Added	Amount of Working Solution Added	Final Volume
QC3				
QC2				
QC1				

The following items were considered in the method validation: Matrix Effect, Extraction Efficiency, Stability Sample Preparation, Room Temperature Stability, Freeze-Thaw Stability, Extract Stability, Storage Stability, and Interference Assessment for Duloxetine.

Results

Selectivity

No chromatographic interferences were observed at the retention times of the analytes in any of the human control plasma samples analyzed.

Carryover

Carryover was evaluated in each analytical run of the validation by placement of a zero sample after each calibration standard at the upper limit of quantitation (ULQ). The carryover was considered acceptable if the peak area in the zero sample was <20% of the mean LLQ standard peak area.

Standard Curves and Back Calculated Results

The calibration curves for tolterodine and 5-hydroxymethyl tolterodine were fit by a weighted (1/x2) quadratic regression and met all acceptance criteria. The coefficient of

determination (r2) was ≥ — for tolterodine, and ≥ — for 5-hydroxymethyl tolterodine.

Limits of Quantitation/Range

The limits of quantitation for the tolterodine and 5-hydroxymethyl tolterodine assay are — — The precision (RSD) values were — , for tolterodine, and — , for 5-hydroxymethyl tolterodine in plasma. The accuracy (RE) values were — for tolterodine and — for 5-hydroxymethyl tolterodine in human plasma. The LLQ of — ng/mL is an acceptable lower limit of quantitation for tolterodine and 5-hydroxymethyl tolterodine in human plasma.

Accuracy and Precision

Intra-Day Precision and Accuracy

Validation samples were analyzed for tolterodine and 5-hydroxymethyl tolterodine with six replicates within each validation run at — The intra-day relative standard deviation (RSD, precision) and relative error (RE, accuracy) were :

	RSD Range	**RE Range**
Tolterodine	/	
5-Hydroxymethyl Tolterodine		

One level of QC sample was used to determine the effect of dilution on the determination of tolterodine and 5-hydroxymethyl tolterodine in human plasma. VAL-QC4 — ng/mL) was diluted 50-fold and analyzed. The intra-day precision (RSD) and accuracy (RE) of the dilution QC samples were:

	RSD Range	**RE Range**
Tolterodine		/
5-Hydroxymethyl Tolterodine		

Inter-Day Precision and Accuracy

Inter-day RSD and RE for validation samples analyzed at the concentrations listed above were:

	RSD Range	**RE Range**
Tolterodine		
5-Hydroxymethyl Tolterodine		/

The inter-day precision (RSD) and accuracy (RE) of dilution QC samples were:

	RSD	**RE**
Tolterodine	/	
5-Hydroxymethyl Tolterodine		

Matrix Effects
The mean matrix effect of human plasma extract on the quantification of — ng/mL samples of tolterodine and 5-hydroxymethyl tolterodine were — . for tolterodine and 5-hydroxymethyl tolterodine, respectively, indicating · —

Extraction Efficiency
The mean overall extraction recoveries of tolterodine and 5-hydroxymethyl tolterodine values (at 0.8 and 40 ng/mL) were — , for tolterodine and — for 5-hydroxymethyl tolterodine.

The RSD for any individual level for either pre- or post-extract determinations was ≤ — for both analytes. The recovery value (at — ng/mL [2H6]tolterodine) was — for [2H6]tolterodine. The RSD values for pre- or post-extract determinations were — , for the internal standard compound.

Stability Results
Room Temperature Stability
The RE values of the room-temperature QC samples of tolterodine and 5-hydroxymethyl tolterodine in low, high, and dilutionQC samples after storage for — hours at room temperature were:

	RE Range
Tolterodine	/
5-Hydroxymethyl Tolterodine	

These data indicate acceptable stability of tolterodine and 5-hydroxymethyl tolterodine in human plasma at room temperature for at least 24 hours.

Freeze-Thaw Stability
The RE values of the freeze/thaw QC samples of tolterodine and 5-hydroxymethyl tolterodine in low, high, and dilution QC samples after — freeze/thaw cycles at approximately -20 °C were:

	RE Range
Tolterodine	/
5-Hydroxymethyl Tolterodine	

The RE values of the freeze/thaw QC samples of tolterodine and 5-hydroxymethyl tolterodine in low, high, and dilution QC samples after — freeze/thaw cycles at approximately -70 °C were:

	RE Range
Tolterodine	/
5-Hydroxymethyl Tolterodine	

These results indicate acceptable stability of tolterodine and 5-hydroxymethyl tolterodine in human plasma for at least — freeze/thaw cycles at approximately -20 and -70 °C.

Extract Stability

The RE values of the extract stability samples after storage for — , at room temperature were:

	RE Range
Tolterodine	/
5-Hydroxymethyl Tolterodine	

Storage Stability

The RE values of the human plasma QC samples of tolterodine and 5-hydroxymethyl tolterodine in low, high, and dilution QC samples stored at approximately -20 °C were :

	RE Range
Tolterodine	
5-Hydroxymethyl Tolterodine	

The results indicate acceptable stability of tolterodine and 5-hydroxymethyl tolterodine in human plasma for up to — at approximately -20 °C.

The RE values of the human plasma QC samples of tolterodine and 5-hydroxymethyl tolterodine in low, high, and dilution QC samples stored at approximately -70 °C for at least — were:

	RE Range
Tolterodine	/
5-Hydroxymethyl Tolterodine	

These results indicate acceptable stability of tolterodine and 5-hydroxymethyl tolterodine in human plasma for at least — , at approximately -70 °C.

Interference Assessment for Duloxetine

The RE values of the human plasma QC samples in low, high, and dilution QC samples for tolterodine and 5-hydroxymethyl tolterodine were:

	RE Range
Tolterodine	
5-Hydroxymethyl Tolterodine	/

These results indicate that the presence of duloxetine (– ng/mL) does not interfere with the quantitation of tolterodine and 5-hydroxymethyl tolterodine for the human plasma assay.

4.3.4 SBCH – Safety and tolerance of duloxetine in healthy females at supratherapeutic doses achieved by a progressive 1- to 3-day titration

Clinical Study Synopsis: Study F1J-LC-SBCH

Title: Safety and Tolerance of Duloxetine in Healthy Females at Supratherapeutic Doses Achieved by a Progressive 1-to 3-Day Titration

Investigators: This single-center study includes 1 principal investigator.
Study Centers: There is 1 study center.
Dates of Study: September 2003- ongoing
Clinical Phase: Phase 1
Objectives:

- To assess the safety and tolerance of duloxetine at doses up to 200 mg BID when administered to healthy women.
- To assess the feasibility of alternative dose titration schedules for duloxetine
- To assess steady-state exposure to duloxetine at the highest dose tolerated.

Methodology: Open-label Dose-Escalation Study.
Number of Subjects: 12 Females
Diagnosis and Inclusion Healthy females subjects
Dosage and Administration: Test Product: Duloxetine HCL

Subjects will be escalated up to a target duloxetine dose of 200 mg BID according to the following planned schedule:

duloxetine 60 mg BID x 1-3 days, duloxetine 120 mg BID x 1-3 days,
duloxetine 160 mg BID x 4 days, and finally,
duloxetine 200 mg BID x 3½ days

CT 505844: Duloxetine capsules, 20 mg
CT 505845: Duloxetine capsules, 30 mg

Duration of Treatment: 14 Days

Criteria for Evaluation: Safety—Safety parameters include adverse events, vital signs, electrocardiograms and clinical laboratory tests.

Statistical Methods: Pending study completion
Publications Based on the Study: Pending study completion

Summary and Conclusions:

Preliminary review of data revealed that although the limits of tolerability may have been reached, no clinically significant safety concerns, and no serious adverse events have been reported. One subject decided to discontinue due to tremulousness and dizziness. Two subjects were discontinued by the investigator due to hypotension and dizziness. One subject did complete the study but did not complete the 200-mg dose level due to hypertension and ECG changes.

4.3.5 SBCG – Tolerability and safety of 40 and 100 mg duloxetine BID given over 7 days in healthy female subjects. A randomized, placebo-controlled double-blind tiral

Abbreviated Clinical Study Synopsis: Study F1J-BI-SBCG

Name of Sponsor Company:

Name of Active Ingredient: Duloxetine Hydrochloride

Title of Study: Tolerability and safety of 40 mg and 100 mg duloxetine BID given over 7 days in healthy female subjects. A randomised, placebo-controlled double-blind trial.

Investigator(s): This single-center study included one principal investigator, Dr —
Study Center(s): This study was conducted at 1 study center.
Publication(s) Based on the Study: There are no publications as of 01 October 2003.

Length of Study:
Date of first subject enrolled: 17 June 2003
Date of last subject completed: 04 August 2003

Phase of Development: 1

Objectives: To assess the safety and tolerability of 100 mg of duloxetine BID compared to 40 mg of duloxetine BID or placebo for 7 days.
Methodology: Treatment with 40 mg or 100 mg duloxetine BID or placebo was assessed in a parallel design

Number of Subjects:
Planned: 32 subjects (40 mg [12]; 100 mg [12]; placebo [8])
Randomized: 32 subjects
Completed: 26 subjects

Diagnosis and Main Criteria for Inclusion: Healthy female subjects as determined by results of screening. Signed written informed consent in accordance with GCP and local legislation. Age ε40 years . BMI ≥18.5 and ≤29.9 kg/m2
Test Product, Dose and Mode of Administration: Duloxetine to 20 mg capsules, 5 capsules twice daily given orally or Duloxetine 20 mg, 2 capsules twice daily and 3 capsules placebo twice daily given orally
Duration of Treatment: 7 days
Reference Therapy, Dose and Mode of Administration: Placebo given orally.

Criteria for Evaluation:
Safety: This abbreviated report for the study does not include any analyses of safety.
Statistical Methods: No analyses have been completed for this abbreviated study report.
Summary and Conclusions: As of 01 October 2003 no serious adverse events or deaths have occurred.

4.3.6 SBAZ - PK study of duloxetine in Japanese and Caucasian subjects

This study was submitted on 12/22/03 to the NDA 21-427, and reviewed by Dr. R. Kavanagh.

4.3.7 HMAX(a) – Report Amendment Summary – single dose pharmacokinetics of duloxetine in patients with Cirrhosis compared with healthy subjects

Overview

The overall changes and rationale for the changes made to this study report are as follows:

Error in the concentration axis of Figure HMAX.13.2 in Section 13 of main report, which illustrates simulated plasma concentration-time profiles of duloxetine given once daily to cirrhotic and healthy subjects. According to note-to-file created for the report, this error likely resulted from a misspecified dosing input when using WinNonlin Pro (Version 3.1) to perform nonparametric superposition. The simulations of duloxetine concentration-time profiles have been corrected by re-running this program with an adequate dosing input. The comparisons between the original and corrected curves indicate that this error does not affect the overall conclusions of the study report.

Revised Study Report Sections

Revised from :

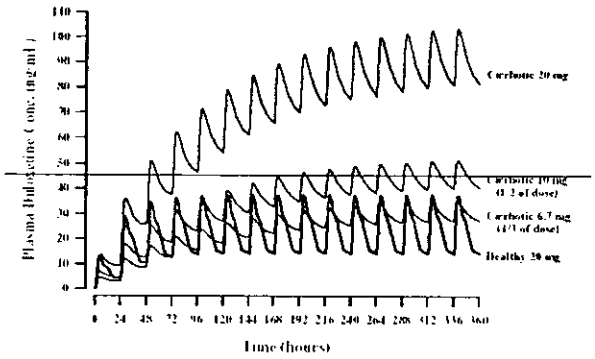


Figure HMAX.13.2. Simulations of duloxetine plasma concentration-time curves following QD administration of full (20 mg), half (10 mg), and one-third (6.7 mg) duloxetine dose for a typical cirrhotic subject compared to a 20 mg QD concentration profile for a typical healthy subject.

Revised to :

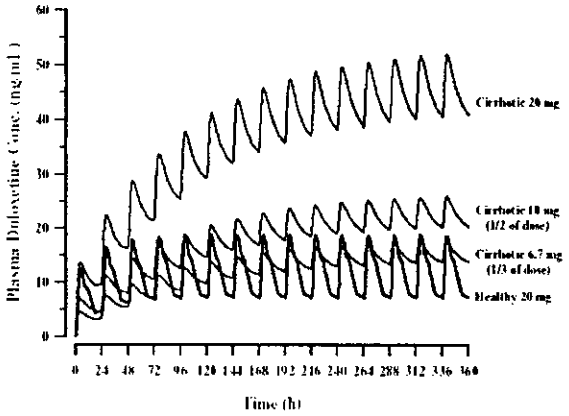


Figure HMAX.13.2. Simulations of duloxetine plasma concentration-time curves following QD administration of full (20 mg), half (10 mg), and one-third (6.7 mg) duloxetine dose for a typical cirrhotic subject compared to a 20 mg QD concentration profile for a typical healthy subject.

4.3.8 Pooled Population pharmacokinetic analysis for studies: HMAQ, HMAU, HMAVa, and SAAW.—Renal PK datasets

Summary

Population pharmacokinetic techniques were used to evaluate duloxetine pharmacokinetics in patients with urinary incontinence, major depression, and painful diabetic neuropathy. Pharmacokinetic, demographic and laboratory data were combined from four clinical trials: F1J-MC-HMAQ (Duloxetine Versus Placebo in the Treatment of Major Depression), F1J-MC-HMAU (Long-Term Open-Label Treatment with Duloxetine Hydrochloride for Evaluation of Safety in Major Depression), F1J-MCHMAV(a) (Duloxetine Versus Placebo in the Treatment of Patients with Painful Diabetic Neuropathy), and F1J-MC-SAAW (Duloxetine Versus Placebo in the Relief of Stress Incontinence). Patients in these studies received duloxetine doses ranging from 20 mg QD to 60 mg BID. The objectives of the population pharmacokinetic analysis were to characterize the pharmacokinetics of duloxetine in these patient populations, to examine the effect of mild and moderate renal impairment on the disposition of duloxetine, and to identify patient factors that influence duloxetine pharmacokinetics.

Methods

A population pharmacokinetic model was developed for duloxetine by fitting the concentration-time data using NONMEM and PREDPP. A one-compartment structural model was used. Patient factors of clinical and demographic importance were identified *a priori* and their influence on the model parameters was evaluated. Potentially

significant factors were added to the base model in combination to develop a full model. Subsequently, patient factors in the full model were removed individually so that a final model retaining significant patient factors could be developed. The final model was evaluated using parameter sensitivity and leverage analyses.
The influence of estimated Cockcroft-Gault creatinine clearance (CGCL) on duloxetine disposition was evaluated on both the base and final pharmacokinetic models by estimating duloxetine clearance separately for patients classified as having normal (CGCL >90 mL/min), mildly impaired (CGCL >60 – 90 mL/min), and moderately impaired (CGCL >30 – 60 mL/min) renal function. Bootstrap analyses were performed to calculate confidence intervals for the resulting parameter estimates.

Results and Discussion

A one-compartment model with first-order absorption adequately described duloxetine pharmacokinetics in these study populations. The model incorporated inter-patient variability on both apparent clearance (CL/F) and apparent volume of distribution (V/F). A combined additive/proportional residual error model was used.
The base model estimated the typical value of CL/F and V/F to be 53.7 L/hr and 1260 L, respectively. Inter-patient variability was large for both CL/F (64.8%) and V/F (117%).

Four covariates with significant influence on duloxetine disposition were retained in the final model: Gender, smoking status, dose, and age. The model incorporated the effects of gender and smoking status on duloxetine bioavailability, and duloxetine dose and patient age on CL/F. The inclusion of these covariates in the model reduced inter-patient variability in duloxetine CL/F to 54.3%, and inter-patient variability in V/F to 100%.
Gender and smoking status both had statistically significant effects on duloxetine pharmacokinetics. These effects were parameterized as changes in duloxetine bioavailability. Male patients were estimated to have 44.1% lower bioavailability than female patients; increasing CL/F by 79%. Smokers were estimated to have 31.8% lower bioavailability than non-smokers; increasing CL/F by 47%. Thus, on average, female patients and non-smokers are predicted to have higher duloxetine concentrations than are male patients or smokers receiving a similar dose. Nonetheless, because of large interpatient variability, there is substantial overlap in the range of possible concentration values across patients of different genders or smoking status.
Duloxetine dose significantly influenced CL/F, with CL/F decreasing with increasing daily dose over the dose range investigated. As daily dose increased from 20 mg to 120 mg, the predicted CL/F for a female non-smoker decreased 23% from 49.0 to 37.8 L/hr. Similarly, the predicted CL/F decreased with advancing age. As age increased from the mean of 48 years to the maximum of 84 years, the predicted duloxetine CL/F for a female non-smoker decreased 35% from 51.1 to 33.1 L/hr.
Overall, the combined effects of gender, smoking, age, and dose reduced inter-patient variability in CL/F from 64.8% in the base model to 54.3% in the final model. Unidentified inter-patient variability in CL/F remained substantial, and intra-patient variability remained high (30.1%). Thus, specific dose recommendations based upon these patient factors are not likely to be clinically relevant and do not appear to be warranted.
When evaluated using the final pharmacokinetic model, the 95% confidence intervals for

CL/F estimates from the normal, mild, and moderate renal function categories were 47.4 to 59.0 L/hr, 45.2 to 55.8 L/hr, and 45.9 to 59.1 L/hr, respectively. These results show essentially no difference in CL/F between renal function categories and a substantial overlap in estimated CL/F values.

The results of this analysis suggest that duloxetine can be administered to patients being treated for urinary incontinence, major depression, or painful diabetic neuropathy without regard to age, gender, or smoking status over the dose range of 20 mg QD to 60 mg BID. Furthermore, no dosage adjustment is necessary when administering duloxetine to patients with mild or moderate degrees of renal impairment.

Brief Overview of Studies

F1J-MC-HMAQ

Study F1J-MC-HMAQ (HMAQ) was a Phase 2, multicenter, double-blind, randomized, placebo-controlled trial consisting of two identical studies (A and B) done in parallel. Following a screening period, enrolled patients were randomly assigned to receive duloxetine 20 mg to 60 mg BID, fluoxetine 20 mg QD, or placebo during a 10-week period of double-blind active treatment. Appendix 1.a provides the protocol containing the inclusion/exclusion criteria. A total of 367 (A: 173; B: 194) patients were enrolled by multiple investigators in the United States and 152 (A: 70; B: 82) of them were randomized to the duloxetine treatment group. The primary objective was to demonstrate that duloxetine 20 mg to 60 mg BID was superior to placebo in the acute treatment of patients with major depression as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Secondary objectives included the characterization of population pharmacokinetics of duloxetine.

F1J-MC-HMAU

Study F1J-MC-HMAU (HMAU) was a Phase 3, multicenter, long-term, open-label trial of outpatients meeting DSM-IV criteria for major depressive disorder. A total of 1000 patients were to be enrolled, with the intention of having ε300 patients complete 6 months of treatment and ε100 patients complete 12 months of treatment. Interim data were available from 1282 patients enrolled by multiple investigators in Argentina, Brazil, Canada, Colombia, Mexico, Venezuela, and the United States. Appendix 1.b provides the protocol containing the inclusion/exclusion criteria. The initial dose of duloxetine was 40 mg BID. The subsequent dose could be adjusted to 20 mg BID (through Visit 4), 40 mg BID, or 60 mg BID based upon the investigator's clinical evaluation of tolerability and efficacy. The primary clinical objective of this study was to evaluate the safety of duloxetine 40 mg BID to 60 mg BID for up to 52 weeks in patients diagnosed with major depressive disorder. Secondary objectives included the characterization of population pharmacokinetics of duloxetine.

F1J-MC-HMAV(a)

Study F1J-MC-HMAV (HMAV) was a Phase 3, multicenter, double-blind, randomized, placebo-controlled trial consisting of two parallel studies (a and b) each enrolling approximately 330 patients with painful diabetic neuropathy. Following a screening period, enrolled patients were randomly assigned to receive duloxetine 60 mg QD, duloxetine 60 mg BID, or placebo during a 13-week period of double-blind active treatment. Appendix 1.c provides the protocol containing the inclusion/exclusion criteria.

A total of 334 patients were enrolled by multiple investigators in the United States and 226 of them were randomized to the duloxetine treatment groups. The primary objective was to assess the efficacy of duloxetine compared with placebo on the reduction of pain severity in patients with painful diabetic neuropathy. A secondary objective of the study was to evaluate steady-state plasma concentrations of duloxetine in patients receiving 60 mg BID and 60 mg QD.
At the time of this report, HMAV(a) had been completed and data from this phase are included in this population pharmacokinetic analysis. HMAV(b) is ongoing, so data are not yet available from patients participating in that phase of the study.

F1J-MC-SAAW

Study F1J-MC-SAAW (SAAW) was a Phase 2, multicenter, double-blind, placebocontrolled, randomized study of the efficacy of duloxetine in the treatment of stress urinary incontinence. After the screening period, patients were randomly assigned to receive duloxetine at 20 mg QD, 20 mg BID, 40 mg (escalated from 20 mg) BID, or placebo during a 12-week, double-blind active therapy treatment period. A total of 553 female patients were enrolled by multiple investigators in the United States. Approximately one-fourth of these patients were randomly assigned to placebo (n=138), one-fourth to duloxetine 20 mg QD (n=138), one-fourth to duloxetine 20 mg BID (n=137), and one-fourth to duloxetine 40 mg BID (n=140). The inclusion/exclusion criteria can be found in the protocol (Appendix 1.d).
The primary clinical objective of this study was to compare the efficacy, as determined by incontinence episode frequency, of duloxetine with that of placebo in the treatment of stress urinary incontinence. Secondary objectives included the characterization of population pharmacokinetics of duloxetine.

Scope and Rationale of Pharmacokinetic Analysis

The primary objective of this analysis was to examine the effect of mild and moderate renal impairment on the disposition of duloxetine by evaluating the influence of estimated Cockcroft-Gault creatinine clearance on the pharmacokinetic parameters. Other patient factors of clinical and demographic importance, which might affect the pharmacokinetics of duloxetine, were also identified *a priori*. The population approach allowed the influence of these factors on duloxetine pharmacokinetics to be evaluated. Appendix 2 provides an analysis plan outlining all population pharmacokinetic analyses. The data used in the analysis were obtained from four studies. Sparse blood sampling from (a) all duloxetine-treated patients in HMAQ, (b) a prospectively defined subset of duloxetine-treated patients (those enrolled in one study site in Colombia and two study sites in Mexico) in HMAU, (c) specific investigator sites in HMAV(a), and (d) specific sites in SAAW were used to evaluate the pharmacokinetics of duloxetine using population techniques. Data from Study HMAV(a) were pooled with previously analyzed data from Studies HMAQ, HMAU, and SAAW in order to include pharmacokinetic observations from patients with the widest available range of renal function values.

Objectives

The objectives of the pooled population pharmacokinetic analysis were to:
. characterize the pharmacokinetics of duloxetine in patients with urinary incontinence, major depression, and painful diabetic neuropathy,
. examine the effect of mild and moderate renal impairment on the disposition of duloxetine,
. identify other patient-specific factors that influence the disposition of duloxetine.

Summary of Study Designs

Study HMAQ consisted of three periods: a screening phase (2 to 10 days), a doubleblind-active-therapy phase (10 weeks), and a no-study-drug phase (7 days). Patients were screened at Visit 1 and those qualified for entry were randomized to one of three treatment groups: fluoxetine 20 mg QD, duloxetine 20 mg to 60 mg BID, or placebo. During the active therapy phase, patients were allowed to begin receiving study medication as early as Visit 2 or as late as Visit 4 and continued up to Visit 12 for a maximum of 10 weeks. Pharmacokinetic sampling was conducted at Visits 4, 6, 8, 10, 12, and early discontinuation.

Study HMAU consisted of three periods: a screening phase (3 to 8 days), an open-label therapy phase (52 weeks), and a no-study-drug phase (2 weeks). Patients were screened at Visit 1 and those qualified for entry began taking duloxetine 40 mg BID during the open-label therapy phase. Patients unable to tolerate the initial dose could have their dose decreased to 20 mg BID up to Visit 4. At any point after Visit 4, patients who could not tolerate a minimum dose of 40 mg BID were discontinued from the study. In order to optimize antidepressant therapy, the patient's dose could be adjusted up to 60 mg BID or down to 40 mg BID, based on the investigator's clinical evaluation of tolerability and efficacy. Pharmacokinetic sampling was conducted at Visits 3, 4, 5, 6, 13, and early discontinuation.

Study HMAV(a) consisted of three periods: a screening period (2 to 3 weeks), an acute therapy period (13 weeks), and an open-label extension period (52 weeks). Patients were screened at Visit 1 and those qualified for entry were randomized to one of three treatment groups: duloxetine 60 mg QD, duloxetine 60 mg BID, or placebo. Pharmacokinetic sampling was conducted during the acute therapy period, at Visits 6, 8, 10, and early discontinuation.

Study SAAW consisted of three periods: a screening period (including a 2-week no-drug lead-in period followed by a 2-week placebo lead-in period), a double-blind, active treatment period (12 weeks), and a de-escalation period (4 weeks). Patients were screened at Visits 1 and 2 and those who were qualified to continue were randomly assigned to one of four treatment arms: 20 mg QD duloxetine, 20 mg BID duloxetine, duloxetine dose escalation from 20 mg BID (1 week) to 30 mg BID (1 week) to 40 mg BID (10 weeks), or placebo. There was a post-treatment period of 4 weeks to allow for dose de-escalation, then patients returned for a follow-up at Visit 7. Pharmacokinetic sampling was conducted at Visits 3, 4, 5, 6, and early discontinuation.

Doses and Formulations

F1J-MC-HMAQ

Study medication dispensed in this study consisted of the following:
. capsules containing duloxetine 10-mg and 20-mg as enteric-coated pellets,
. placebo identical in appearance to duloxetine capsules,
. fluoxetine 20-mg capsules,
. placebo identical in appearance to fluoxetine capsules.
Patients were instructed to take four capsules at approximately the same time (± 1 hour) upon arising in the morning and three capsules at least 1 hour before dinner in the evening every day. No dosage reduction of study medication was allowed.

F1J-MC-HMAU

Study medication dispensed in this study was duloxetine 20-mg capsules containing enteric-coated pellets. Patients began therapy with 40 mg BID by taking two capsules in the morning and two capsules in the evening. Patients who needed dose reduction prior to or at Visit 3 took one capsule in the morning and one capsule in the evening. At Visit 4 and thereafter, patients took three capsules in the morning and three capsules in the evening when their dosage was adjusted to 60 mg BID. Dose adjustments were based on the physician's clinical evaluation of tolerability and efficacy.

F1J-MC-HMAV(a)

Study medication dispensed in this study was duloxetine 30-mg capsules containing enteric-coated pellets, and placebo identical in appearance to duloxetine capsules. Patients randomized to all treatment groups were instructed to take two capsules of study drug every morning and two capsules of study drug every evening. Patients in the duloxetine treatment group who were unable to tolerate 60 mg BID, per the clinician's judgment, may have been dose-reduced to 60 mg QD.

F1J-MC-SAAW

Study materials were capsules containing 10 mg or 20 mg of duloxetine as enteric-coated pellets and placebo capsules indistinguishable from duloxetine capsules. The duloxetine and/or placebo capsules were administered following a twice-daily schedule. Patients randomized to the 20-mg QD dose received one placebo and one 20-mg duloxetine capsule in the morning and two placebo capsules in the afternoon. Patients randomized to the 20-mg BID dose received one placebo and one 20-mg duloxetine capsule for the AM and PM doses. Patients randomized to the 40-mg BID dose received their AM and PM doses as follows:
. one placebo and one duloxetine 20-mg capsule at 20 mg BID (Week 1 of the Visit 3 to 4 interval),
. one 10-mg and one 20-mg duloxetine capsule at 30 mg BID (Week 2 of the Visit 3 to 4 interval),
. two 20-mg duloxetine capsules at 40 mg BID (Week 3 of the Visit 3 to 4 interval and Visits 4 through 6).
Patients randomized to placebo received two placebo capsules twice-a-day.
The clinical study reports for each of these four studies contain listings of dosage form lot

numbers for all clinical trial material.

Sample and Data Collection

Biological Sampling

Sparse sampling strategies were included in the study designs of each of the four studies. Blood samples were collected from patients for determination of duloxetine concentrations in plasma. The actual time of blood sampling and the patient-reported time of the two prior doses of study drug were recorded. Each study site was provided with laboratory kits and detailed instructions for collecting blood samples for shipment to the central laboratory. For some studies, only certain study sites or investigators participated in the collection of these biological samples. These specific sites and investigators were identified by study coordinators as those capable of performing the procedures necessary to collect and process blood samples.

F1J-MC-HMAQ

For patients enrolled in HMAQ, a single blood sample was collected at each of Visits 4, 6, 8, 10 and 12, as well as early discontinuation. Up to five samples were allowed from each patient.

F1J-MC-HMAU

For the prospectively defined sites in Study HMAU (1 in Colombia and 2 in Mexico), pharmacokinetic sampling occurred at Visits 3, 4, 5, 6, 13 and early discontinuation. A single blood sample was collected at Visits 3, 5, 13 and early discontinuation. Two blood samples were collected at Visits 4 and 6, but a patient could refuse the second draw without constituting a protocol violation. Up to seven samples were allowed from each patient.

F1J-MC-HMAV(a)

Pharmacokinetic sampling was performed during the acute therapy period (Study Period II). A maximum of three blood samples were collected from each duloxetine-treated patient: one sample at Visits 6, 8, and 10 or early discontinuation.

F1J-MC-SAAW

One blood sample was obtained at Visits 4, 5, and early discontinuation in Study SAAW. Two blood samples were obtained at Visits 3 and 6.

Data Assembly and Editing

Duloxetine plasma concentrations were combined with dosing information and demographic/laboratory data (for example, age and body weight) using SAS. to produce datasets for the nonlinear mixed-effects modeling program (NONMEM, Version V). The NONMEM datasets from each study were then combined using S-PLUS 6 for UNIX. Appendix 4 provides definitions of the variables used in the pooled NONMEM dataset. The actual time of drug administration on the day of blood sample collection was

recorded by patient self-report or by study personnel. Patients were also asked to provide the date and time of the previous two doses prior to each blood draw. Dose records were created in the NONMEM datasets corresponding to these actual dosing times, assuming that patients followed the protocol designs and took their study medication as instructed throughout each study.

Figure 8.1 provides a summary of data disposition. The datasets received from [redacted] contained 2279 bioanalytical results from 588 patients. Since 461 observations (approximately 20%) were below the quantitation limit of the assay, there were 1818 quantifiable duloxetine concentrations from 483 patients. In addition, 51 observations with quantifiable duloxetine concentrations were omitted from the NONMEM dataset due to a lack of adequate dosing and sample date/time information essential to pharmacokinetic analysis. As a result, 1767 duloxetine concentrations from 463 patients were included in the NONMEM dataset. Appendix 5 contains the concentration records omitted from the analysis.

Population Pharmacokinetic Modeling Strategy

A population pharmacokinetic model was developed for duloxetine by fitting the concentration-time data using NONMEM and PREDPP. Figure 8.2 illustrates the general process for the development of a population pharmacokinetic model. The final mixedeffects model was used to characterize patient factors influencing duloxetine disposition and to provide individual estimates of duloxetine exposure.

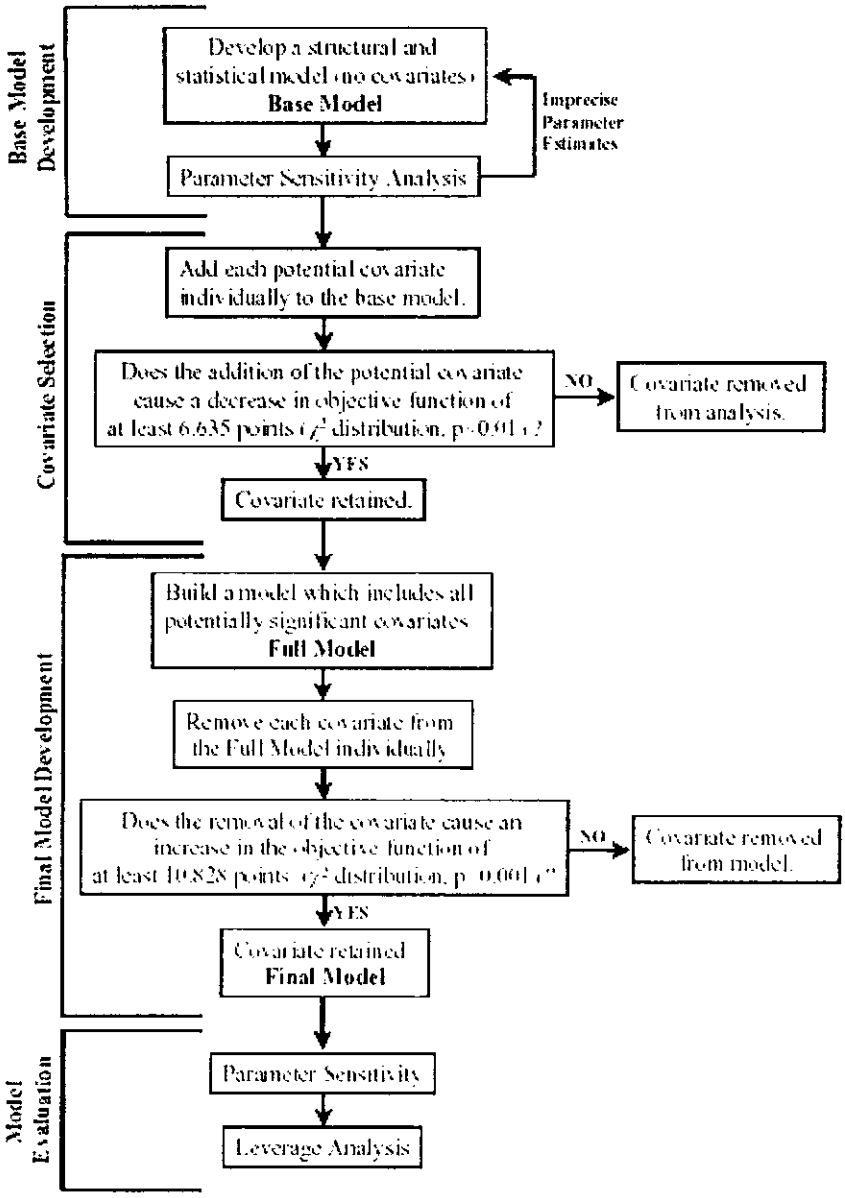


Figure 8.2. General process for pharmacokinetic model development. Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

Pharmacostatistical Model Development

Base Model Development

One-compartment models were systematically evaluated to identify the model that best described duloxetine pharmacokinetics in patients with major depression, urinary incontinence, and painful diabetic neuropathy. The First Order Conditional Estimation (FOCE) method with interaction estimation was used (Beal and Sheiner 1992).

One-compartment models were parameterized in terms of the absorption rate (Ka), CL/F, and V/F. Data analyses were conducted using the PREDPP subroutines ADVAN2 and TRANS2. Three inter-patient variability ( ) models were tested: 1) on CL/F, 2) on CL/F and V/F, and 3) on CL/F and V/F with covariance (omega block). With each assessment of inter-patient variability, two residual error (Σ) models were evaluated: 1) proportional, and 2) combined additive and proportional.
Parameter sensitivity analyses were performed on the final selected base model (Section 8.3.1.4) to ensure that all pharmacokinetic parameters were well estimated.

Covariate Model Development

Table 8.1 includes patient factors examined as potential covariates in the pharmacokinetic analysis. Continuous covariates were tested for influence on CL/F and V/F using linear, exponential, and power models as shown in Equations 3 through 5. Gender, origin, study code, smoking status, and alcohol use were tested for influence on CL/F and V/F using a categorical model, as shown in Equation 6. Gender, smoking status, and dose were also evaluated for influence on duloxetine bioavailability.

Linear Model $P = \cup 1 \cdot (1 + \cup 2 \cdot (COV-MEAN))$ Eq. 3
Exponential Model $P = \cup 1 \cdot EXP(\cup 2 \cdot (COV-MEAN))$ Eq. 4
Power Model $P = \cup 1 \cdot (COV/MEAN)^{\cup 2}$ Eq. 5
Categorical Model $P = \cup 1 \cdot (1 + \cup 2 \cdot IND)$ Eq. 6
where P is the individual's estimate of a parameter, $\cup 1$ represents the typical value of a parameter, $\cup 2$ represents the effect of a covariate, COV is the value of a covariate, and MEAN is the population mean of a covariate. IND is an indicator variable with a value of either 0 or 1 assigned for values of a categorical covariate (for example, smoker and non-smoker).
Potentially significant covariates were identified as those which, when added to the base model individually, decreased the objective function ε6.635 points ($p<0.01$).

Table 8.1. Patient Factors Assessed in the Population Pharmacokinetic Analysis Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

Age	Duloxetine dose
Body weight	Cockcroft-Gault creatinine clearance
Gender	Total bilirubin
Origin	Gamma-glutamyl transferase (GGT)
Smoking status (yes/no)	Alanine transaminase (ALT/SGPT)
Alcohol Use (yes/no)	Aspartate transaminase (AST/SGOT)
Study code	Serum creatinine

Final Model Development

Potentially significant covariates were added to the base model in combination to establish a full model containing all possible covariates. The process was then reversed, with potential covariates being removed individually from the full model. Covariates retained in the final model were those resulting in a significant increase in the minimal value of the objective function (MOF) (ε10.828 points, 1 degree of freedom, $p<0.001$), when removed from the full model.

Model Evaluation

The methodologies used to evaluate the robustness of the final population pharmacokinetic model are summarized below.

Parameter Sensitivity Analysis

Parameter sensitivity analysis examines the overall shape of the parameter space, confirms the absence of local minima, and identifies 95% confidence intervals using a process developed at Eli Lilly and Company (Allerheiligen et al. 1994; O'Brien et al. 1998). The analysis was performed by fixing the parameter of interest to ± 5%, 10%, 15%, 20%, 30%, and 40% of the population estimate and allowing NONMEM to estimate all other parameters. Changes in the objective function were used to assess the effect of altering the parameter value on the overall fit of the plasma concentration versus time data. The curve produced by the objective function versus parameter value relationship was fit using polynomial regression to obtain a 95% confidence interval. Assuming a chi-square distribution, the values which produce a change in the objective function of 3.841 points represent the 95% confidence limits for that parameter.

Leverage Analysis

The leverage analysis technique was designed to evaluate the contribution or "leverage" of selected patients on the model using a process developed at Eli Lilly and Company (Allerheiligen et al. 1994, O'Brien et al. 1998). For each of 10 runs from a single leverage analysis, a subset of 10% of the patients are randomly omitted such that each patient is omitted from the analysis exactly once. The final model is run using the remaining 90% of the data. This procedure was performed twice with different subsets of the patients omitted. The parameter estimates from all runs were compared with the 95% confidence intervals calculated in the parameter sensitivity analysis.

Evaluation of Renal Function

Estimated creatinine clearance was evaluated as both a continuous and categorical covariate. The criteria used to categorize the state of a patient's renal function is shown below (Table 8.2).

Table 8.2. Renal Impairment Classification Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

Renal Function	Cockcroft-Gault Creatinine Clearance (mL/min)
Normal	>90
Mild Impairment	>60 - 90
Moderate Impairment	>30 - 60
Severe Impairment	≤30

The effect of creatinine clearance on duloxetine CL/F was also evaluated on the final model after all other significant covariate effects had been incorporated.

A bootstrap analysis was performed on both the single covariate and full model creatinine clearance parameters to obtain 95% confidence intervals for the parameter estimates. This procedure was carried out using S-PLUS 6 for UNIX, using random re-sampling

with replacement to create 500 bootstrap dataset replicates. The confidence intervals calculated from the bootstrap analysis were used to assess the power of this analysis to detect a relationship between creatinine clearance and the disposition of duloxetine.

Pharmacokinetic Results

Patient Characteristics

The pharmacokinetic evaluation included data from 463 patients given duloxetine 20 mg QD, 20 mg BID, 30 mg BID, 40 mg BID, 60 mg QD, or 60 mg BID on different occasions. Table 9.1 and Table 9.2 provide summaries of patient demographics at study entry. Appendix 7 provides histograms depicting patient characteristics (for example, distribution of age) and laboratory values for those patients included in the pharmacokinetic analysis.

Table 9.1. Summary of Baseline Demographics for Patients Included in the Pharmacokinetic Evaluation Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

Study Code	Age (year)	Weight (kg)	CGCL (mL/min)
HMAQ			
Range	18.7 – 62.7	42.7 – 138	49.8 – 189
Mean (CV%)	41.1 (24.6)	82.4 (23.3)	94.5 (27.5)
n [a]	142	142	142
HMAU			
Range	18.7 - 70.7	45.0 - 110	30.0 – 119
Mean (CV%)	43.9 (29.4)	65.2 (20.6)	72.9 (23.4)
n [a]	81	81	81
HMAV(a)			
Range	31.7 – 84.2	56.8 - 188	29.9 285
Mean (CV%)	59.5 (18.2)	102 (22.8)	91.5 (41.4)
n [a]	112	112	112
SAAW			
Range	28.0 – 64.0	50.8 – 150	40.7 - 185
Mean (CV%)	49.3 (16.3)	78.0 (21.3)	83.0 (27.9)
n [a]	128	128	128
Overall			
Range	18.7 - 84.2	42.7 – 188	29.9 – 285
Mean (CV%)	48.3 (25.9)	82.9 (27.0)	86.8 (32.8)
n [a]	463	463	463

Abbreviations: CGCL = Cockcroft-Gault creatinine clearance, CV = coefficient of variation.
a n = Number of patients included in the pharmacokinetic analysis.

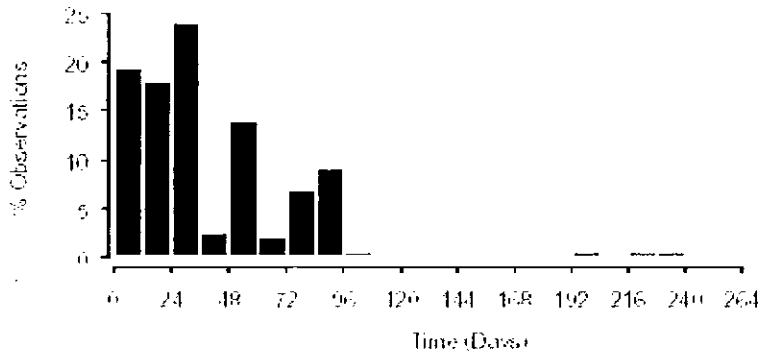
Table 9.2. Summary of Baseline Demographics for Patients Included in the Pharmacokinetic Evaluation Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

Demographic	Category	Number of Patients				
		HMAQ	HMAU	HMAV(a)	SAAW	Overall
Gender	Female	94	56	43	128	321
	Male	48	25	69	0	142
Smoking Status [a]	No	106	54	95	108	363
	Yes	36	26	17	19	98
Alcohol Use [b]	No	60	63	85	50	258
	Yes	82	17	27	78	204
Origin	Caucasian	125	0	97	118	340
	African Descent	9	0	3	4	16
	Hispanic	5	81	7	2	95
	Western Asian	1	0	2	0	3
	Eastern Asian	2	0	0	4	6
	Other	0	0	3	0	3

[a] Smoking information was unavailable for Patient 2273 (Study SAAW) and Patient 5174 (Study HMAU).
[b] Information on alcohol use was unavailable for Patient 5174 (Study HMAU).

Blood Sample Collection

Blood samples were collected according to predefined schedules for each study (Section 8.1.2.1). The number of quantifiable samples per patient ranged from 1 to 7. Figure 9.1 illustrates the distribution of plasma observations obtained relative to duration of treatment (days) and time from the last dose (hours) in the NONMEM dataset. The resultant data distribution was appropriate for the estimation of population pharmacokinetic parameters.



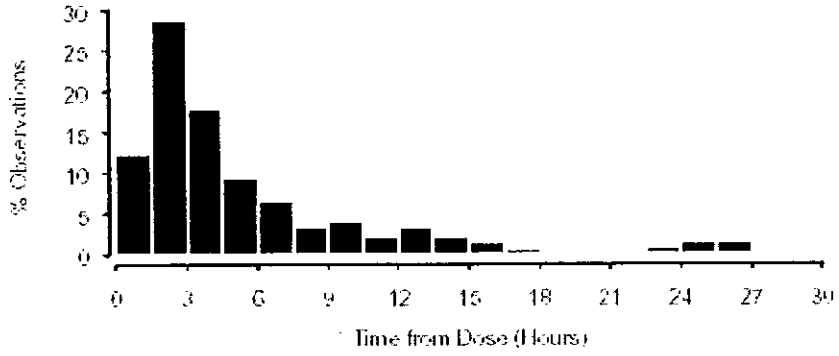


Figure 9.1. Frequency distribution of observations (plasma duloxetine concentrations) versus time on therapy (top) and time from last dose (bottom).
Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW
Twenty-five concentrations at sampling times greater than 30 hours postdose are excluded from the Time From Dose graph.

Observed Concentrations

Observed duloxetine concentrations in plasma were evaluated in patients from whom adequate concentrations, doses, dosing times, and sampling times could be obtained during duloxetine treatment. Table 9.3 summarizes observed plasma duloxetine concentrations by treatment group. Figure 9.2 and Figure 9.3 describe the time course of observed concentrations for individual patients receiving duloxetine 20 mg QD, 20 mg BID, 30 mg BID, 40 mg BID, 60 mg QD, or 60 mg BID.

Table 9.3. Observed Plasma Concentrations of Duloxetine
Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

Study Code	Dose	20 mg QD	20 mg BID	30 mg BID	40 mg BID	60 mg QD	60 mg BID
HMAQ	Mean (%CV)		30.4 (70.9%)	36.0 (107%)	65.2 (73.8%)		114 (72.0%)
	Median		26.0	24.6	52.5		90.9
	Range						
	n [a]		138	18	111		206
	N [b]		130	18	109		114
HMAU	Mean (%CV)		63.6 (46.0%)		75.7 (63.2%)		133 (52.3%)
	Median		66.8		67.1		118
	Range						
	n [a]		5		277		183
	N [b]		4		77		54
HMAV(a)	Mean (%CV)					41.6 (83.1%)	95.5 (69.8%)
	Median					33.0	86.5
	Range						
	n [a]					145	129
	N [b]					56	56
SAAW	Mean (%CV)	20.8 (87.7%)	29.9 (69.2%)		103 (71.6%)		
	Median	16.8	28.3		84.6		
	Range						
	n [a]	204	219		132		
	N [b]	47	72		37		
Overall	Mean (%CV)	20.8 (87.7%)	30.5 (70.1%)	36.0 (107%)	80.5 (71.2%)	41.6 (83.1%)	116 (64.9%)
	Median	16.9	27.6	24.6	69.1	33.0	98.1
	Range						
	n [a]	204	362	18	520	145	518
	N [b]	47	206	18	223	56	224

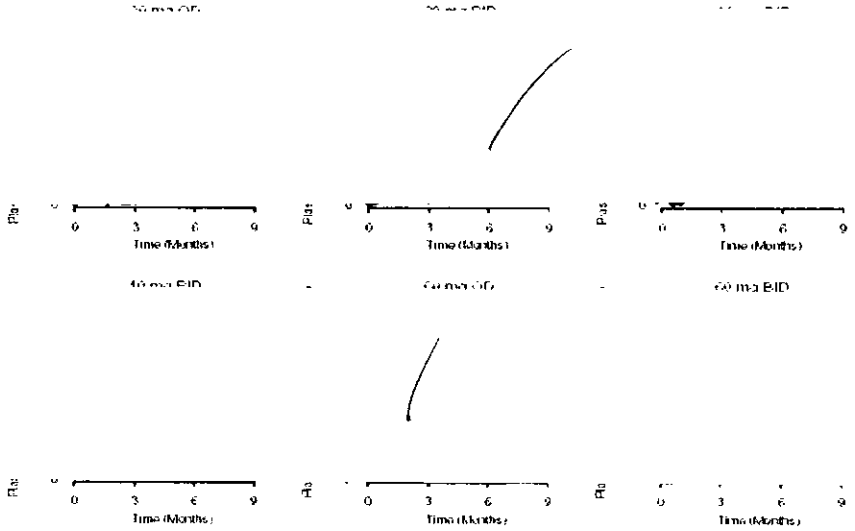


Figure 9.2. Observed plasma duloxetine concentrations versus time on therapy for individual patients.
Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

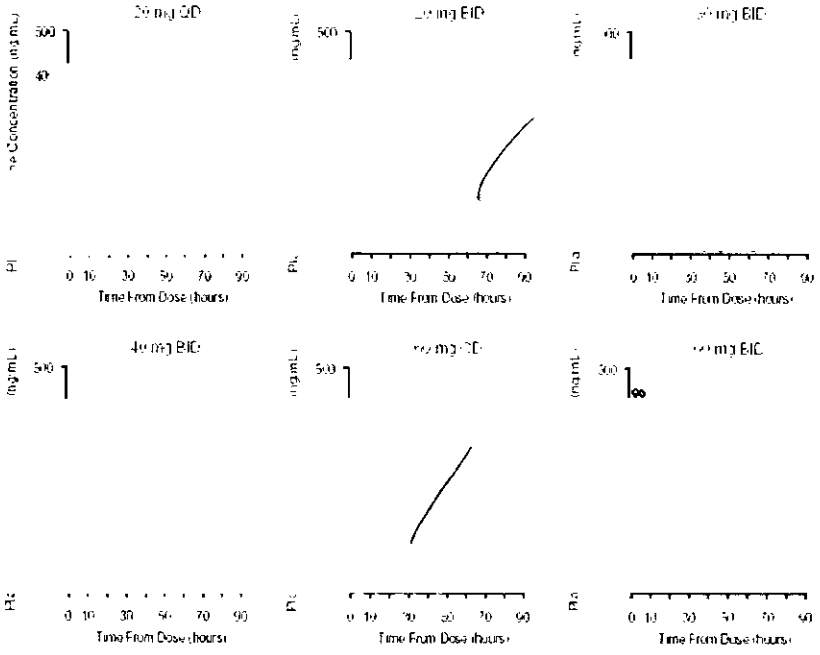


Figure 9.3. Observed plasma duloxetine concentrations versus time from the most recent dose for individual
patients. Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

Base Pharmacokinetic Model

A one-compartment model parameterized in terms of Ka, CL/F, and V/F was selected as an appropriate base structural model. Exponential terms were used to describe the interpatient variability in CL/F and V/F. An additive/proportional term was used to describe the residual error. Table 9.4 provides the parameter values in the base model.

Table 9.4. Pharmacokinetic Parameters in Base Population Model Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

	Population	Inter-patient
Parameter Description	**Estimate**	**Variability**
	(%SEE)	**(%SEE)**
Rate of Absorption		
Parameter for Ka (hr^{-1})	0.209 (12.7)	
Apparent Clearance		
Parameter for CL/F (L/hr)	53.7 (3.13)	64.8% (8.26)
Apparent Volume of Distribution		
Parameter for V/F (L)	1260 (9.37)	117% (15.1)
Residual Error		
Proportional	30.0% (8.27)	
Additive (ng/mL)	5.22	(23.9)

Abbreviations: SEE = standard error of the estimate; Ka = absorption rate constant; CL/F = apparent clearance; V/F = apparent volume of distribution; F = bioavailability.

Goodness-of-fit for this base population model is represented graphically (Figure 9.4) by the agreement between individual predicted (IPRED) and observed concentrations, as well as by individual weighted residual (IWRES) values.

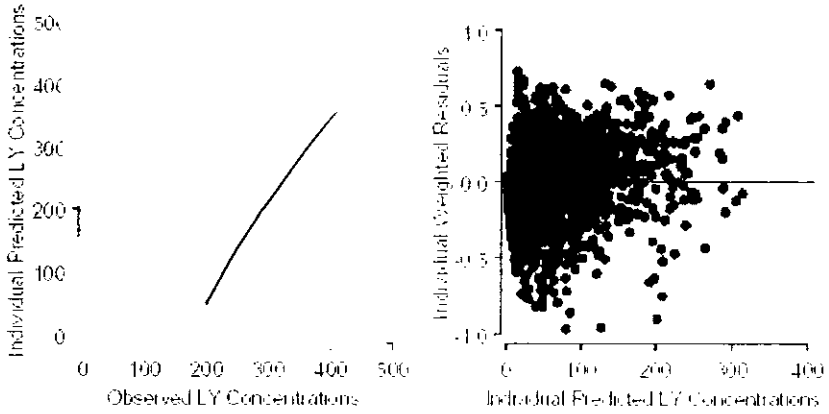


Figure 9.4. Individual predicted versus observed concentrations and individual weighted residuals versus individual predicted concentrations for base pharmacokinetic model. Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

Final Pharmacokinetic Model

Four covariates with significant influence on duloxetine disposition were retained in the final model. The model incorporated the effects of gender and smoking status on duloxetine bioavailability, and the effects of duloxetine dose and patient age on CL/F. Parameter estimates from the final population pharmacokinetic model, which accounts for the effects of these covariates, are shown (Table 9.5).

The inclusion of these covariates in the model reduced the inter-patient variability in duloxetine CL/F from 64.8% to 54.3%, and reduced inter-patient variability in V/F from 117% to 100%. Residual error did not change significantly from the base model.

Details of the model development process, covariate selection, and evaluation process are provided (Appendix 8).

Table 9.5. Pharmacokinetic Parameters in Final Population Model Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

	Population	Inter-patient
Parameter Description	**Estimate**	**Variability**
	(%SEE)	**(%SEE)**
Rate of Absorption		
Parameter for Ka (hr^{-1})	0.212 (13.5)	
Clearance		
Parameter for CL/F (L/hr)	51.6 (4.84)	54.3% (9.11)
Effect of daily dose on CL/F [a]	-0.00260 (17.9)	
Effect of age on CL/F [b]	-0.00970 (23.4)	
Volume of Distribution		
Parameter for V/F (L)	984 (12.3)	100% (18.7)
Bioavailability		
Effect of smoking status on F [c]	-0.318 (13.5)	
Effect of gender on F [d]	-0.441 (7.69)	
Residual Error		
Proportional	30.1% (8.28)	
Additive (ng/mL)	5.06	(23.0)

Abbreviations: SEE = standard error of the estimate; Ka = absorption rate constant; CL/F = apparent clearance; V/F = apparent volume of distribution; F = bioavailability.

a CL/F = 51.6 · Exp[-0.00260 · Dose]

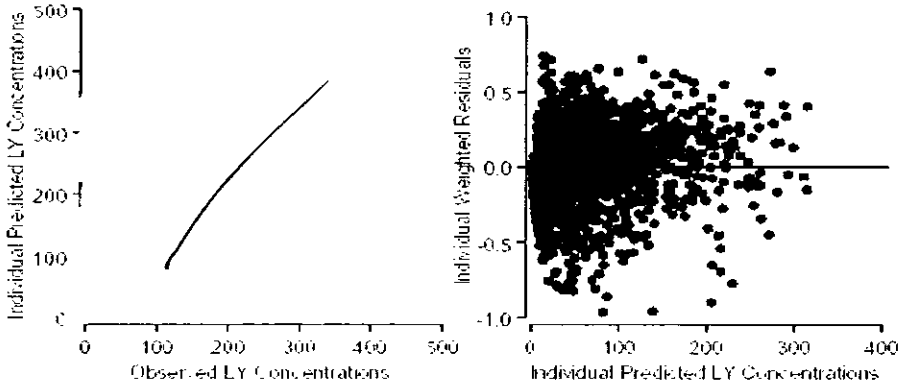
b CL/F = 51.6 · [1 - 0.00970 · (Age - 47)]

c F (smokers) = F (non-smokers) · [1 0.318]

d F (males) = F (females) · [1 – 0.441]

Goodness-of-fit for this population model is represented graphically (Figure 9.5) by the agreement between individual predicted (IPRED) and observed concentrations, as well as by individual weighted residual (IWRES) values.

Figure 9.5. Individual predicted versus observed concentrations and individual weighted residuals versus individual predicted concentrations for final pharmacokinetic model. Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW



Effects of Gender, Smoking Status, Dose, and Age on Duloxetine Pharmacokinetics

Effects of Gender and Smoking Status

Gender and smoking status both had a significant influence on duloxetine pharmacokinetics. These effects were parameterized as differences in duloxetine bioavailability. Male patients were estimated to have 44.1% lower bioavailability than female patients, while smokers were estimated to have 31.8% lower bioavailability than non-smokers. Thus, on average, female patients receiving the same duloxetine dose as male patients are predicted to have higher systemic exposure. Similarly, non-smokers are predicted to have higher exposure than smokers, on average. The predicted effect of gender and smoking status on duloxetine concentrations for typical patients is illustrated (Figure 9.6). Nonetheless, because of large inter-patient variability, there is substantial overlap in the range of possible concentration values across patients of different genders or smoking status.

Effect of Duloxetine Dose

Patients included in the pharmacokinetic evaluation received duloxetine doses ranging from 20 mg QD to 60 mg BID, resulting in a daily dose of 20 to 120 mg. Duloxetine dose had a significant influence on duloxetine CL/F, with CL/F decreasing with increasing daily dose over the dose range investigated. As daily dose increased from 20 mg to 120 mg, the predicted CL/F for a female non-smoker decreased from 49.0 to 37.8 L/hr. Thus, a 5-fold increase in daily dose resulted in a 23% decrease in CL/F. The predicted effect of dose on duloxetine concentrations for typical patients is illustrated (Figure 9.6).

Effect of Age

The patients included in this analysis ranged from 18 to 84 years of age. Age was found to have a significant influence on duloxetine CL/F, with CL/F decreasing with increasing age. As age increased from the mean value of 48 to the maximum of 84 years, the predicted duloxetine CL/F for a female non-smoker decreased from 51.1 to 33.1 L/hr. Thus, a 75% increase in age resulted in a 35% decline in CL/F. The predicted effect of age on duloxetine concentrations for typical patients is illustrated (Figure 9.6).

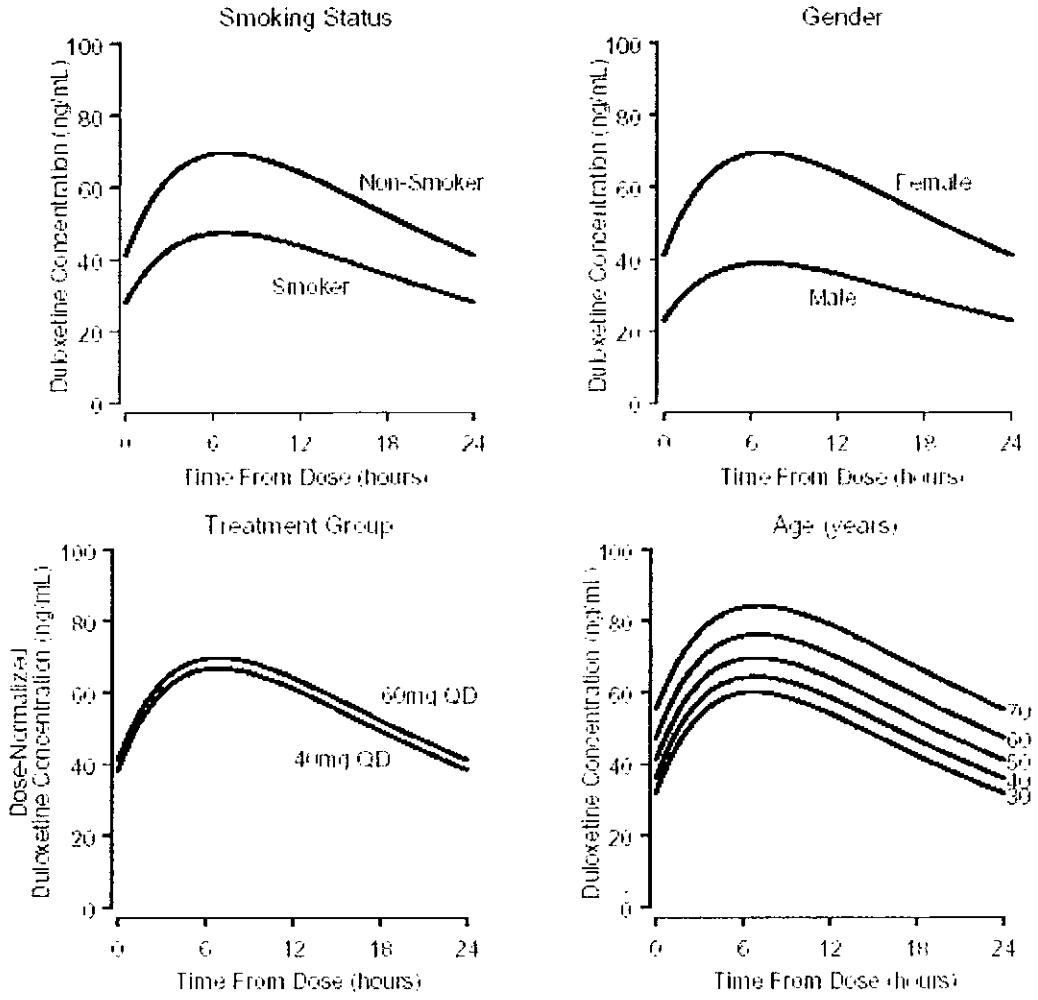


Figure 9.6. Final population pharmacokinetic model: Predicted effect of covariates on plasma duloxetine concentrations.
Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

Except where noted, steady-state duloxetine concentrations are for a 50-yearold non-smoking female receiving 60 mg of duloxetine once daily.
The 40 mg concentrations in the treatment group graph are normalized to 60 mg by multiplying concentrations by 60/40.

Variability in Duloxetine Concentrations Predicted by Final Pharmacokinetic Model

Variability in the final population pharmacokinetic model reflects the combination of inter-patient variability in pharmacokinetic parameters and intra-patient variability characterized by residual error. The predicted concentration-time profile of duloxetine, as well as the ranges of duloxetine concentrations predicted from the inter-patient and intra-patient variability terms are illustrated (Figure 9.7). For a 50-year-old female nonsmoker receiving duloxetine 60mg QD, the predicted inter-quartile ranges for maximum concentration and average steady-state concentration are 53.9 – 101 ng/mL and 41.5 – 81.9 ng/mL respectively.

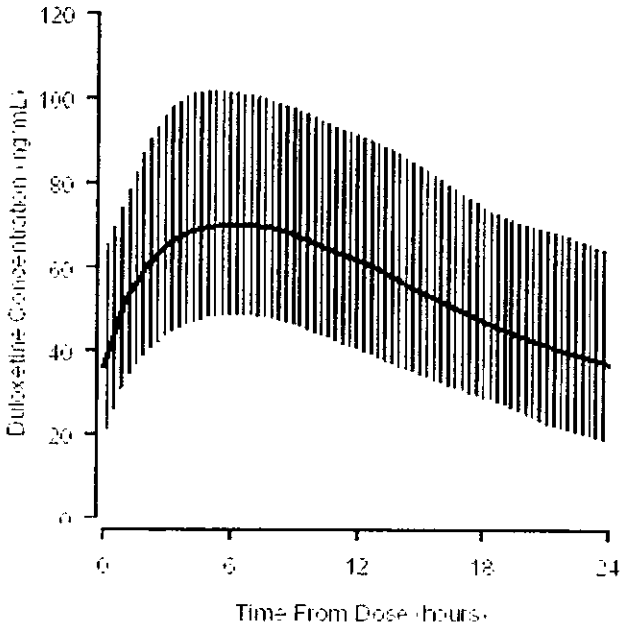


Figure 9.7. Final population pharmacokinetic model: Predicted variability of plasma duloxetine concentrations. Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

Shaded regions represents 25th and 75th percentile of duloxetine concentrations calculated from 1000 simulation iterations. Simulated steadystate concentrations are for a patient receiving 60 mg of duloxetine once daily. The patient is 50-year-old non-smoking female.

Model Evaluation

Parameter sensitivity analysis showed that all parameters were estimated with adequate precision. The leverage analysis showed that all parameter estimates from the patient subsets were within the 95% confidence intervals. No subset of the patient population had undue influence on the parameter estimates.

Evaluation of the Effect of Renal Function on the Pharmacokinetics of Duloxetine

Estimated CGCL ranged from 29.9 to 285 mL/min in this patient population. Of the 463 patients included in this analysis, 262 had CGCL values between 60 and 90 mL/min (mild renal impairment), while 89 had values between 30 and 60 mL/min (moderate renal impairment). Two patients had CGCL values below 30 mL/min (29.992 and 29.940), and were defined as moderately impaired for the purpose of this analysis. Thus, the analysis dataset contains an ample range of CGCL values to evaluate the impact of mild and moderate renal impairment on the pharmacokinetics of duloxetine.

The influence of CGCL on duloxetine disposition was first evaluated graphically by examining relationships between CGCL and individual CL/F values (empirical Bayesian estimates) from the base pharmacokinetic model (Figure 9.8 and Figure 9.9). Visual examination of these plots does not suggest a relationship between CGCL values and duloxetine CL/F.

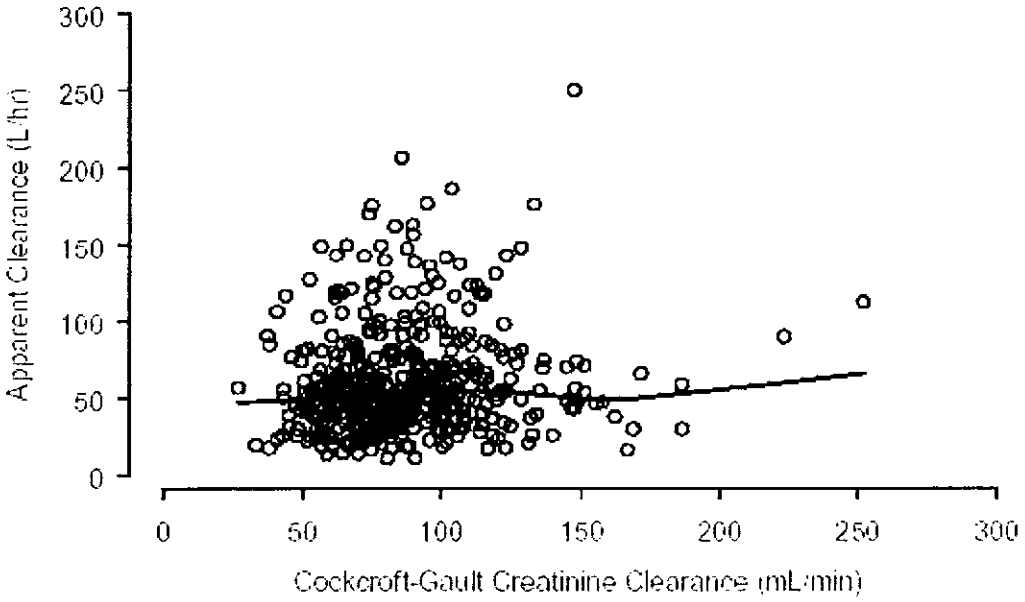


Figure 9.8. Relationship between estimated creatinine clearance and individual CL/F values from base pharmacokinetic model. Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

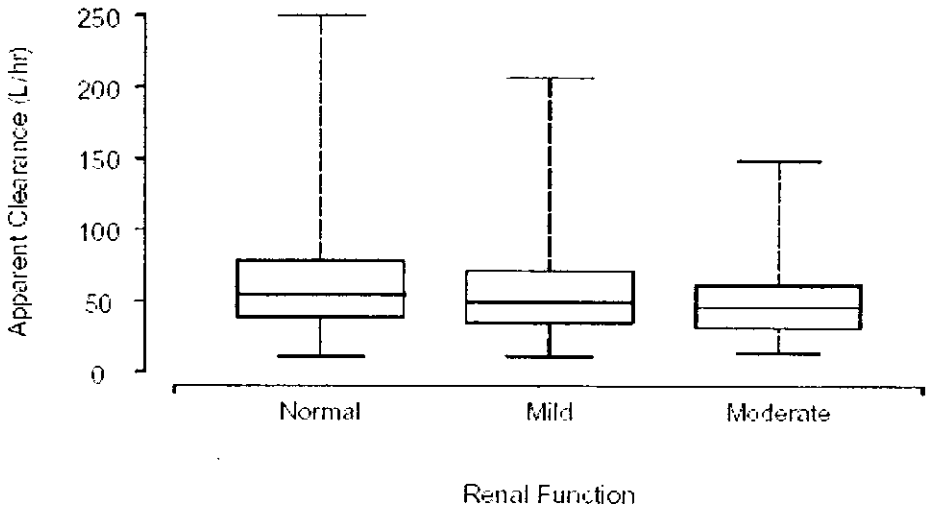


Figure 9.9. Distribution of individual CL/F values from base pharmacokinetic model by renal classification (estimated Cockcroft-Gault creatinine clearance).
Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

The influence of renal impairment on duloxetine CL/F was evaluated as a covariate on both the base and final pharmacokinetic models. The inclusion of CGCL as a covariate did not improve the goodness-of-fit statistics (.MOF < 10.828 points), suggesting no statistically significant effect of CGCL on duloxetine pharmacokinetics.
To assess the precision of parameter estimates for these models, two bootstrap analyses were performed. A total of 500 bootstrap replicates were created by random sampling with replacement from the analysis dataset. These bootstrap replicates were fit to models estimating CL/F separately for the three classifications of renal impairment.
Figure 9.10 illustrates the range of CL/F predictions from the bootstrap analysis of CGCL as a covariate in the base pharmacokinetic model. The CL/F estimates from the normal, mild, and moderate renal categories had 95% confidence intervals of 52.9 to 63.0 L/hr, 47.9 to 55.2 L/hr, and 44.0 to 54.7 L/hr, respectively. While this shows a trend in duloxetine CL/F with CGCL, the effects of gender and age are not accounted for in this model. Gender and age both contribute to the calculation of CGCL and have been shown to influence duloxetine CL/F. As a result, the normal renal group contains 38% male patients with a mean age of 45, while the mild and moderate groups contain 27% and 24% males, respectively, with mean ages of 48 and 59. These demographic differences would be expected to contribute to differences in duloxetine CL/F between the renal function categories.

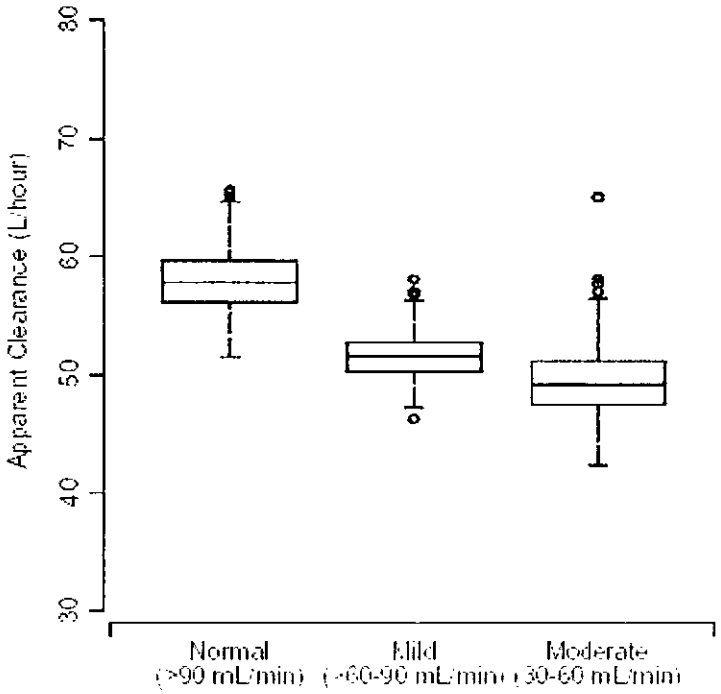


Figure 9.10. Predicted duloxetine CL/F values from bootstrap analysis of renal classification (estimated Cockcroft-Gault creatinine clearance) on the base pharmacokinetic model. Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

Figure 9.11 illustrates the range of CL/F predictions from the bootstrap analysis of CGCL as a covariate in the final pharmacokinetic model, which accounts for the known effects of gender and age. The CL/F estimates from the normal, mild, and moderate renal categories had 95% confidence intervals of 47.4 to 59.0 L/hr, 45.2 to 55.8 L/hr, and 45.9 to 59.1 L/hr, respectively. These results show essentially no difference in CL/F between renal function classifications and a substantial overlap in estimated CL/F values.

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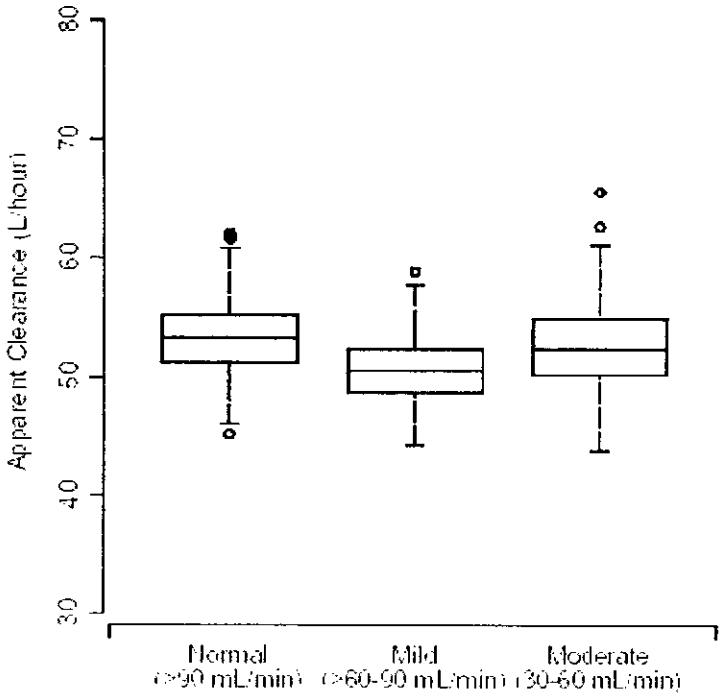

Figure 9.11. Predicted duloxetine CL/F values from bootstrap analysis of renal classification (estimated Cockcroft-Gault creatinine clearance) on the final pharmacokinetic model. Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

The final population pharmacokinetic model was used to predict the average steady-state concentration ($C_{ss,B}$) for each patient receiving duloxetine based upon the individual's CL/F values (empirical Bayesian estimates). These $C_{ss,B}$ values provide estimates of duloxetine systemic exposure in individual patients at their assigned dose levels. Table 9.6 summarizes $C_{ss,B}$ by dose for these patients with respect to classification of renal function. There is substantial overlap in $C_{ss,B}$ values across renal impairment classifications.

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Table 9.6. Steady-State Concentrations of Duloxetine From Individual Bayesian Parameter Estimates
Studies F1J-MC-HMAQ, F1J-MC-HMAU, F1J-MC-HMAV(a), and F1J-MC-SAAW

ss,B	20 mg QD	20 mg BID	30 mg BID	40 mg BID	60 mg QD	60 mg BID
All Patients						
Mean (ng/mL)	20.0	33.4	38.9	72.6	48.5	115
CV (%)	65.8	56.3	65.1	59.5	59.5	52.7
Range (ng/mL)						
n[a]	47	206	18	223	56	224
Normal						
Mean (ng/mL)	18.5	32.7	45.5	64.8	40.9	106
CV (%)	81.0	53.5	68.8	62.6	51.3	59.8
Range (ng/mL)						
n[a]	18	85	10	77	29	87
Mild						
Mean (ng/mL)	21.7	32.3	25.9	73.6	59.1	117
CV (%)	58.7	58.5	31.6	57.4	64.4	47.1
Range (ng/mL)						
n[a]	22	101	6	120	21	100
Moderate						
Mean (ng/mL)	18.7	41.9	44.6	91.0	48.7	134
CV (%)	54.7	53.3	33.0	55.4	24.0	49.8
Range (ng/mL)						
n[a]	7	20	2	26	6	37

a: Number of patients participating in a dosing regimen.

Discussion

The pharmacokinetics of duloxetine were evaluated in patients with major depression, urinary incontinence, and painful diabetic neuropathy, participating in Studies HMAQ, HMAU, HMAV, and SAAW. Patients in this analysis received doses of duloxetine ranging from 20 mg QD to 60 mg BID. This pooled analysis was performed to examine the effect of mild and moderate renal impairment on duloxetine pharmacokinetics, and to identify other patient-specific factors that influence the disposition of duloxetine. Consistent with the results from prior population analyses, this analysis revealed that gender, smoking status, duloxetine dose, and age significantly influence duloxetine pharmacokinetics. Despite statistical significance, the combined effects of gender, smoking, dose, and age only decreased inter-patient variability in CL/F from 64.8% in the base model to 54.3% in the final model. Because of this large inter-patient variability, dose adjustments based upon gender, smoking status, or age do not appear to be justified. Gender was found to have a significant influence on duloxetine pharmacokinetics in this analysis. This effect was parameterized as a change in bioavailability, with male patients being estimated to have 44% lower bioavailability than female patients; increasing CL/F by 79%. Gender effects on duloxetine pharmacokinetics have also been observed in

healthy subjects following single and multiple dosing of 60-mg duloxetine (F1J-BDHMAR and F1J-LC-HMBN). Gender differences in CYP1A2 activity (Relling et al. 1992) may account, at least in part, for differences in duloxetine pharmacokinetics between male and female patients. This hypothesis is supported by in vitro data indicating that CYP1A2 is involved in duloxetine metabolism (ADME Report 72, Lilly Research Laboratories, 2001). Due to higher CYP1A2 activity in males, larger amounts of duloxetine may be metabolized, resulting in the appearance of lower bioavailability than female patients.

Smoking is also believed to increase the expression of CYP1A2 activity among different individuals (Sesardic et al. 1988). In this analysis, the effect of smoking was parameterized as a change in bioavailability. Smokers were estimated to have 32% lower bioavailability than non-smokers; increasing CL/F by 47%. This observation suggests that duloxetine pharmacokinetics are indeed affected by changes in CYP1A2 activity. As in the observed gender effect, higher CYP1A2 activity in smokers may lead to greater metabolism of duloxetine, resulting in the appearance of lower bioavailability in smokers than in non-smokers.

The daily dose of duloxetine was found to significantly influence CL/F, with CL/F decreasing with increasing dose. In vivo data using desipramine as the substrate showed that duloxetine is a weak inhibitor of CYP2D6-mediated metabolism (F1J-LC-HMAZ: Duloxetine/Desipramine Interaction Study). Duloxetine is also a substrate for CYP2D6 (F1J-FW-SBAG: Evaluation of the Effect of Paroxetine on the Pharmacokinetic Profile of Duloxetine in Healthy Subjects). The observed effect of dose on CL/F indicates that duloxetine may inhibit its own metabolism, but the magnitude of this effect is small with CL/F decreasing by only 23% over a 5-fold increase in daily dose from 20 to 120 mg.

Patient age was also found to influence the CL/F of duloxetine such that CL/F decreases with advancing age. This relationship between duloxetine CL/F and age has been reported in previous population pharmacokinetic analyses of urinary incontinence patients (F1J-MC-SAAB and F1J-MC-SAAW). Study F1J-LC-SAAY was conducted to further evaluate the effect of age on duloxetine pharmacokinetics. The results established that *a priori* dosage adjustment in the elderly is not necessary.

Unexplained inter-patient variability in CL/F (54.3%) and intra-patient variability (30.1%) remain high, resulting in high variability in predicted duloxetine concentrations. For a 50-year-old female non-smoker receiving duloxetine 60mg QD the predicted interquartile ranges for maximum concentration and average steady-state concentration are 53.9 – 101 ng/mL and 41.5 – 81.9 ng/mL respectively. Given this magnitude of variability in duloxetine concentrations and the magnitude of the identified covariate effects, specific dose recommendations based on these patient factors are not likely to be clinically relevant.

The effect of renal impairment on the pharmacokinetics of duloxetine was evaluated using estimated CGCL. Values for CGCL ranged from 29.9 to 285 mL/min in this patient population. Of the 463 patients included in this analysis, 262 had a CGCL value between 60 and 90 mL/min (mild renal impairment), while 89 had values between 30 and 60 mL/min (moderate renal impairment). This provides an ample range of CGCL values to evaluate the impact of mild and moderate renal impairment on the pharmacokinetics of duloxetine.

When evaluated on the final pharmacokinetic model, the 95% confidence intervals for

CL/F estimates from the normal, mild, and moderate renal function categories were 47.4 to 59.0 L/hr, 45.2 to 55.8 L/hr, and 45.9 to 59.1 L/hr, respectively. These results show essentially no difference between renal function categories and a substantial overlap in estimated CL/F. This suggests that mild and moderate renal impairment have very little effect on duloxetine pharmacokinetics.

Conclusions

. The pharmacokinetics of duloxetine were adequately characterized by a onecompartment model. The typical values of CL/F and V/F were 51.6 L/hr and 984 L, respectively, for a female non-smoker. Inter-patient pharmacokinetic variability was large, estimated as 54.3% for CL/F and 100% for V/F.

. Gender and smoking status both had statistically significant effects on duloxetine pharmacokinetics. These effects were parameterized as changes in duloxetine bioavailability. Male patients were estimated to have 44.1% lower bioavailability than female patients; increasing CL/F by 79%. Smokers were estimated to have 31.8% lower bioavailability than non-smokers; increasing CL/F by 47%. Nonetheless, because of the high inter-patient variability in CL/F, dose adjustments based upon gender or smoking status do not appear to be warranted.

. Duloxetine CL/F was dose-dependent across the dose range of 20 mg QD to 60 mg BID. The estimated CL/F decreased only 23% across this 6-fold range of daily duloxetine doses.

. Age had a statistically significant influence on duloxetine CL/F. As age increased from the mean value of 48 to the maximum of 84 years, the predicted duloxetine CL/F for a female non-smoker decreased from 51.1 to 33.1 L/hr. Thus, a 75% increase in age resulted in a 35% decline in CL/F.

. Unexplained inter-patient variability in CL/F (54.3%) and intra-patient variability (30.1%) remain high, resulting in high variability in predicted duloxetine concentrations. Given the relative magnitude of variability and the identified covariate effects, specific dose recommendations based upon these patient factors are not likely to be clinically relevant.

. No significant association was found between duloxetine pharmacokinetics and estimated Cockcroft-Gault creatinine clearance (CGCL range: 29.9 to 285 mL/min).

Application of Results

. Duloxetine can be administered to patients being treated for urinary incontinence, major depression, and diabetic neuropathic pain without regard to age, gender, or smoking status over the dose range 20 mg to 60 mg BID.

. No dosage adjustment is necessary when administering duloxetine to patients with mild or moderate renal impairment.

4.3.9 HMCU – Reports of human PD studies – other Studies – Key Japanese studies conducted by —

This study was submitted on 12/22/03 to the NDA 21-427, and reviewed by Dr. R. Kavanagh.

4.3.10 Population Pharmacokinetic Analyses of studies: HMAG, HMAH, HMAI, SAAH, SAAI, and SAAL

Summary

Duloxetine plasma concentration data from six clinical studies were analyzed for this summary report. The plasma concentration data are summarized by study using descriptive statistics. The principal objective was to assess patient factors (gender and smoking) that may influence duloxetine plasma concentrations in the patient population. The following general conclusions have been formed by examining the descriptive analyses:

. Variability in duloxetine plasma concentrations between patients is large (approximately 60% to 80%)
. Mean duloxetine plasma concentrations increase in a dose-related manner.
. Female patients on average have higher duloxetine concentrations than male patients.
. Patients who smoke on average have lower duloxetine plasma concentrations.

Brief Overview of Studies Included in The Analysis

Study F1J-MC-HMAG was a double-blind, stratified, randomized, parallel study. Study Period I involved no drug therapy. In Study Period II, patients were randomized to either duloxetine 20 mg or placebo treatment. Investigators could reduce the dose to 10 mg per day due to adverse events or increase the dose to 30 mg per day in case of insufficient response. Plasma duloxetine concentrations (n = 89) were available from a total of 46 patients for pharmacokinetic evaluation.

Study F1J-MC-HMAH was a double-blind, placebo-controlled, randomized, parallel clinical study. Patients were randomly assigned to one of two treatments: placebo or duloxetine. Patients who met the criteria for entry were enrolled in the study for a period of up to 57 weeks. Patients who initially were assigned to duloxetine 20 mg/day and who did not respond adequately to therapy were randomly assigned to either continue the duloxetine 20-mg/day dose or be assigned to an increased dose of duloxetine 30 mg/day. Duloxetine plasma concentrations (n = 224) were available from a total of 80 patients for pharmacokinetic evaluation.

Study F1J-MC-HMAI was a randomized, parallel, double-blind, placebo- and active comparator-controlled study employing three different doses of duloxetine (5, 10, and 20 mg/day). Doses of duloxetine remained fixed for each dosing group. Duloxetine plasma

concentrations (n = 466) were available from a total of 217 patients for pharmacokinetic evaluation.
Study F1J-MC-SAAH was a double-blind, placebo-controlled, randomized, parallel study. Patients who met the entry criteria were randomized to receive placebo or duloxetine 30 mg/day for three days, escalating to 40 mg/day for 4-7 days. At Visit 4, the dose of duloxetine was adjusted to 10, 20, 30, or 40 mg/day. Duloxetine plasma concentrations (n = 39) were available from a total of 27 patients for pharmacokinetic evaluation.
Study F1J-MC-SAAI was a double-blind, placebo-controlled, randomized, parallel study of duloxetine administered at 30 and 40 mg/day. Patients were randomized to a 4-week treatment with either duloxetine 30 mg/day or placebo. At the conclusion of this 4-week treatment, patients were determined to be either responders or non-responders. Responders were then continued on their current treatment for the next 4 weeks. Nonresponders to duloxetine 30 mg/day had their dose increased to 40 mg/day for the next 4 weeks. Nonresponders to placebo were treated with duloxetine 30 mg/day for the next 4 weeks. Duloxetine plasma concentrations (n = 129) were available from a total of 63 patients for pharmacokinetic evaluation.

Study F1J-MC-SAAL was a multicenter, placebo-controlled, double-blind, randomized, crossover study. This study was designed to last 12 weeks in female subjects with symptoms of urinary urgency and frequency. The study design was 1 week prescreen, 1 week placebo lead-in, 4 weeks active treatment (duloxetine treatment involved 30 mg/day for 1 week and then escalating to 40 mg/day for 3 weeks), 1 week placebo washout, 4 weeks active treatment, and 1 week posttreatment follow-up. Duloxetine plasma concentrations data available from study SAAL were collected on days when duloxetine treatment was not administered. These concentrations were therefore not utilized for pharmacokinetic evaluation.
Studies HMAG, HMAH and HMAI were conducted in MDD patients while studies SAAH, SAAI and SAAL were carried out in SUI patients.

Summary of Study

Duloxetine plasma concentration data from six clinical studies were analyzed for this summary report. A brief description of each study is provided here:
In Study F1J-MC-HMAG patients were randomized to either duloxetine 20 mg or placebo treatment. The dose could be reduced to 10 mg per day due to adverse events or increased to 30 mg per day in case of insufficient response.
In Study F1J-MC-HMAH patients were randomized to either one of two treatments: placebo or duloxetine. Patients who initially were assigned to duloxetine 20 mg/day and who did not respond adequately to therapy were randomly assigned to either continue the duloxetine 20-mg/day dose or be assigned to an increased dose of duloxetine 30 mg/day.
In Study F1J-MC-HMAI involved three different doses of duloxetine (5, 10, and 20 mg/day). Doses of duloxetine remained fixed for each dosing group.
In Study F1J-MC-SAAH patients were randomized to receive placebo or duloxetine 30 mg/day for three days, escalating to 40 mg/day for 4 to 7 days. At Visit 4, the dose of duloxetine was adjusted to 10, 20, 30, or 40 mg/day.
In Study F1J-MC-SAAI patients were randomized to a 4-week treatment with either duloxetine 30 mg/day or placebo. At the conclusion of this 4-week treatment, responders

were continued on their current treatment for the next 4 weeks. Nonresponders to duloxetine 30 mg/day had their dose increased to 40 mg/day for the next 4 weeks. Nonresponders to placebo were treated with duloxetine 30 mg/day for the next 4 weeks. Study F1J-MC-SAAL was designed to last 12 weeks in female subjects with symptoms of urinary urgency and frequency. The study design was 1 week prescreen, 1 week placebo lead-in, 4 weeks active treatment (duloxetine treatment involved 30 mg/day for 1 week and then escalating to 40 mg/day for 3 weeks), 1 week placebo washout, 4 weeks active treatment, and 1 week posttreatment follow-up. Duloxetine plasma concentrations data available from study SAAL were collected on days when duloxetine treatment was not administered. These concentrations were therefore not utilized for pharmacokinetic evaluation.

Scope and Rationale of Pharmacokinetic Analysis

Study HMAG: Sparse blood samples were collected at Visits 3, 7, 10, and 15 or at the patient's last visit if discontinued prior to Visit 15 for determination of duloxetine plasma concentration. Blood samples were also collected for patients who required an increase in their dose during the visit at which the dose was increased.
Study HMAH: Sparse blood samples for determination of drug concentration in plasma were collected at Visits 1, 5, 9, 12, 14, 17, 20, 23, and at the patient's last visit.
Study HMAI: Sparse blood samples were collected at Visits 1, 8, 12, 16, 20, and 23 or at the patient's last visit if discontinued prior to Visit 23 for determination of duloxetine plasma concentration.
Study SAAH: Sparse blood samples were collected at Visits 1, 4, 6, and 7 or at the patient's last visit if discontinued early for determination of duloxetine plasma concentration.
Study SAAI: Sparse blood samples were collected at Visits 1, 4, 5, 6, and 7 or at the patient's last visit if discontinued early.
Study SAAL: Sparse blood samples were collected at Visits 1, 7, and 12 or at the patient's last visit if discontinued early.
Plasma concentration data are summarized using descriptive statistics for each of these studies.

Objectives

The objectives for the pharmacokinetic analyses were to:
. Summarize the plasma concentrations.
. Identify patient factors such as gender and smoking habits that may have an influence on duloxetine plasma concentrations in the patient population.

Formulation(s)

HMAG - Duloxetine HCl Tablets, 10 mg free base
HMAH - Duloxetine HCl Tablets, 10mg and 20 mg free base
HMAI - Duloxetine HCl Tablets, 5mg and 10 mg and 20 mg free base
SAAH - Duloxetine HCl Capsules (10 mg and 20 mg free base) in blister packs
SAAI - Duloxetine HCl Capsules (10 mg and 20 mg free base)
SAAL - Duloxetine Capsules (10 mg and 20 mg free base) in blister packs

Population Pharmacokinetic/Pharmacodynamic Modeling Strategy

Based upon the nature of these data from a variety of studies, specific and extensive pharmacokinetic modeling of the results was not regarded as being able to yield informative results. Therefore, the plasma concentration data have been summarized using descriptive statistics.

Changes in the Conduct of the Study or Planned Analyses

Descriptive statistics were performed, by study, on the plasma concentration data. Population pharmacokinetic analysis using NONMEM was planned for study HMAI as specified in the protocol. However, the HMAI study was superceded by the results of studies HMAU and HMAQ. Therefore plasma concentration data for study HMAI have also only been summarized by descriptive statistics.

Pharmacokinetic Results

The pharmacokinetic evaluation included data from 46 patients from study HMAG, 80 patients from study HMAH, 217 patients from study HMAI, 27 patients from study SAAH, and 63 patients from study SAAI. Appendix 1 provides individual plasma concentration data listings. Table 9.1 summarizes duloxetine plasma concentrations from different studies by dose and Figure 9.1 shows a plot of the same data.

Table 9.1. Descriptive Statistics For Plasma Concentrations (ng/mL) of Duloxetine (by dose) for Patients Included in the Pharmacokinetic Analysis from Studies HMAG, HMAH, HMAI, SAAH, and SAAI.

		Dose (mg)				
Study		**5**	**10**	**20**	**30**	**40**
HMAG	Mean	--	--	15.0	13.4	--
	SD	--	--	10.4	7.61	--
	Minimum	--	--			--
	Median	--	--	11.9	12.0	--
	Maximum	--	--			--
	CV%	--	--	69.4	56.9	--
	N	--	--	86	3	--
HMAH	Mean	--	--	12.7	--	--
	SD	--	--	9.92	--	--
	Minimum	--	--		--	--
	Median	--	--	10.2	--	--
	Maximum	--	--		--	--
	CV%	--	--	77.9	--	--
	N	--	--	224	--	--
HMAI	Mean	4.91	7.11	16.3	--	--
	SD	3.51	5.36	12.5	--	--
	Minimum				--	--
	Median	3.62	5.50	12.9	--	--

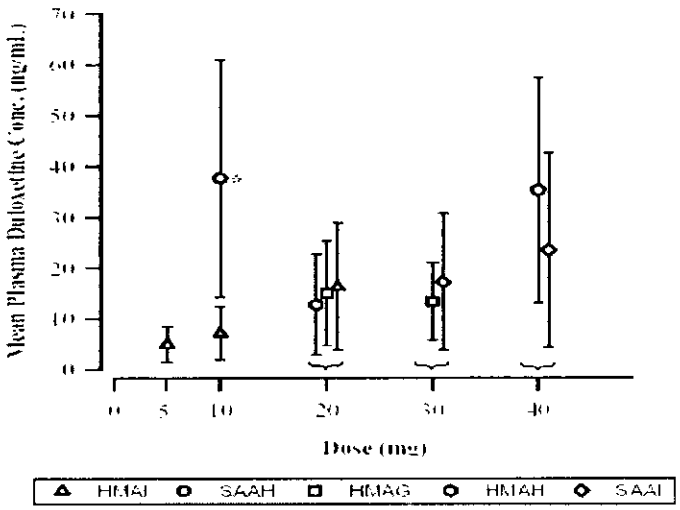
	Maximum				--	--
	CV%	71.4	75.4	76.7	--	--
	N	118	173	175	--	--
SAAH	Mean	--	37.6[a]	--	--	35.2
	SD	--	23.3	--	--	22.2
	Minimum	--		--	--	
	Median	--	36.2	--	--	28.5
	Maximum	--		--	--	
	CV%	--	62.0	--	--	63.3
	N	--	11	--	--	28
SAAI	Mean	--	--	--	17.2	23.4
	SD	--	--	--	13.5	19.1
	Minimum	--	--	--		
	Median	--	--	--	13.6	16.4
	Maximum	--	--	--		
	CV%	--	--	--	78.6	81.8
	N	--	--	--	92	37

a Data likely reflect prior doses of 40 mg (See Text in Section 9.1 Pharmacokinetic Results)

The mean plasma concentrations for different doses within each study are consistent for studies HMAI and SAAI. There appears to be a dose-related increase in the plasma concentration that would be anticipated as the dose of duloxetine is increased. Nevertheless, there is substantial variability in the range of concentration at all dose levels. In studies of this nature (sparse sampling in patients) this variability might be attributable to a variety of uncontrolled factors such as compliance to the prescribed dosage regimen, and other extraneous factors. Nonetheless, these data reflect the typical exposure that might be achieved in such a patient population and in general is commensurate with the concentrations observed in other population and clinical pharmacology studies.

Studies HMAG and HMAH were carried out at a singe dose level. In Study HMAG, 3 patients with qualified plasma duloxetine concentrations had a dose escalation to 30 mg. The plasma sample was taken on the day of dose escalation. Since not enough time had elapsed between the sample collection at 30-mg dose and day of dose escalation, a dose-dependent increase in concentrations was not achieved. This is reflected in the mean concentration of these 3 individuals.

Figure 9.1. Mean (SD) plasma concentrations (ng/ml) of duloxetine (by dose) for patients included in the pharmacokinetic analysis from studies HMAG, HMAH, HMAI, SAAH, and SAAI.



Some data points plotted at 20, 30, or 40 mg on the dose axis have been moved to the right or left off the grid to improve data clarity.

* See note in text (Section 9.1 Pharmacokinetic Results) regarding these data.

For Study SAAH, there appears to be a lack of dose proportionality. The data for the 10-mg dose for this study were collected only on Visit 4. On this visit, the dose was lowered from 40 mg to 10 mg. Hence the higher concentrations are reflective of prior exposure to the 40-mg dose. The data at the 10-mg dose are comparable with the data for the 40-mg dose confirming that steady-state plasma concentrations had not yet been achieved at the 10-mg dose level.

Table 9.2 and Table 9.3 summarize duloxetine plasma concentrations from different studies by gender and smoking status at different dose levels, respectively. The mean concentrations for female patients were higher than the mean concentrations for male patients for different dose groups. Also, smoking resulted in a decrease in plasma concentrations (in studies HMAG, HMAH, HMAI and SAAH). There appears to be a clear trend of lower plasma concentrations in smokers as compared to non-smokers in each study.

Table 9.2. Descriptive Statistics For Plasma Concentrations (ng/mL) of Duloxetine (by Gender) for Patients Included in the Pharmacokinetic Analysis From Studies HMAG, HMAH, HMAI, SAAH, and SAAI.

		Dose									
		5 mg		10 mg		20 mg		30 mg		40 mg	
Study		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
HMAG	Mean	--	--	--	--	17.1	12.3		NC	--	--
	SD	--	--	--	--	11.2	8.79		NC	--	--
	Minimum	--	--	--	--					--	--
	Median	--	--	--	--	14.9	8.91		12	--	--
	Maximum	--	--	--	--					--	--
	CV%	--	--	--	--	65.3	71.5		NC	--	--
	N	--	--	--	--	49	37		1	--	--
HMAH	Mean	--	--	--	--	14.9	8.72	--	--	--	--
	SD	--	--	--	--	10.9	6.15	--	--	--	--
	Minimum	--	--	--	--				--	--	--
	Median	--	--	--	--	12.2	6.98	--	--	--	--
	Maximum	--	--	--	--				--	--	--
	CV%	--	--	--	--	72.8	70.5	--	--	--	--
	N	--	--	--	--	144	80	--	--	--	--
HMAI	Mean	5.05	4.56	7.79	5.68	17.3	14.9	--	--	--	--
	SD	3.67	3.11	6.01	3.24	13.5	10.9	--	--	--	--
	Minimum							--	--	--	--
	Median	3.69	3.48	6.2	4.45	14.5	10.6	--	--	--	--
	Maximum							--	--	--	--
	CV%	72.5	68.2	77.1	57.1	78	73.1	--	--	--	--
	N	84	34	117	56	105	70	--	--	--	--
SAAH	Mean	--	--	33.1	[a]49.7[a]	--	--	--	--	38.7	13.9
	SD	--	--	23.4	22.3	--	--	--	--	22	5.45
	Minimum	--	--			--	--	--	--		
	Median	--	--	28.3	48.9	--	--	--	--	33	14.3
	Maximum	--	--			--	--	--	--		
	CV%	--	--	70.7	44.9	--	--	--	--	56.9	39.2
	N	--	--	8	3	--	--	--	--	24	4
SAAI	Mean	--	--	--	--	--	--	--	17.2	--	23.4
	SD	--	--	--	--	--	--	--	13.5	--	19.1
	Minimum	--	--	--	--	--	--	--			
	Median	--	--	--	--	--	--	--	13.6	--	16.4
	Maximum	--	--	--	--	--	--	--			
	CV%	--	--	--	--	--	--	--	78.6	--	81.8
	N	--	--	--	--	--	--	--	92	--	37

Abbreviation: NC = Not Calculated

a Data likely reflect prior doses of 40 mg (See Text in Section 9.1 Pharmacokinetic Results)

Table 9.3. Descriptive Statistics For Plasma Concentrations (ng/mL) of Duloxetine (by Smoking Status) for Patients Included in Pharmacokinetic Analysis from Studies HMAG, HMAH, HMAI, SAAH, and SAAI.

	Dose									
	5 mg		10 mg		20 mg		30 mg		40 mg	
Study	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker
HMAG Mean	--	--	--	--	9.77	16.2	--	13.4	--	--
SD	--	--	--	--	6.46	10.8	--	7.61	--	--
Minimum	--	--	--	--					--	--
Median	--	--	--	--	7.87	13.3	--	12	--	--
Maximum	--	--	--	--					--	--
CV%	--	--	--	--	66	66.6	--	56.9	--	--
N	--	--	--	--	16	70	--	3	--	--
HMAH Mean	--	--	--	--	7.65	14.5	--	--	--	--
SD	--	--	--	--	5.69	10.5	--	--	--	--
Minimum	--	--	--	--			--	--	--	--
Median	--	--	--	--	6.13	11.6	--	--	--	--
Maximum	--	--	--	--			--	--	--	--
CV%	--	--	--	--	74.5	72.3	--	--	--	--
N	--	--	--	--	57	167	--	--	--	--
HMAI Mean	4.36	5.17	6.75	7.76	12.6	18.3	--	--	--	--
SD	2.77	3.8	4.13	6.88	6.49	14.4	--	--	--	--
Minimum							--	--	--	--
Median	3.39	3.65	5.97	5.41	11	15.4	--	--	--	--
Maximum							--	--	--	--
CV%	63.7	73.4	61.2	88.7	51.5	78.7	--	--	--	--
N	38	80	103	67	60	115	--	--	--	--

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Table 9.3. (concluded)Descriptive Statistics For Plasma Concentrations (ng/mL) of Duloxetine (by Smoking Status) for Patients Included in Pharmacokinetic Analysis From Studies HMAG, HMAH, HMAI, SAAH, and SAAI.

		Dose									
		5 mg		10 mg		20 mg		30 mg		40 mg	
Study		Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker
SAAH	Mean	--	--	29.2[a]	42.4[a]	--	--	--	--	28.9	37.7
	SD	--	--	20.3	25	--	--	--	--	21.1	22.7
	Minimum	--	--			--	--	--	--		
	Median	--	--	28.3	40.5	--	--	--	--	22.4	29.9
	Maximum	--	--			--	--	--	--		
	CV%	--	--	69.3	59	--	--	--	--	73.3	60.2
	N	--	--	4	7	--	--	--	--	8	20
SAAI	Mean	--	--	--	--	--	--	28.5	16.2	29.4	21.5
	SD	--	--	--	--	--	--	25.1	11.9	22.2	18.1
	Minimum	--	--	--	--	--	--				
	Median	--	--	--	--	--	--	12.8	13.6	17.9	15.3
	Maximum	--	--	--	--	--	--				
	CV%	--	--	--	--	--	--	88	73.1	75.4	84.2
	N	--	--	--	--	--	--	7	85	9	28

a.Data likely reflect prior doses of 40 mg (See text in Section 9.1 PK results)

Discussion

A gender difference in mean concentrations was observed in Studies HMAG, HMAH and HMAI. The mean duloxetine plasma concentrations in female patients were between 11% to 71% higher than those for male patients. Study SAAH only had limited data to assess gender difference and Study SAAI only had data from male patients.

An impact of smoking on the plasma concentrations of duloxetine was observed in Studies HMAG, HMAH and HMAI. The mean duloxetine plasma concentrations for smokers were between 13% to 47% of those observed in nonsmokers. Studies SAAH and SAAI only had very limited data from smokers upon which to assess the impact of smoking.

The effects of gender and smoking on the plasma concentrations of duloxetine collaborate the findings in other studies. It is believed that these effects are mediated through their impact on the CYP1A2 enzyme (Relling et al 1992). Smoking induces CYP1A2 activity and females have been characterized as having less activity for this enzyme (Sesardic et al 1988).

Conclusions

. The mean duloxetine plasma concentrations increased in a dose-related manner.

. The female patients had higher duloxetine concentrations than the male patients likely due to lower levels of CYP1A2 expression in these patients.

. Smoking resulted in a decrease in plasma duloxetine concentration likely due to the induction of CYP1A2 enzyme activity.
. The effect of gender and smoking is in agreement with results from the population pharmacokinetic analysis of HMAQ/HMAU [Population Pharmacokinetic Analyses of Studies: F1J-MC-HMAQ: Duloxetine Versus Placebo in the Treatment of Major Depression and F1J-MC-HMAU: Long-Term Open-Label Treatment with Duloxetine Hydrochloride for Evaluation of Safety in Major Depression]. Due to limitations on pharmacokinetic evaluations carried out in this study, specific recommendations should be followed from results of population analysis from studies HMAQ and HMAU.

Application of Results

. The effects of gender and smoking are in agreement with results from the population pharmacokinetic analysis of HMAQ/HMAU [Population Pharmacokinetic Analyses of Studies HMAQ/HMAU]. Understanding or identifying factors that may potentially impact the variability in drug concentrations is important as these relationships give a partial accounting regarding the overall variability in duloxetine plasma concentration.
. The factors impacting the concentration data coincide with results from other studies and suggest that dose, gender, and smoking habits specifically impact the average or typical duloxetine concentration for sub-populations of patients given this drug. In spite of identifying these trends in duloxetine concentration, the overall variability in duloxetine concentration values within each sub-population is large. Thus, these patient demographic characteristics do not identify sub-population characteristics that specifically require a different dosage regimen to attain or maintain equivalent drug exposure. But the knowledge of these differences may assist in the understanding regarding the expected average or typical drug exposure and can be considered as possible factors regarding the choice of a dosage regimen for a specific patient.
. The plasma concentrations of duloxetine that have been observed in this series of six studies provide a perspective on the possible range of drug exposure that may typically be achieved following the daily administration of duloxetine doses from 5 mg to 40 mg.

4.4 Pharmacometrics Consult

Consult for :

Pooled Population pharmacokinetic analysis for studies: HMAQ, HMAU, HMAVa, and SAAW.—Renal PK datasets

NDA 21-733 (Duloxetine) PPK, renal function, and dose adjustment
Review comments

He Sun, pharmacometrics
DPE2/OCPB

July 29, 2004

Issues regarding the modeling process:

- The sponsor's effort to conduct the PPK modeling and simulation is very much appreciated.

- Clearly, the prediction is low (biased) at higher concentration range, indicating a possible problem in structure model. Maybe a 2-compartment model is more appropriate for this data.

- Blood samples were collected within the initial 6 hours after dosing and are distributed within the initial 72 hours after starting the trial. Considering the t1/2 of the drug is about 12-16 hrs in normal health subject and maybe even longer in renally impaired and elderly, the blood sampling time-points appear to be collected not at optimal times. The impact of such a sampling schedule on CL/F estimate is unknown.

- The inclusion of covariates (Gender, smoking status, dose and age) in the model decreased inter-subject variability of CL/F from 64.8% to 54.3%, suggesting a large inherent inter-subject variability for the drug. However, inter-occasion and inter-study variability was not tested in the model building process.

Issues regarding renal function on drug CL/F:

- Renal function is confounded by age, and the ability of detecting renal function as a significant covariate for CL/F was influenced by the fact that the data were provided from multi-sources. Since age has been found to be a significant covariate for CL/F and the range of CLcr were for mild and moderate only, whether CL/F correlates with CLcr is not conclusive.

- The inter-subject and intra-subject variability of CL/F is large. Although the influence of mild and moderate renal function impairments on CL/F is unknown, dose adjustment for mild and moderate renal function alone is not needed.

Issues regarding dose adjustment:

The impact of age, sex, smoking status, and dose are statistical significant factors that modify drug bioavailability and CL/F. Renal function is possibly another factor that may affect CL/F. Although each individual factors changes the CL/F to a degree smaller than or similar to the inherent inter- and intra- subject variability, it is important to examine the combined affect, to judge the need of dose adjustments.

4.5 Dosage adjustment analysis

On August 12th, 2004, OCPB Briefing was held. At the meeting, duloxetine dosage adjustment in patients with renal and hepatic impairments, and drug-drug interaction was discussed. Following the discussion a further analysis (Dr. He Sun) was conducted and presented below.

DOSE ADJUSTMENT RECOMMENDATION:

Based on exposure–response (safety/efficacy) relationship information, modeling and simulations incorporating relevant patient demographic variables, the following dose adjustment proposal is provided. The existing data and modeling/simulation indicated that sub-population with the highest duloxetine exposure will be female elderly non-smokers.

Duloxetine exposure (mean AUC) is approximately 5-fold higher in moderately impaired hepatic patients who took 20 mg capsule (exposure equivalent to approximately 150 mg daily dose). Therefore, the following recommendation is proposed in hepatic impaired patients :

3. For renal impaired patients:

Since duloxetine exposure is approximately doubled in end stage renal disease (ESRD) patients who took a 60 mg capsule (two major metabolites' exposures were 7-9-fold higher),

4. Concomitant Drugs:

Duloxetine exposure (mean AUC) is approximately 5.6-fold higher in patients who were taking fluvoxaime (100 mg/day multi-dosing) and duloxetine. Duloxetine exposure (mean AUC) is approximately 1.6-fold higher in patients who were taking paroxetine (a single 20 mg dose) and duloxetine.

1A2 inhibitors – Given the increase in duloxetine exposure in patients who are on concomitant drugs, which will inhibit CYP1A2 metabolism (e.g. fluvoxamine), use only

2D6 inhibitors – Given the possibility of increase in exposure in patients who are on concomitant drugs which will inhibit CYP2D6 metabolism (e.g. paroxetine), use

These recommendations will greatly expand the utility of this important drug for treating neuropathic pain patients, including renally and/or hepatically impaired patients as well as certain drug interaction situations. These patient sub-populations are currently excluded in the label.

s.

BACKGROUND INFORMATION

1. Exposure-Response Relationship for Safety :

- Frequency of Adverse Events (Serves as justification for need for dose titration) - AEs reported as reason for discontinuation - the following figures (1,2) and table (designated as Table ISS.6.1.11) indicate dose related increase in adverse events for, for example, nausea, dizziness, somnolence, even with small numbers of patients (~200 per dose).

Figure 1: AE reports as reason for discontinuation : linear dose plot

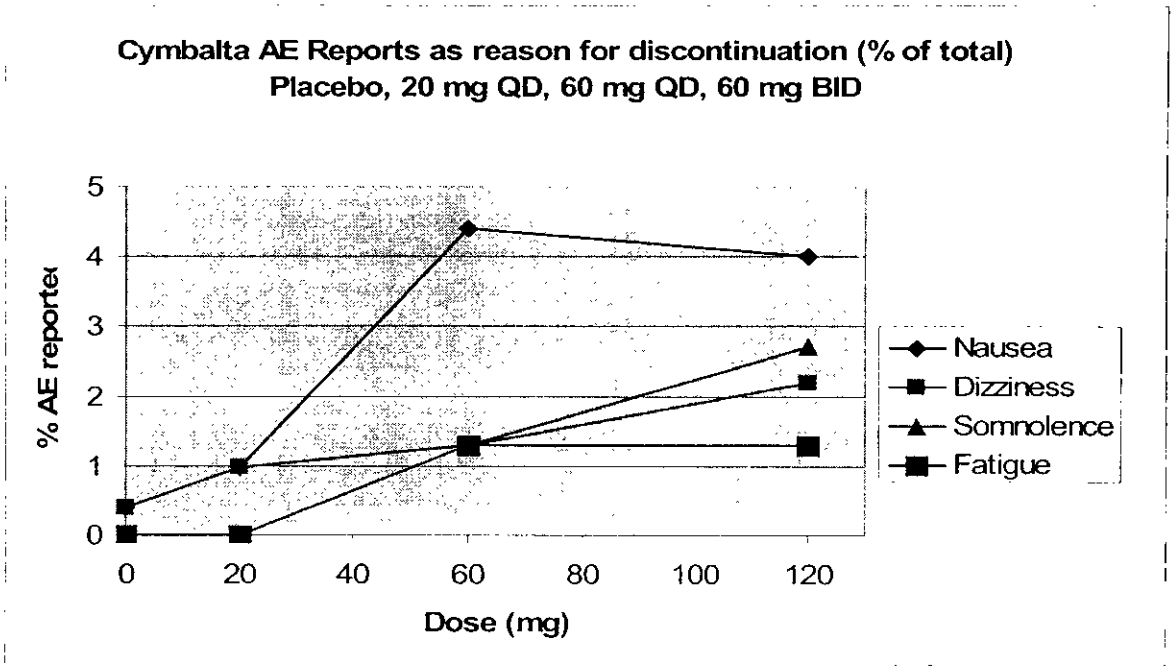

Figure 2: AE reports as reason for discontinuation : log dose plot

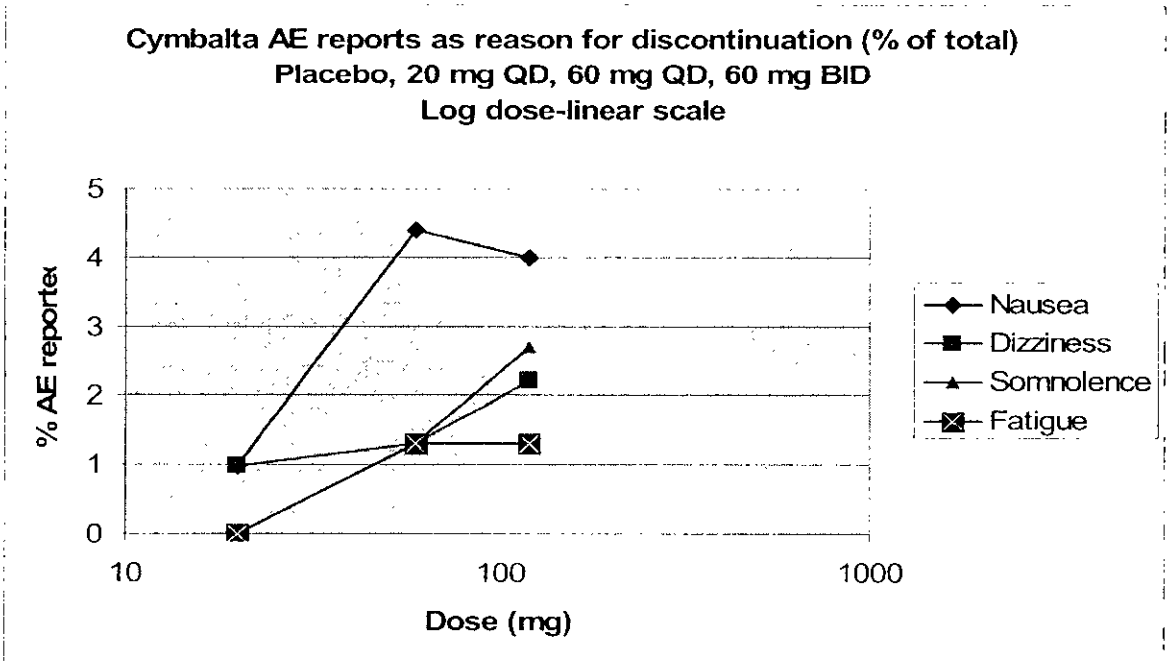

Table ISS.6.1.11. Adverse Events Reported as Reason for Discontinuation
All Randomized Patients
Placebo-Controlled Primary Integrated Safety Database

Event	PLACEBO (N=223) n(%)	DLX20QD (N=115) n(%)	DLX60QD (N=229) n(%)	DLX60BID (N=225) n(%)	TOTAL DULOX (N=569) n(%)	TOTAL DULOX VS. PLA p-Value CMH(a) (Exact)(b)	DLX60QD VS. PLA p-Value CMH(a) (Exact)(b)	DLX60BID VS. PLA p-Value CMH(a) (Exact)(b)
OVERALL	16(7.2%)	5(4.3%)	32(14.0%)	42(18.7%)	79(13.9%)	.007 (.008)	.019 (.022)	<.001 (<.001)
Nausea	1(0.4%)	1(0.9%)	10(4.4%)	9(4.0%)	20(3.5%)	.011 (.013)	.007 (.011)	.012 (.020)
Dizziness	1(0.4%)	1(0.9%)	3(1.3%)	5(2.2%)	9(1.6%)	.201 (.297)	.334 (.623)	.099 (.216)
Somnolence	0(0.0%)	0(0.0%)	3(1.3%)	6(2.7%)	9(1.6%)	.057 (.069)	.095 (.240)	.014 (.030)
Fatigue	0(0.0%)	0(0.0%)	3(1.3%)	3(1.3%)	6(1.1%)	.107 (.192)	.095 (.240)	.099 (.240)
Hypersomnia	0(0.0%)	0(0.0%)	2(0.9%)	2(0.9%)	4(0.7%)	.246 (.581)	.155 (.499)	.153 (.499)
Insomnia	1(0.4%)	0(0.0%)	1(0.4%)	1(0.4%)	2(0.4%)	.822 (1.00)	.907 (1.00)	.995 (1.00)
Confusional state	0(0.0%)	0(0.0%)	1(0.4%)	1(0.4%)	2(0.4%)	.412 (1.00)	.315 (1.00)	.313 (1.00)

(a) - Cochran-Mantel-Haenszel test for general association, controlling for study.
(b) - Fishers exact test
MEDDRA VERSION: 6.1
visits: 101-199
Program: RMP.FIJSUNSG.SASPGM(PQRDCS1A)
Data: RMP.SAS.FIJM.MCSAFESW.Q403

Table ISS.6.1.11. Adverse Events Reported as Reason for Discontinuation
All Randomized Patients
Placebo-Controlled Primary Integrated Safety Database (Continued)

Event	PLACEBO (N=223) n(%)	DLX20QD (N=115) n(%)	DLX60QD (N=229) n(%)	DLX60BID (N=225) n(%)	TOTAL DULOX (N=569) n(%)	TOTAL DULOX VS. PLA p-Value CMH(a) (Exact)(b)	DLX60QD VS. PLA p-Value CMH(a) (Exact)(b)	DLX60BID VS. PLA p-Value CMH(a) (Exact)(b)
Electrocardiogram QT prolonged	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	1(0.2%)	.499 (1.00)	()	.326 (1.00)
Erectile dysfunction	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	1(0.2%)	.562 (1.00)	()	.313 (1.00)
Hepatic enzyme increased	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	1(0.2%)	.499 (1.00)	()	.326 (1.00)
Hot flush	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	1(0.2%)	.499 (1.00)	()	.326 (1.00)
Hyperglycaemia	1(0.4%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	.085 (.282)	.319 (.499)	.322 (.499)
Libido decreased	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	1(0.2%)	.499 (1.00)	()	.326 (1.00)
Loose stools	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	1(0.2%)	562 (1.00)	()	.313 (1.00)

(a) - Cochran-Mantel-Haenszel test for general association, controlling for study.
(b) - Fishers exact test
MEDDRA VERSION: 6.1
visits: 101-199
Program: RMP.FIJSUNSG.SASPGM(PQRDCS1A)
Data: RMP.SAS.FIJM.MCSAFESW.Q403

- Treatment-Emergent AEs - the figures (3 and 4) and a table (designated as Table ISS.6.1.14) below shows those treatment-emergent adverse events (TEAE) that were reported at a significantly greater frequency by patients in the duloxetine as compared to the placebo group in the placebo controlled primary database. Overall, statistically significantly more duloxetine-treated patients experienced TEAEs compared with placebo-treated patients. Incidence of TEAEs appear to be dose related.

Figure 3: Treatment-emergent AEs : linear dose plot

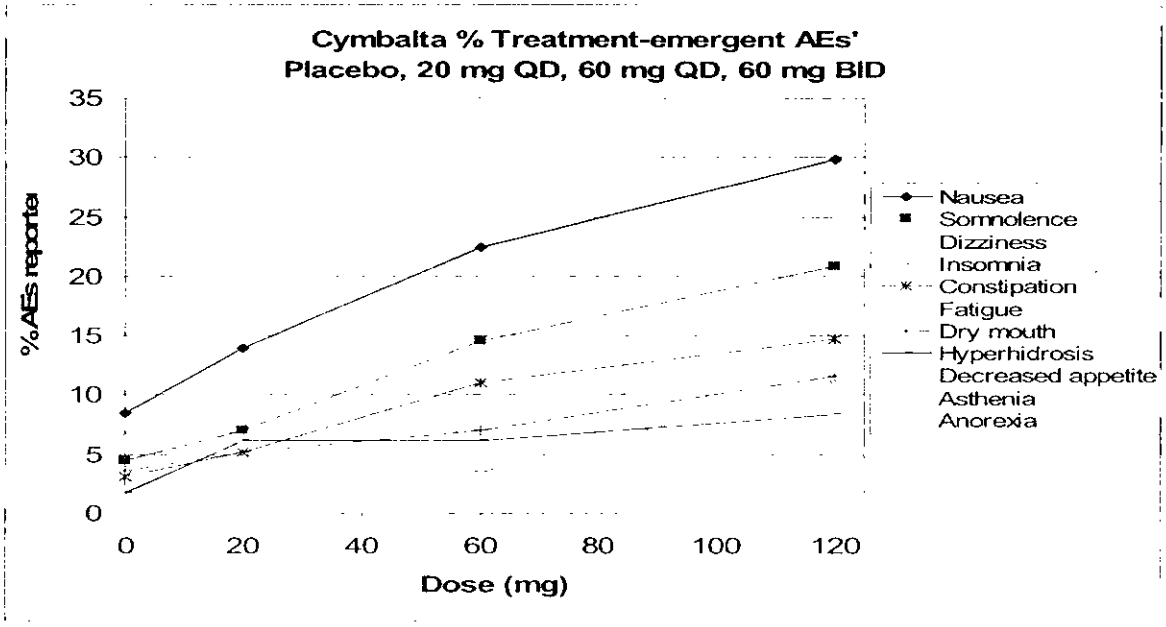

Figure 4 : Treatment-emergent AEs - log dose plot

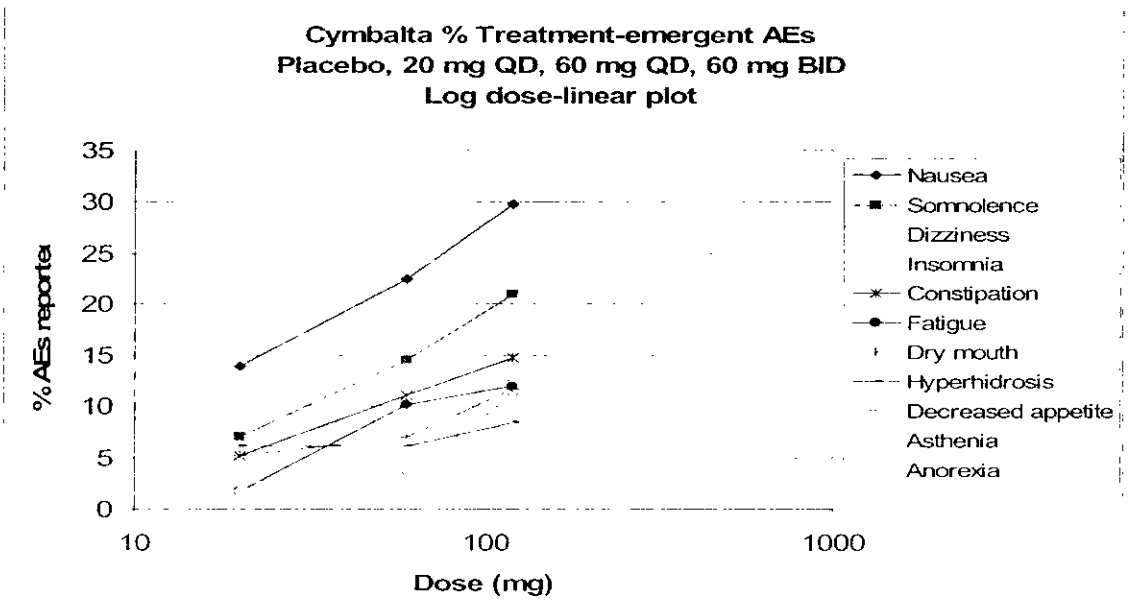

Table ISS.6.1.14. Treatment-Emergent Adverse Events Reported at a Statistically Significantly Higher Rate by Duloxetine-Treated Patients Compared with Placebo-Treated Patients
All Randomized Patients
Placebo-Controlled Primary Safety Database

	Placebo-Controlled							
						p-val [b]		
Event [a]	PBO N=223 %	DLX 20QD N=115 %	DLX 60QD N=228 %	DLX 60BID N=225 %	DLX TOTAL N=568 %	60QD vs PBO	60BID vs PBO	DLX TOTAL vs PBO
Nausea	8.5	13.9	22.4	29.8	23.6	<.001	<.001	<.001
Somnolence	4.5	7.0	14.5	20.9	15.5	<.001	<.001	<.001
Dizziness	6.3	9.1	13.6	16.9	13.4	.010	.001	.005
Insomnia	6.7	8.7	8.3	12.9	10.2	.483	.025	.188
Constipation	3.1	5.2	11.0	14.7	11.3	.001	.001	<.001
Diarrhoea	5.8	13.0	11.4	6.7	9.9	.033	.686	.069
Fatigue	4.9	1.7	10.1	12.0	9.2	.039	.007	.030
Dry mouth	3.6	5.2	7.0	11.6	8.5	.097	.001	.024
Hyperhidrosis	1.8	6.1	6.1	8.4	7.0	.019	.001	.004
Decreased appetite	0.4	2.6	3.5	11.1	6.3	.021	.001	.001
Asthenia	1.3	1.7	3.9	8.0	5.1	.088	<.001	.014
Anorexia	0.4	2.6	2.6	5.3	3.7	.061	.002	.015
Pharyngolaryngeal pain	1.3	2.6	0.9	5.8	3.2	.630	.012	.141
Myalgia	0.4	2.6	0.9	3.6	2.3	.557	.018	.101
Erectile dysfunction	0.0	0.0	1.3	4.4	2.3	.060	.002	.015
Tremor	0.0	0.0	0.9	4.9	2.3	.155	.001	.020
Lethargy	0.0	0.0	2.2	2.2	1.8	.028	.026	.033

(continued)

	Placebo-Controlled							
						p-val [b]		
Event [a]	PBO N=223 %	DLX 20QD N=115 %	DLX 60QD N=228 %	DLX 60BID N=225 %	DLX TOTAL N=568 %	60QD vs PBO	60BID vs PBO	DLX TOTAL vs PBO
Hypersomnia	0.0	0.0	1.8	1.8	1.4	.046	.046	.077
Urinary retention	0.0	0.0	2.2	1.3	1.4	.026	.083	.077
Fall	0.0	1.7	1.8	0.0	1.1	.047	-	.129
Sleep disorder	0.0	0.0	1.8	0.9	1.1	.046	.159	.129
Agitation	0.0	0.0	1.8	0.4	0.9	.047	.326	.146

2. Exposure-response relationship for efficacy :

- The data indicate the likelihood of efficacy at lower doses which, in certain sub-populations, will result in equivalent exposure as higher dose
- There were two pivotal P3 studies, HMAW Study and HMAV study.

The following figures (5- 10) provide information regarding dose-response for efficacy.

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Study HMAW

Figure 5. Mean Change in Average 24-Hour Pain Study HMAW
($p<0.05$ versus placebo for Cymbalta 60 mg QD and 60 mg BID at all time points)

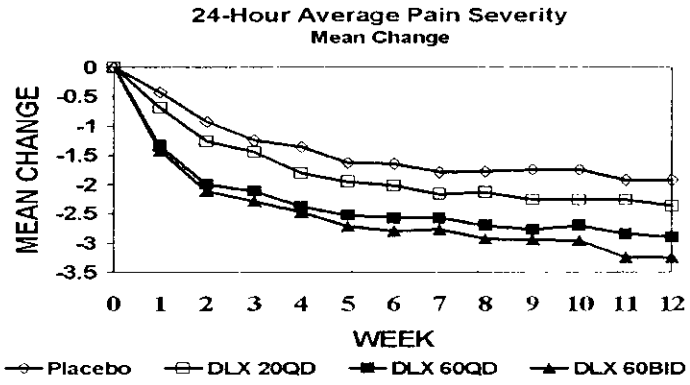


Figure 6 : Study HMAW linear dose plot

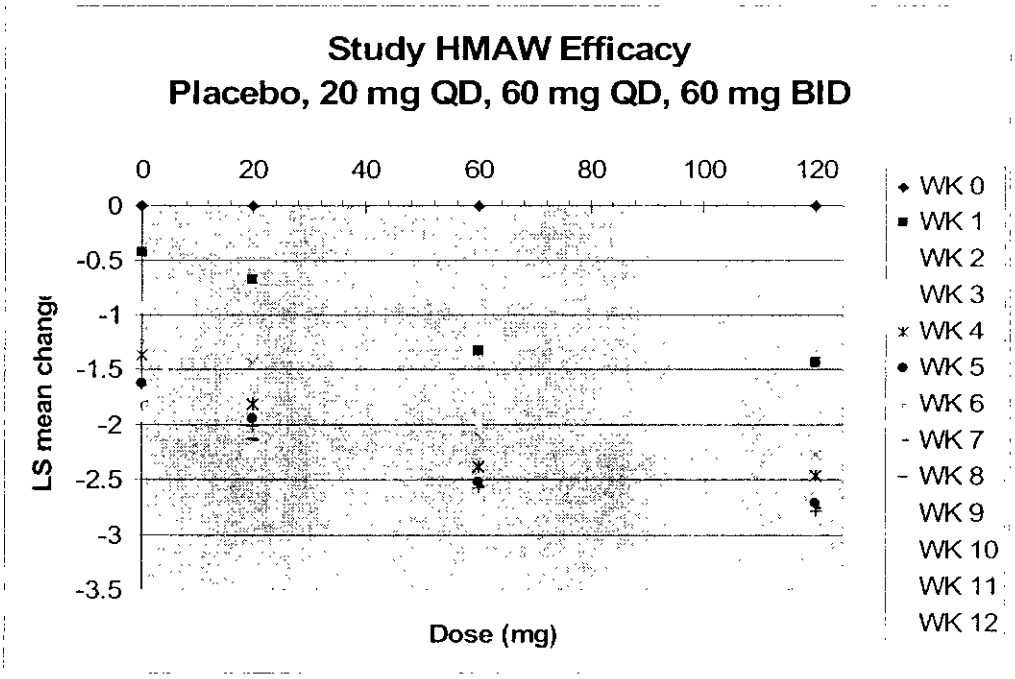
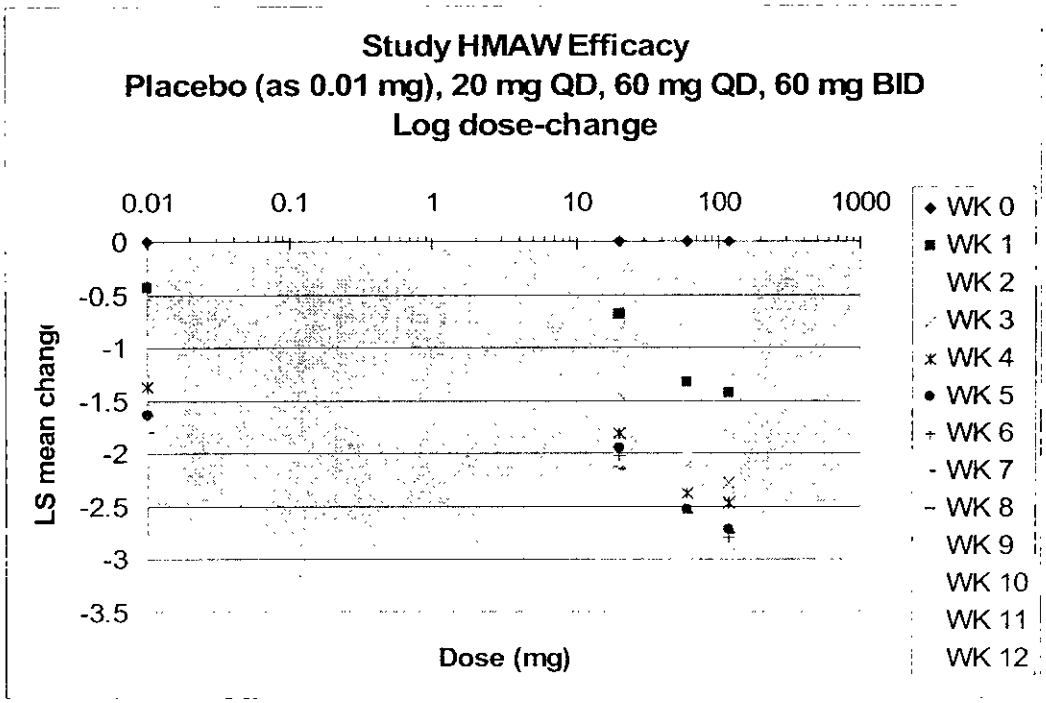


Figure 7 : Study HMAW log-dose plot



HMAV Study

Figure 8. Mean Change in Average 24-Hour Pain - Study HMAV
($p<0.05$ versus placebo for Cymbalta 60 mg QD and 60 mg BID at all time points)

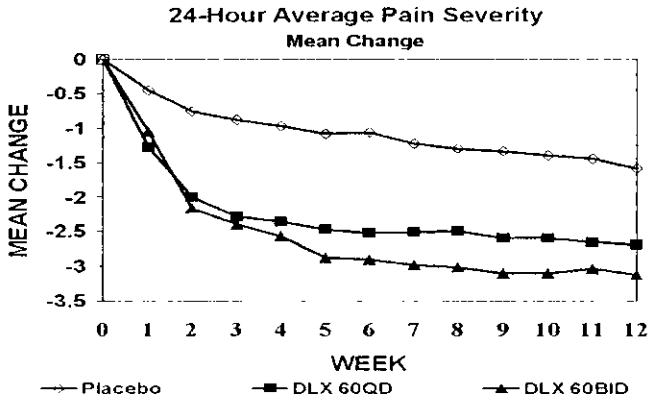


Figure 9 : linear dose plot

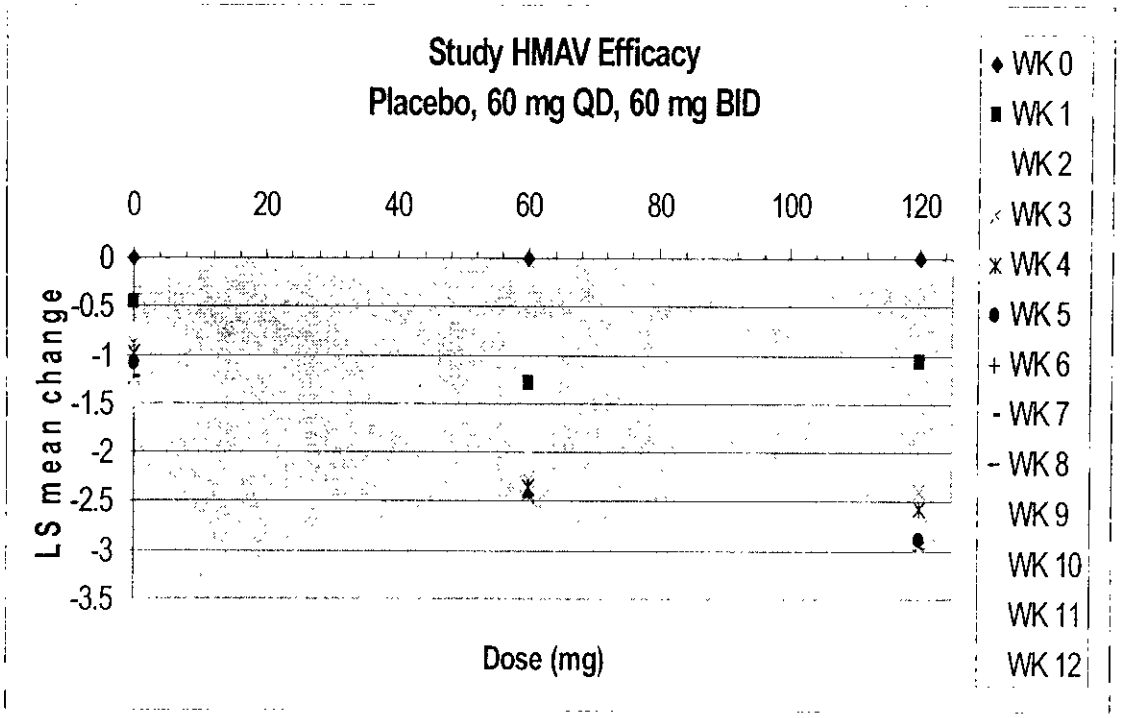
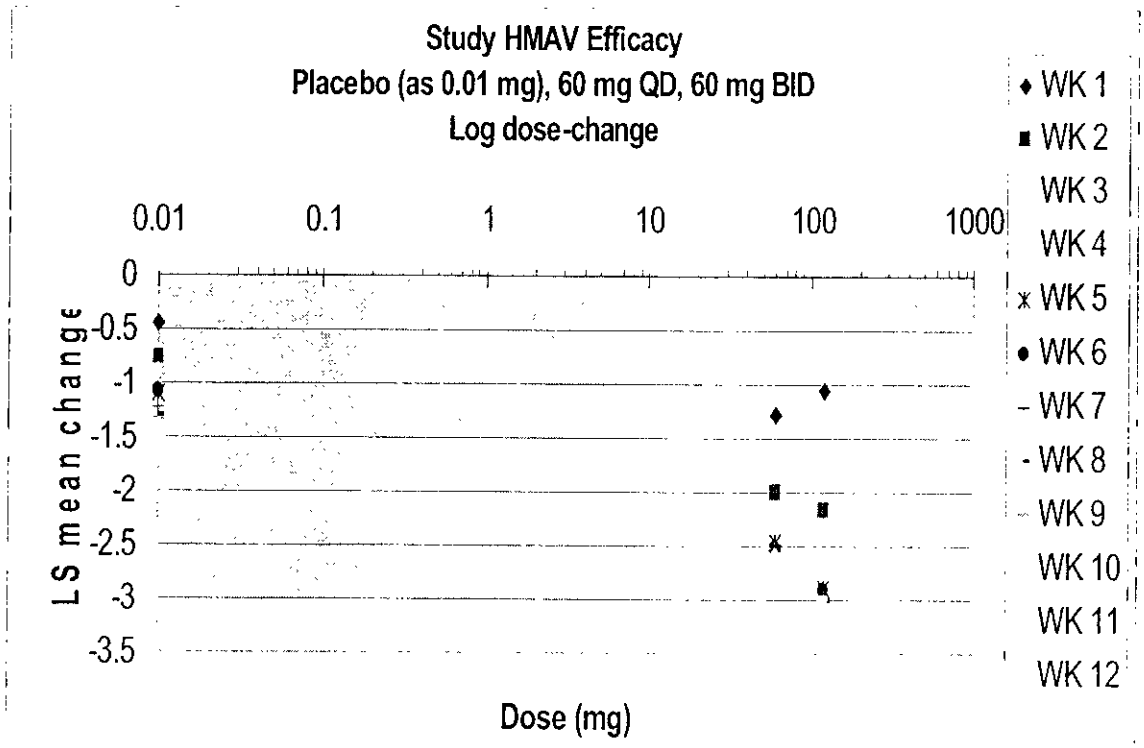


Figure 10 : log-dose plot



3. Exposure-efficacy relationship and dose selection

The Applicat's conclusion/results presented provide evidence that duloxetine is an effective agent for the treatment of DNP. Duloxetine has been examined in clinical studies of patients with DNP in doses up to 60 mg BID. Robust efficacy at a dose of 60 mg QD has been demonstrated in two placebo-controlled, randomized, double blind studies. In establishing a dose recommendation for duloxetine, the following factors have been considered: the advantage of a once-daily dose regimen, especially with regard to ease of use and the associated advantage for patient compliance; and recognition that 60 mg QD represents the lowest consistently effective total daily dose. Therefore, the recommended
— effective dose of duloxetine in the treatment of DNP is 60 mg once daily.

Agency Conclusion - This proposed dosing does not take into consideration the large differences in exposure expected within the general patient population related to, for example, age, gender and smoking.

4. Simulations

Steady-state Concentraiton (Css) under various conditions

Based on the sponsor's population pharmacokinetics/dynamic modeling final results, clinical trial simulations were performed. Simulation results show that the difference in relative exposure across various population groups can be as high as 10 fold, when considering multiple factors (see Figure 11 and Table 1).

Figure 11. Comparison of Css for combined demographic factors.

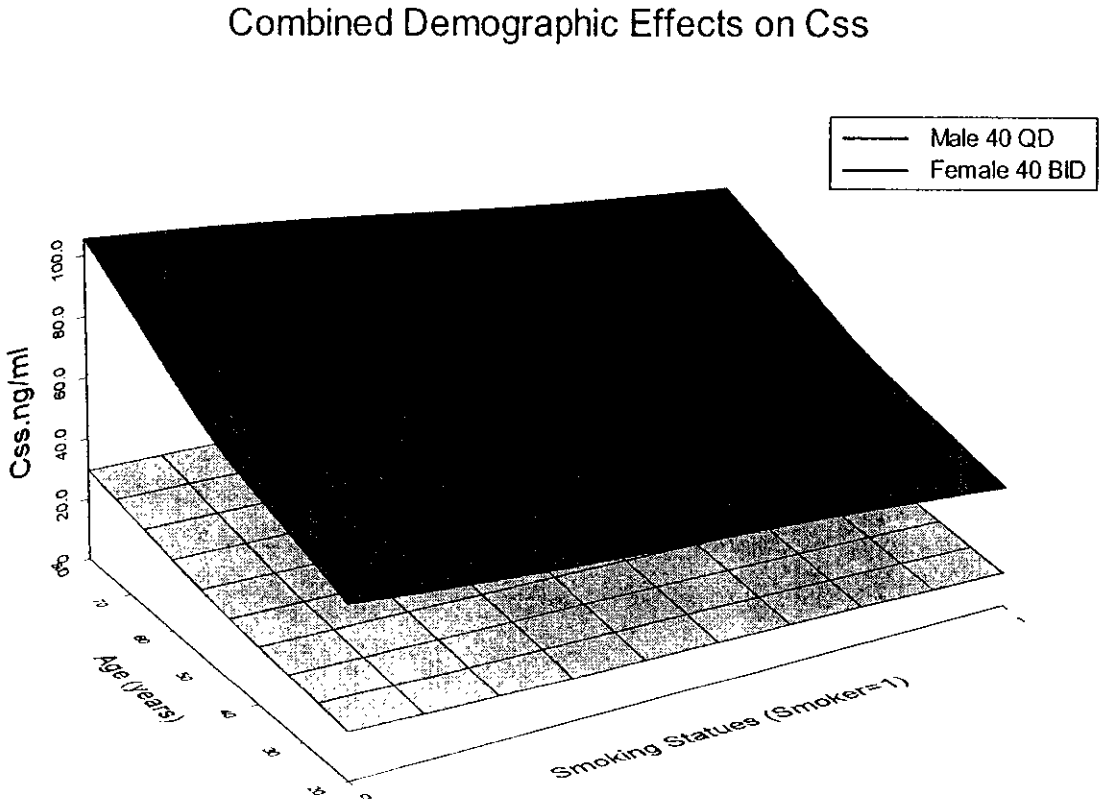


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Table 1. Specific numeric Css values.

Data shows that, with 40mg BID, the steady state plasma mean concentration (Css) is 10.83 ng/ml for a 20 year old young smoker male, and is 105.43 ng/ml for an elderly non-smoker female. The concentration differed by 10 fold. Note, the 54% intrinsic unexplained variability in CL/F is an additional factor above the change in the mean Css concentrations.

Resulting Css		Conditions					
CL (L/hr)	Css (ng/ml)	Dose (mg)	Dosing rate (Qhr)	Daily dose	Age (years)	Smoke=1 NS = 0	Male=1 Female = 0
58.68		40	24	40	20	0	0
45.15		40	24	40	50	0	0
31.62		40	24	40	80	0	0
86.04		40	24	40	20	1	0
66.20		40	24	40	50	1	0
46.36		40	24	40	80	1	0
104.98		40	24	40	20	0	1
80.77		40	24	40	50	0	1
56.56		40	24	40	80	0	1
153.93		40	24	40	20	1	1
118.43		40	24	40	50	1	1
82.93		40	24	40	80	1	1
58.68		40	12	80	20	0	0
45.15		40	12	80	50	0	0
31.62		40	12	80	80	0	0
86.04		40	12	80	20	1	0
66.20		40	12	80	50	1	0
46.36		40	12	80	80	1	0
104.98		40	12	80	20	0	1
80.77		40	12	80	50	0	1
56.56		40	12	80	80	0	1
153.93		40	12	80	20	1	1
118.43		40	12	80	50	1	1
82.93		40	12	80	80	1	1

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/s/

David Lee
8/26/04 10:01:05 AM
BIOPHARMACEUTICS
Two other NDAs submitted to Agency for duloxetine -
21-427 (depression), 21-556 (stress urinary incontinence);

Suresh Doddapaneni
8/27/04 08:21:24 AM
BIOPHARMACEUTICS