CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-427

Clinical Pharmacology and Biopharmaceutics Review #2

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-427
Type of Submission:	NDA
Generic Name:	Duloxetine HCl — Release Capsules
Formulation:	Encapsulated Enteric Coated Pellets
Strengths:	20 mg, 30 mg, — 60 mg
Route of Administration:	PO
Brand Name:	Cymbalta™
Sponsor:	Lilly Indianapolis, Indiana
Submission Dates:	November 12, 2001* February 26, 2002* February 26, 2002 A March 12, 2002* March 15, 2002 March 28, 2002 March 29, 2002 April 24, 2002
Related INDs:	— 38,838 — —
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

* **Biopharmaceutic and Clinical Pharmacology Informatiion** was contained in these submissions

1 RECOMMENDATION

1.1 ACCEPTABILITY OF THE SUBMISSION

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed NDA #21-427 submitted November 12, 2001.

OCPB finds this application acceptable provided that currently outstanding issues are adequately addressed. Comments should be communicated to the sponsor (see Section 3 Comments

Comments to the Medical officer

Comment 1

Duloxetine should be contraindicated in ESRD. Risks in severe renal insufficiency are unknown (Clcr < 30 ml/min); due the lack of safety information in this group contraindication should also be considered.

Comment 2

Duloxetine should not be administered to patients with mild, moderate, or severe hepatic insufficiency. Due to the 5 fold increase in exposure and the high incidence of AEs in a limited number of patients receiving a single low dose of duloxetine, duloxetine should not be given to any patient with any degree of hepatic insufficiency. In addition, the epoxide intermediate is an additional risk for progression in these patients.

1.2 COMMENTS TO THE SPONSOR

Please convey the comments in § 3.2.1 Proposed Phase IV Commitments, § 3.2.2 Dissolution, and § 3.3 Labeling Comments to the sponsor.

1.2.1 PROPOSED PHASE IV COMMITMENTS

Commitment 1

Due to the possibility of naphthol formation in an acidic environment, the sponsor is requested to perform 2 *in vitro* dissolution experiments in order to elucidate the robustness of the stability of the enteric coating.

a) [redacted]

b) [redacted]

APPEARS THIS WAY
ON ORIGINAL

2 EXECUTIVE SUMMARY

2.1 REVIEW ISSUES / QUESTIONS

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 [ ]

Has a biowaiver been requested?

The sponsor requests a biowaiver for the 30 mg and 40 mg capsule strengths. In assessing this request the following conclusions were made:

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

b) The 20 mg, 30 mg, 60 mg capsules are encapsulated beaded formulations that only differ by and are thus compositionally proportional

c) Dissolution of 3 x 20 mg capsules are similar to one 60 mg capsule, and the dissolution performance of the 30 mg and 40 mg capsules are similar to the 20 mg capsule strength.

A biowaiver is granted for the 30 mg and 40 mg 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 α1 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 – Duloxetine should be contraindicated in ESRD. Risks in severe renal insufficiency are unknown (Clcr < 30 ml/min); due the lack of safety information in this group contraindication should also be considered.

* **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 —

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 — , 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 ——— 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 caution should be used if duloxetine is co-administered with medications that are predominantly metabolized by the CYP2D6 system and which have a narrow therapeutic index.

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 advise avoidance of the use of duloxetine in women who may become pregnant and post-marketing surveillence is suggested. Animal studies are unlikely to be of utility as they will either underpredict or overpredict the risk depending upon the animal model used.

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 similar to marketed SSRIs regarding platelet aggregation and recommending avoidance of concomitant use with tryptophan should be considered for duloxetine.

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

Yes.

APPEARS THIS WAY
ON ORIGINAL

3 COMMENTS

3.1 COMMENTS TO THE MEDICAL OFFICER

Comment 1

Duloxetine should be contraindicated in ESRD. Risks in severe renal insufficiency are unknown (Clcr < 30 ml/min); due the lack of safety information in this group contraindication should also be considered.

Comment 2

Duloxetine should not be administered to patients with mild, moderate, or severe hepatic insufficiency. Due to the 5 fold increase in exposure and the high incidence of AEs in a limited number of patients receiving a single low dose of duloxetine, duloxetine should not be given to any patient with any degree of hepatic insufficiency. In addition, the epoxide intermediate is an additional risk for progression in these patients.

3.2 COMMENTS TO THE SPONSOR

Please convey the comments in § 3.2.1 Proposed Phase IV Commitments, § 3.2.2 Dissolution, and § 3.3 Labeling Comments to the sponsor.

3.2.1 PROPOSED PHASE IV COMMITMENTS

Commitment 1

Due to the possibility of naphthol formation in an acidic environment, the sponsor is requested to perform 2 *in vitro* dissolution experiments in order to elucidate the robustness of the stability of the enteric coating.

a) [

b) [ ]

3.2.2 DISSOLUTION

- Please adopt the following dissolution method and specifications for all four strengths of Duloxetine HCl — Release Capsules.

Table 1 Proposed Product Dissolution Methods and Specifications

Strength(s)	**20 mg, 30 mg, 40mg and 60 mg** Capsules 20% w/w Pellets
Apparatus Type	USP Dissolution Apparatus 1 (Baskets)
Media	
A Gastric Challenge:	0.1 N Hydrochloric Acid in Water
B Media 2:	50 mM pH 6.8 Phosphate Buffer in Water
Volume	1000 mL
Speed of Rotation (Rate of Flow for Flow-through Apparatus)	100 RPM
Sampling Time(s)	
A Sampling Time(s) for Gastric Challenge:	120 minutes
B Sampling Time(s) for Media 2:	15 minutes 30 minutes 45 minutes 60 minutes
Analytical Method	HPLC with UV detection at —
Dissolution Specifications (Based on USP Drug Release<724>)	
A Dissolution Specification for Gastric Challenge:	Meets USP requirements of not more than — dissolved in 120 minutes.
B Dissolution Specification for Media 2:	Meets USP requirements of **Q** = — dissolved in 60 minutes.

3.3 LABELING COMMENTS

- The sponsor is requested to adopt OCPB proposed labeling as outlined under the labeling section (see Section 6 on page 16).

4 SIGNATURES

/S/

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D. — Date

Senior Reviewer / Pharmacometrician
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

/S/

Ray Baweja, Ph.D. — Date

Team Leader
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

OCPB Briefing Meeting:

Date: Thursday, August 22, 2002

Time: 10:00 – 11:30 AM

Location: WOC2 Conference Room C 3rd Floor

Level: Optional Inter-Division

Attendees: Kavanagh R, Baweja R, Marroum P, Hunt J, Venitz J, Jackson A, Reynolds K, Laughren T, Andreason P, Rosloff B, Fossom L, John C

CC: NDA 21-427 (orig., 1 copy)
HFD-120 (Katz R, Laughren T, Andreason P, Rosloff B, Oliver T, Fossom L, John C)
HFD-860 (Kavanagh, Baweja, Mehta, Marroum)
Central Document Room (Barbara Murphy)

5 TABLE OF CONTENTS

6 LABELING

Proposed deletions are marked by addition a single line ~~strikeout~~ to text to be deleted.

Proposed additions are marked by addition of a single underline to proposed additions.

31 pages redacted from this section of the approval package consisted of draft labeling

7 CHEMISTRY

7.1 DRUG SUBSTANCE

7.1.1 NOMENCLATURE

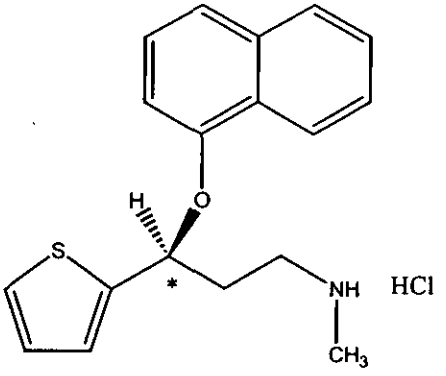
International Non-Proprietary Name (INN):	Duloxetine
Non-Proprietary Name (USAN):	Duloxetine hydrochloride
Chemical Name (USAN):	(S)-(+)-N-methyl-γ-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride
Proprietary (Brand) Name:	Cymbalta
Lilly Compound Number:	LY246916 (LY248686 hydrochloride)
Chemical Abstracts Service Number (CAS):	136434-34-9

7.1.2 FORMULAE

Molecular Formula:	$C_{18}H_{19}NOS \bullet HCl$
Molecular Weight:	333.88 for HCl Salt 297.41 for Base

Structural Formula:

Figure 1 Duloxetine HCl Structural Formula



7.1.3 STEREOCHEMISTRY:

Duloxetine has a single chiral center, allowing 2 enantiomers.

The S(+) stereochemical configuration is the enantiomer proposed for marketing. It was used in all clinical studies, and its structure is shown in Figure 1.

7.1.4 PHYSICAL CHEMICAL PROPERTIES

7.1.4.1 Stability

Duloxetine hydrochloride is acid-labile.

According to the sponsor, 'Fifty percent of duloxetine is transformed to Compound 292117, 1-naphthol, the thienyl-alcohol within 60 minutes at pH values between 1.1 and 1.3. Human gastric pH values are as low as 1.2 under fasting conditions. The sponsor quotes the usual range of fasting human gastric pH is 1.4 to 2.1 (median 1.7) in normal healthy volunteers.

Acid stability was tested in human gastric pH fluid at pH values ranging from — About — degradation occurred at pH values of — (see Table 2).

Table 2 Summary of Kinetic Degradation Data

Condition	Degradation Rate (hr^{-1})	Half Life ($t_{½}$) (hr)	$t_{90\%}$ (hr)

The instability of duloxetine in acid media was the motivation for development of an enteric-coated formulation.'

7.1.4.2 Solubility

Table 3 Solubility

Solvent	Descriptive Term	USP Definition (Transformed)	Average Equilibrium Solubility at — (mg/ml)	Average Intrinsic Dissolution Rate at 37°C (mg/min/cm^2)
	Slightly Soluble	mg/ml	NA	NA
	Slightly Soluble	mg/ml	NA	NA
	Sparingly Soluble	mg/ml	NA	NA
pH 7.0 (USP Buffer)	Slightly Soluble	mg/ml	NA	NA
	Slightly Soluble	mg/ml		
	Slightly Soluble	mg/ml		
	Slightly Soluble	mg/ml		

a n = 3, NA – Not assessed

Freely soluble
Not Reported
Slightly Soluble

7.1.4.3 Dissociation Constant (pKa)

[redacted]

7.1.4.4 Polymorphism

[redacted]

7.1.4.5 Hygroscopicity

'No hygroscopic issues have been observed.'

7.2 DRUG PRODUCT

7.2.1 COMMERCIAL DOSAGE FORM:

The proposed to-be-marketed commercial dosage form is an encapsulated enteric-coated pellet formulation dosage form where duloxetine forms 20% of the total capsule weight. The enteric coating protects duloxetine, which is acid labile, from the acidic conditions of the stomach. A schematic of the pellet is shown in Figure 2.

Figure 2 Pellet Schematic

[redacted]

The enteric coating begins to dissolve at pH values above 5.5. At the low pH values of the stomach, the enteric coating keeps the duloxetine hydrochloride from being released in the stomach. At pH values above 5.5, the enteric coating dissolves and the release of duloxetine hydrochloride occurs as an immediate release dosage form.

7.2.2 DEVELOPMENT FORMULATIONS USED IN CLINICAL TRIALS

Three duloxetine hydrochloride concentrations have been used in this enteric-coated pellet formulation in clinical trials to assess the administration of duloxetine in the treatment of depression

Pellets containing approximately 5% w/w, 10% w/w and 20% w/w duloxetine hydrochloride have been filled into gelatin capsules in sufficient quantities to deliver the equivalent of 5 mg to 60 mg duloxetine per capsule. Pellets of 5% w/w duloxetine hydrochloride have been used to prepare 5 mg and 10 mg capsules. Pellets of 10% w/w duloxetine hydrochloride have been used to prepare 20 mg capsules. Duloxetine 20 mg, 30 mg, 40 mg and 60 mg capsules have been prepared with 20% w/w duloxetine hydrochloride pellets.

The 10% pellet weight capsules were used in clinical efficacy studies, and the to-be-marketed 20% formulation has been compared to the 10% capsules in a bioequivalence study, (see Study HMBG in § 8.5.1).

Redacted 1

page(s) of trade secret and/or confidential commercial information (b4)

7.2.4 BATCH FORMULAE

The following pellet batch formulae will be used in manufacturing and may be used as stated or in multiples or fractions thereof. The intended commercial batch size may range from [ ] kg.

Table 5 Theoretical Batch Formulae

Capsule Strength	Number of Capsules	
	Equivalent to [ ] kg of Duloxetine Hydrochloride 20% Enteric Coated Pellets[a]	Equivalent to [ ] kg of Duloxetine Hydrochloride 20% Enteric Coated Pellets[a]
20 mg		
30 mg		
40 mg		
60 mg		

a Based on a unit formula fill weight [ ] mg/capsule to provide 20, 30, 40, and 60 mg of duloxetine base, respectively.

7.3 BIOANALYSIS

7.3.1 DULOXETINE

A number of different assays and assay methods were used to quantify duloxetine. Methods included [ ]. The [ ] methods tended to be unacceptable due to excessive variability, bias, or interference with endogenous substances. The two LC/MS/MS methods were both acceptable and the more accurate one was used for the pivotal bioequivalence study and the pivotal multiple dose PK study with the to-be-marketed formulation. See § 10.3 appendix 3 bioanalytic assay methods used in clinical studies and § 10.4 appendix 4 bioanalytic assay method validation summary for additional information.

7.3.2 METABOLITES

N-Desmethyl-duloxetine, 4-hydroxy-duloxetine glucuronide, and 5-hydroxy, 6-methoxy-duloxetine sulfate were quantified in a few studies. See § 10.3 appendix 3 bioanalytic assay methods used in clinical studies and § 10.4 appendix 4 bioanalytic assay method validation summary for additional information.

7.3.3 PROBE COMPOUNDS AND DRUGS USED IN DRUG INTERACTION STUDIES

A number of other compounds not structurally related to duloxetine were quantified in a few studies. These included drug interaction studies or studies that used probe compounds for phenotyping. See § 10.3 appendix 3 bioanalytic assay methods used in clinical studies and § 10.4 appendix 4 bioanalytic assay method validation summary for additional information.

7.4 DISSOLUTION

7.4.1 SPONSOR'S PROPOSED PRODUCT DISSOLUTION METHODS AND SPECIFICATIONS

Table 6 Proposed Product Dissolution Methods and Specifications

METHOD ID	BIOSUM.F.1.	BIOSUM.F.2.
METHOD TITLE	Dissolution Method and Specification for **20 mg and 30 mg** Duloxetine HCl 20%(w/w) Capsules Containing Enteric-Coated Pellets	Dissolution Method and Specification for **40 mg and 60 mg** Duloxetine HCl 20%(w/w) Capsules Containing Enteric-Coated
Dosage Form	Market Image Encapsulated Pellets	Market Image Encapsulated Pellets
Strength(s)	**20 mg and 30 mg** Capsules 20% w/w Pellets	**40mg and 60 mg** Capsules 20% w/w Pellets
Apparatus Type	USP Dissolution Apparatus 1 (Baskets)	USP Dissolution Apparatus 1 (Baskets)
Media		
A Gastric Challenge:	0.1 N Hydrochloric Acid in Water	0.1 N Hydrochloric Acid in Water
B Media 2:	50 mM pH 6.8 Phosphate Buffer in Water	50 mM pH 6.8 Phosphate Buffer in Water
Volume	1000 mL	1000 mL
Speed of Rotation (Rate of Flow for Flow-through Apparatus)	100 RPM	100 RPM
Sampling Time(s)		
A Sampling Time(s) for Gastric Challenge:	120 minutes	120 minutes
B Sampling Time(s) for Media 2:	15 minutes 30 minutes 45 minutes 60 minutes	15 minutes 30 minutes 45 minutes 60 minutes
Analytical Method	HPLC with UV detection	HPLC with UV detection
Dissolution Specifications (Based on USP Drug Release<724>)		
A Dissolution Specification for Gastric Challenge:	Meets USP requirements of not more than — dissolved in 120 minutes.*	Meets USP requirements of not more than —dissolved in 120 minutes.*
B Dissolution Specification for Media 2:	Meets USP requirements of **Q** = — dissolved in 60 minutes.	Meets USP requirements of **Q** = — dissolved in 60 minutes.

* Because any duloxetine released during the . This calculation reflects both differences in response factors as well as reaction mechanisms involved in the acid degradation pathway.

7.4.2 CRITIQUE OF DISSOLUTION SPECIFICATIONS

The sponsor's data supports the proposed dissolution specifications. However, in order to keep dissolution specifications consistent across strengths, it is acceptable and recommended that the specification be Q = ___ in 60 minutes for all strengths.

7.4.3 DISSOLUTION DATA FROM PIVOTAL PHASE III STUDIES AND PIVOTAL BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES

7.4.3.1 Description of Pivotal Lots

The lots used in the pivotal phase III clinical efficacy and safety studies by formulation are shown in Table 7 through Table 10.

Table 7 shows pivotal bioavailability and pharmacokinetic studies with the to-be-marketed 20% formulation and their lot numbers.

All pivotal lots are in bold, for those that are shaded individual data is provided, the single lot that is italicized is a 5% formulation.

Table 7 Lots of Duloxetine Hydrochloride Capsules (20% To-Be-Marketed (TBM) Enteric-Coated Pellets) Used in Pivotal Pharmacokinetic & Bioequivalence Studies

Package	Package Lot Number	Dose Form Lot Number	Drug Substance Lot Number	Item Description and Strength
F1J-LC-HMBG – Pivotal Bioequivalence of 20% TBM Formulation and 10% Clinical Trial Formulation. F1J-LC-HMBI – Absolute Bioavailability F1J-LC-HMBN – Single and Multiple Dose PK				
Bottle	CT17676	**CT17696**	031JD0	Capsules Duloxetine HCl equiv. to 60 mg Duloxetine

Table 8 shows other pharmacokinetic studies with the to-be-marketed 20% formulation and their lot numbers.

Table 8 Lots of Duloxetine Hydrochloride Capsules (20% To-Be-Marketed Formulation Enteric-Coated Pellets) Used in Other Phase I & II Pharmacokinetic Studies

Package	Package Lot Number	Dose Form Lot Number	Drug Substance Lot Number	Item Description and Strength
F1J-FW-SBAG – Duloxetine Paroxetine Pharmacokinetic Interaction Study				
Bottle	CT19715	CT18603	032JD0, 034JD0	Capsules Duloxetine HCl equiv. to 20 mg Duloxetine

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Table 9 and Table 10 respectively show pivotal clinical efficacy and safety studies conducted with 5% and 10% clinical trial formulations and their lot numbers

Table 9 Lots of Duloxetine Hydrochloride Capsules (5 and 10%, Clinical Trial Formulation Enteric-Coated Pellets) Used in Pivotal Phase III Efficacy Studies in Major Depressive Disorder

Package	Package Lot Number	Dose Form Lot Number	Drug Substance Lot Number	Item Description and Strength
F1J-MC-HMAQ				
Blister	CT13506	**CT12415**	032JD4	Capsules Duloxetine HCl equiv. to 20 mg Duloxetine
		CT03648	025JD4	Capsules Duloxetine HCl equiv. to 10 mg Duloxetine
	CT13534	**CT12415**	032JD4	Capsules Duloxetine HCl equiv. to 20 mg Duloxetine
	CT14378	***CT03648***	025JD4	Capsules Duloxetine HCl equiv. to 10 mg Duloxetine
		CT12415	032JD4	Capsules Duloxetine HCl equiv. to 20 mg Duloxetine
	CT14381			Capsules Duloxetine HCl equiv. to 20 mg Duloxetine
	CT15917	**CT15732**	040JD4	Capsules Duloxetine HCl equiv. to 20 mg Duloxetine
	CT16312	**CT16273**	033JD4	Capsules Duloxetine HCl equiv. to 10 mg Duloxetine
		CT15732	040JD4	Capsules Duloxetine HCl equiv. to 20 mg Duloxetine
	CT16332			Capsules Duloxetine HCl equiv. to 20 mg Duloxetine
	CT17067			Capsules Duloxetine HCl equiv. to 20 mg Duloxetine
F1J-MC-HMAT				
Blister	CT16423	**CT15797**	041JD4	Capsules Duloxetine HCl equiv. to 20 mg Duloxetine
	CT16744	**CT15732**	040JD4	Capsules Duloxetine HCl equiv. to 20 mg Duloxetine
	CT17335	**CT15935**	033JD4	Capsules Duloxetine HCl equiv. to 20 mg Duloxetine
	CT17968			
F1J-MC-HMBH				
Blister	CT18124	**CT17078**	032JD4, 033JD4, 034JD4, 040JD4	Capsules Duloxetine HCl equiv. to 20 mg Duloxetine

Table 10 Lots of Duloxetine Hydrochloride Capsules (10% Clinical Trial Formulation, Enteric-Coated Pellets) Used in Pivotal Phase III Safety Studies in Major Depressive Disorder

Package	Package Lot Number	Dose Form Lot Number	Drug Substance Lot Number	Item Description and Strength
F1J-MC-HMAU				
Bottle	CT15828	**CT15732**	040JD4	Capsules Duloxetine HCl equiv. to 20 mg Duloxetine
	CT16299	**CT15797**	041JD4	
		CT15935	033JD4	
	CT19092			
	CT16518	**CT17075**	032JD4, 033JD4, 034JD4, 040JD4	
	CT17610			
	CT17617			
	CT16745	**CT17078**		
	CT17204			
	CT19093			
	CT18923	**CT15732**	040JD4	
	CT18409	**CT17488**	033JD0	
	CT19098			
	CT19109			
	CT20489			

7.4.3.2 Dissolution Data for Pivotal Lots

Table 11 shows pivotal bioavailability and pharmacokinetic studies with the 20% to-be-marketed formulation.

Table 11 Dissolution Data that for Capsules Prepared from 20% w/w Pellets (To-Be-Marketed Formulation) and Used in Pharmacokinetic Studies

Test	Lot Number	
	CT17696	CT18603
Capsule Strength	60 mg	20 mg
Date of Manufacture	11 May 2000	28 Nov 2000
Site of Manufacture	Indianapolis	Indianapolis
Batch Size	—	—
	Pilot Batch Size	**Biobatch Size**
Use of Batch	**Pivotal Bioavailability and Bioequivalence Study**	Drug Interaction Study with Paroxetine
Assay, % Label Claim (mg/capsule)		
Uniformity of Dosage Units		
HPLC/B07452, mg/capsule (% RSD)	— (1.78)	— (3.99)
Dissolution, (%)		
n	12[1]	6
Acid Stage (0.1N HCl)	0.4 ± 0.2 (62.9)	1.0 ± 0.7 (69.4)
pH 6.8		
15 minutes	34.9 ± 2.0 (5.6)	36.1 ± 1.3 (3.7)
30 minutes	62.5 ± 3.1 (4.9)	71.3 ± 3.9 (5.4)
45 minutes	76.3 ± 3.2 (4.2)	89.9 ± 4.6 (5.2)
60 minutes	84.4 ± 3.0 (3.6)	99.7 ± 4.2 (4.2)
1-Naphthol (%)[2]	0.01	0.00

1 Stage 2 testing performed
2 1-Naphthol levels are below the ICH level for identification in new drug products, therefore this degradation product will be monitored within the category of "Largest Unspecified Impurity".

Table 12 shows pivotal bioavailability and pharmacokinetic studies with the 5% and 10% clinical trial formulations.

Table 12 Dissolution Data for Duloxetine Capsules Prepared from 5% and 10% w/w Pellets (Clinical Trial Formulations) Used in Pivotal Phase III Efficacy and Safety Trials in Major Depressive Disorder

Test	Capsule Lot Number								
	CT17488	CT15935	CT17075	CT17078	CT16273	CT12415	CT15732	CT15797	*CT03648*[1,2]
Capsule Strength	20 mg	20 mg	20 mg	20 mg	10 mg	20 mg	20 mg	20 mg	10 mg
Date of Manufacture	05 Jun 2000	25 Sep 1997	29 Nov 1999	29 Nov 1999	22 Sept 1997	06 Nov 1995	29 Sep 1997	30 Sep 1997	07 Nov 1994
Site of Manufacture	Indianapolis	Indianapolis	Indianapolis	Indianapolis	Indianapolis	Indianapolis	Indianapolis	Indianapolis	Indianapolis
Batch Size									
Description	Biobatch	Pilot Batch	Pilot Batch	Biobatch	Pilot Batch	Pilot Batch	Pilot Batch	Pilot Batch	Pilot Batch
Use of Batch	Phase III Safety Study in MDD	Phase III Efficacy & Safety Studies in MDD		Phase III Safety Study in MDD	Phase III Efficacy Study in MDD		Phase III Efficacy & Safety Studies in MDD		Phase III Efficacy Study in MDD
Assay, % Label Claim (mg/capsule)									
Uniformity of Dosage Units									
HPLC/B07452, mg/capsule (% CV)									
Dissolution, (%)									
n	12[3]								
Acid Stage (0.1N HCl)	1	0.8 ± 0.5 (61.2)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)
pH 6.8									
15 minutes		59.4 ± 2.4 (4.1)							
30 minutes		87.9 ± 2.4 (2.7)							
45 minutes		99.1 ± 1.8 (1.9)							
60 minutes		102.3 ± 1.3 (1.3)							
1-Naphthol (%)[4]	0.01	0.01	0.01	0.00	0.00	0.00	0.01	0 01	

1 These batches were initially released using different acceptance criteria and methods. They were subsequently re-tested using revised tests. Only the more recent data are provided.
2 Prepared using 5% duloxetine hydrochloride w/w pellets.
3 According to the sponsor twelve capsules were tested, however the batch met stage 1 requirements.
4 1-Naphthol levels are below the ICH level for identification in new drug products; therefore this degradation product will be monitored within the category of "Largest Unspecified Impunty".

7.5 BIOWAIVER REQUEST

7.5.1 DISSOLUTION DATA IN SUPPORT OF BIOWAIVER

Table 13 Duloxetine Dissolution Summary Statistics in Support of Biowaiver for Intermediate Capsules Strengths (30 mg & 40 mg) of 20% (w/w) Enteric Coated Encapsulated Pellet Formulations

Proposed Specification at 60 minutes in pH 6.8 Buffer	Lot Number	Capsule Strength (mg)	Formulation [Pellet EC % (w/w)]	n	% Dissolved[a,b] Time in pH 6.8 Buffer (minutes) 0	15	30	45	60
Q = —	DPD16795	30 mg	20%	12	0.3 ± 0.2 (82.1)	49.1 ± 2.0 (4.1)	78.2 ± 1.8 (2.3)	91.8 ± 1.3 (1.4)	98.9 ± 1.0 (1.0)
	DPD16796	30 mg	20%	12	0.4 ± 0.5 (141.5)	50.0 ± 2.2 (4.3)	79.4 ± 1.8 (2.2)	91.7 ± 1.3 (1.4)	97.1 ± 1.1 (1.1)
	DPD16797	30 mg	20%	12	0.4 ± 0.3 (96.3)	48.5 ± 4.2 (8.7)	75.3 ± 3.8 (5.1)	89.1 ± 2.8 (3.2)	95.0 ± 2.1 (2.2)
Q = —	DPD16798	40 mg	20%	6c	0.7 ± 0.2 24.0	44.5 ± 5.7 (12.7)	73.9 ± 8.4 (11.4)	88.1 ± 8.4 (9.5)	94.5 ± 7.0 (7.5)
				12d	0.6 ± 0.2 (43.5)	45.6 ± 4.2 (9.1)	74.7 ± 5.8 (7.8)	88.8 ± 5.8 (6.5)	95.2 ± 4.9 (5.1)
				11e	***0.5 ± 0.3 (45.9)***	***46.7 ± 1.4 (3.1)***	***76.3 ± 1.5 (2.0)***	***90.4 ± 1.6 (1.7)***	***96.6 ± 1.3 (1.4)***
	DPD16803	40 mg	20%	12	0.6 ± 0.3 (47.5)	47.2 ± 1.9 (4.0)	77.3 ± 0.9 (1.1)	90.4 ± 0.8 (0.8)	96.3 ± 1.0 (1.0)

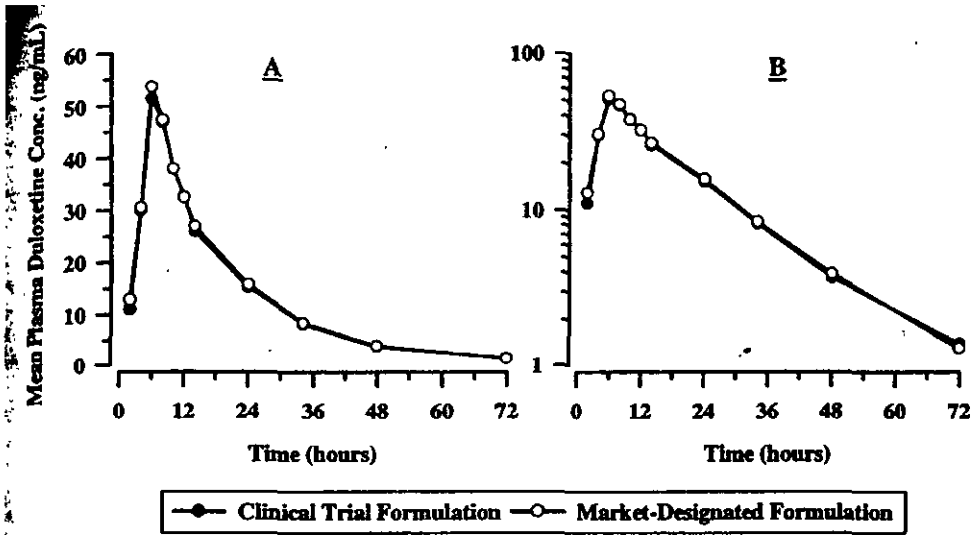
a Values are mean ± SD, (CV), Range
b time 0 is at the end of 2 hour acid incubation
c Stage 1 testing
d Stage 2 testing
e excluding outlier (

8 PHARMACOKINETICS / PHARMACODYNAMICS / CLINICAL PHARMACOLOGY

8.1 PLASMA CONCENTRATION TIME PROFILE

When administered orally as a — . release capsule, duloxetine follows a one-compartment open model with a lag phase and a half-life of approximately 10-12 hours, (See Figure 3).

Figure 3 Mean Plasma Concentration Time Course of Duloxetine To-Be-Marketed and Clinical Trial Formulations, A – Linear Scale; B-Semi-log Scale



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8.2 LINEARITY WITH DOSE

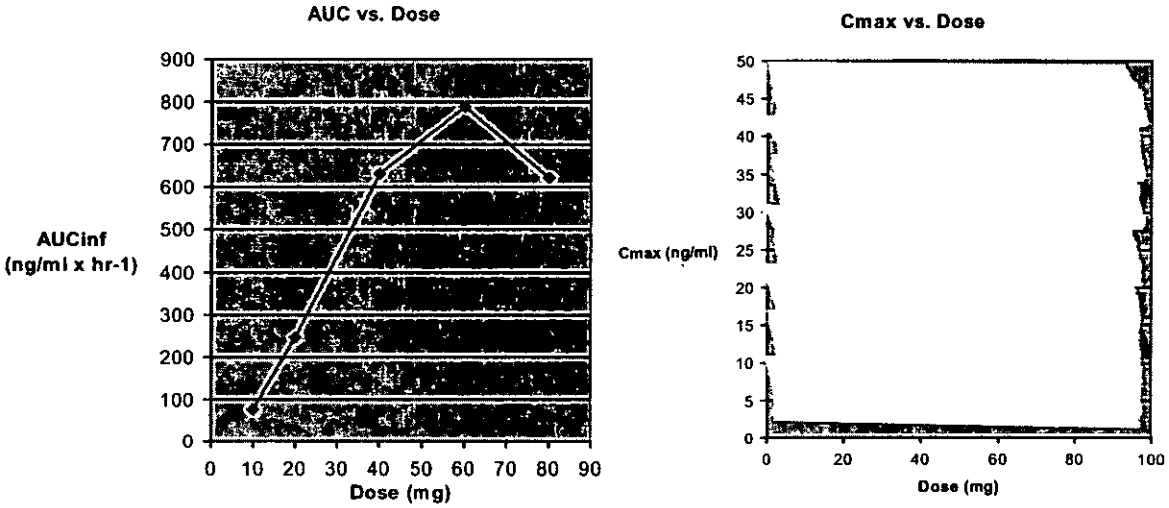
The sponsor claims in the HPBIO summary that there are a number of single and multiple dose studies that provide data for pharmacokinetics vs. dose level. A summary of the study designs of these studies in Table 14, shows that only 3 studies provide evaluable information.

Table 14 Summary of Studies that Sponsor Claims for Dose Linearity Data

Study	Dosing Regimens	# of Subjects				PK Sampling	Comments
HMAA	Single Doses						
	1 mg					No PK Sampling	
	3 mg						
	7 mg						
	10 mg						
	15 mg						
	25 mg						
	35 mg	816				Full PK	Limited number of subjects below 60 mg with PK data prevents use in determining dose linearity
	50 mg		567				
	60 mg fed	816	567	671	506		
	60 mg fasting	816	567		506		
HMAB	SD Fasting	Grp 1 Received 5, 20, 60, 80 mg Grp 2 Received 10, 20, 40, 60 mg Grp 3 Received 10, 20, 60, 80 mg				Only Mean PK Metrics Reported	Groups consisted of 2 – 4 subjects
	5 mg						
	10 mg						
	20 mg						
	40 mg						
	60 mg						
	80 mg						
HMAD	2.5 mg qd x 14 days	Different subjects at each dose level				Full Profiles Days 1, 7, 14, 15	No PK Data obtained as assay didn't work
	5 mg qd x 14 days						
	10 mg qd 14 days						
	20 mg qd x 14 days						
	40 mg qd x 14 days						
HMAP	20 mg bid					Trough only	Linear Troughs
	30 mg bid					Trough only	
	40 mg bid					Full PK profile	
HMAR	40 mg bid x 6					Full Profiles @ each dose level	Dose Non-linearity seen. (see Figure 6)
	60 mg bid x 6						
	80 mg bid x 6						
HMAZ	40 mg q12 h x 6d					PK obtained only with 60 mg at SS	Desipramine Interaction Study
	60 mg q12 h x 15 d						
HMBD	60 mg bid x 7.5					Full Profiles at ss (w/o LZP on day 4 w LZP day 8)	Lorazepam interaction study
HMBN	60 mg SD, QAM & BID					Full profiles obtained with each dosage regimen	Good Study for Time invariance
SBAG	40 mg QD x 5 days					Full Profiles	Duloxetine/ Paroxetine PK Interaction study

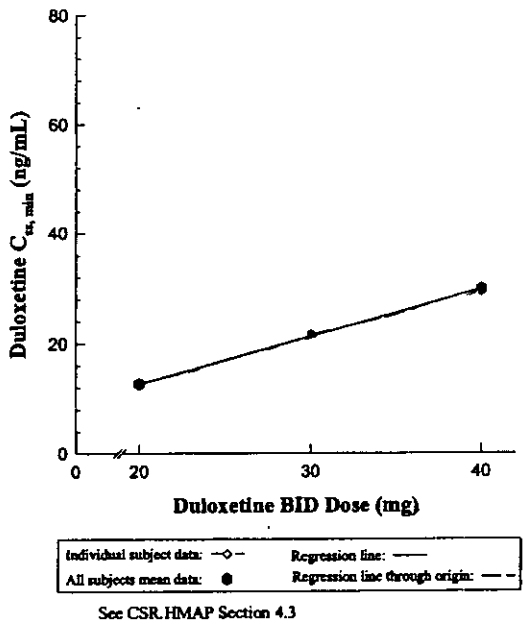
As shown in study HMAB, upon single dose administration with enteric coated tablets duloxetine exhibits apparent linearity with dose up to approximately 40 mg. Above 40-60 mg absorption appears to plateau (See Figure 4 and Table 18). Subjects did receive more than one dose level, consequently due to the limited data, (i.e. few subjects and only a single dose above 60 mg) any conclusions drawn can't be considered definitive.

Figure 4 Single Dose Duloxetine EC Tablets AUC & Cmax vs. Dose (Study HMAB)



However, dose linearity up to at least 40 mg is supported by data from study HMAP, (see Figure 5).

Figure 5 Duloxetine $Cmin^{ss}$ Dose Linearity from 20 mg to 40 mg BID (Study HMAP)

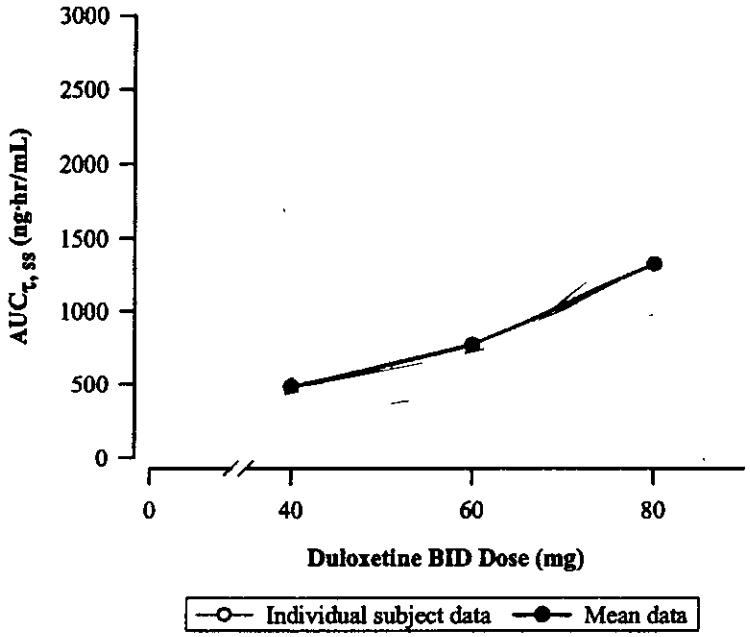


In contrast, when higher doses are studied in study HMAR, there does appear to be a trend for non-linearity in the opposite direction from study HMAB at doses above 60 mg, (i.e. concentrations increase disproportionately in HMAR rather than plateau as in study HMAB (see Table 15 and Figure 6).

Table 15 Duloxetine Pharmacokinetic Metric Linearity in Study HMAR

Duloxetine Dose (mg BID)	Cmin (ng/ml)	Cmax (ng/ml)	AUC (ng/ml x hr)	Ratios To 40 mg				Ratios to 60 mg			
				Expected Ratio	Measured Ratios			Expected Ratio	Measured Ratios		
40	35	—	482	—	—	—	—	—	—	—	—
60	57	—	759	1.5	1.6	1.6	1.6	—	—	—	—
80	94	—	1322	2.0	2.7	2.6	2.7	1.3	1.6	1.6	1.7

Figure 6 Nonlinearity of AUCτ^{ss} with Duloxetine Dose (Study HMAR)



See CSR.HMAR Section 14.2

The following is from the sponsor's statement regarding multiple-dose, dose linearity:

"Duloxetine was given 40, 60, and 80 mg BID to 12 healthy subjects in HMAR, 60 mg BID to 14 healthy subjects in HMAZ, 60 mg BID to 16 healthy subjects in HMBD and 60 mg BID to 11 healthy subjects in HMBN. Capsules containing 10% enteric-coated pellets were used in HMAR, HMAZ, HMBD and capsules containing 20% enteric-coated pellets were used in HMBN. Steady state was achieved by Day 3 of the dosing regimen as predicted by a mean elimination half-life of 11.7 (10.1 to 14.3) hours.

Table BIOSUM.4.6 presents steady-state pharmacokinetic parameters obtained from these clinical pharmacology studies. In general, duloxetine plasma concentrations reach a peak at 6 hours post dose for 40 mg, 60 mg and 80 mg BID. The CL/F value does not appear to differ considering the intersubject variability.

Table 16 Table BIOSUM.4.6. Duloxetine Pharmacokinetic Parameters in Healthy Subjects Receiving BID regimens

Parameter	Arithmetic Mean (CV%)		
	40 mg BID	60 mg BID	80 mg BID
	(n = 12)	(n = 53)	(n = 12)
Tmax (hr)[a]	6.00	6.00	6.00
Cmax,ss (ng/ml)	54.0	118	141
Cmin,ss (ng/ml)	35.3	67.9	93.7
Cav,ss (ng/ml)	40.2	89.5	110
AUCτss (ng·hr/mL)[b]	482	1074	1322
CL/F (L/hr)	104	74.3	82.0

n = number of observations included in means
a median (range)
b τ = 12 hours
See CSR.HMAR Section 11.2, CSR.HMAZ Section 11.2, CSR.HMBD Section 11.2 and CSR.HMBN Section 11.2

In spite of the sponsor's claim that the high variability prohibits concluding nonlinearity, it should be remembered that these are composite values with multiple subpopulations that contribute to the high variability. In spite of this, the trend for nonlinearity is still present even though the artificial high variability imposed by combining data might make finding statistical significance difficult.

8.3 TIME INVARIANCE

Time invariance was examined in study HMBN under two dosing regimens, 60 mg po qd and 60 mg po q12h. It appears that the q12h regimen was examined in order to increase drug exposure over a 24 hour period in the face of the saturation of absorption at single doses above 60 mg, and/or to prolong the duration of the serotonin reuptake blockade, and possibly to minimize AEs.

Single 60 mg doses with the to-be-marketed enteric beaded capsule formulation produced Cmaxs of around — ng/ml with a median lag time of 2-4 hours and a median Tmax of around 6 hours. Median half-life was around 12 hours.

According to the sponsor: *"mean AUCτ,ss on the QD and BID dosing regimens were significantly higher than mean AUC0-∞ after single dosing, reflecting a time-dependent decrease in CL/F. The ratio of LS means (90% CI) for CL/F estimated at steady state relative to that estimated after single dosing was 0.67 (0.59 to 0.75) for QD dosing and 0.61 (0.51 to 0.73) for BID dosing. Moreover, the Vz/F value was significantly decreased following BID dosing compared to single-dose estimates (p = 0.0045). Correspondingly, a slightly longer (~10%) elimination half-life was observed during washout after BID dosing. But these changes do not appear to be consistent or major across all subjects",* (see Figure 7 and Table 19).

Since the half-life is approximately 12 hours, q12 hour dosing should result in a steady state AUC of 1.44 times the AUC after a single dose. The actual ratio is 1.63, (Geometric Mean Ratio 1.62) which may indicate nonlinear pharmacokinetics with increased exposure over time. In addition, the 63% increase AUC along with the approximately 35% decreases in CI/F and V/F, and the increase in half-life are consistent with an approximately 20% decrease in clearance with no change in volume. The potential

basis for this nonlinearity appears to be a saturation of CYP2D6 as will be shown in § 8.6.3 Multiple Dose Metabolite Kinetics and § 8.6.4 In Vitro Metabolism Studies.

Figure 7 Comparative Pharmacokinetic Metrics after Single Doses, and Steady-State QD and BID doses of Duloxetine 60 mg (Study HMBN)

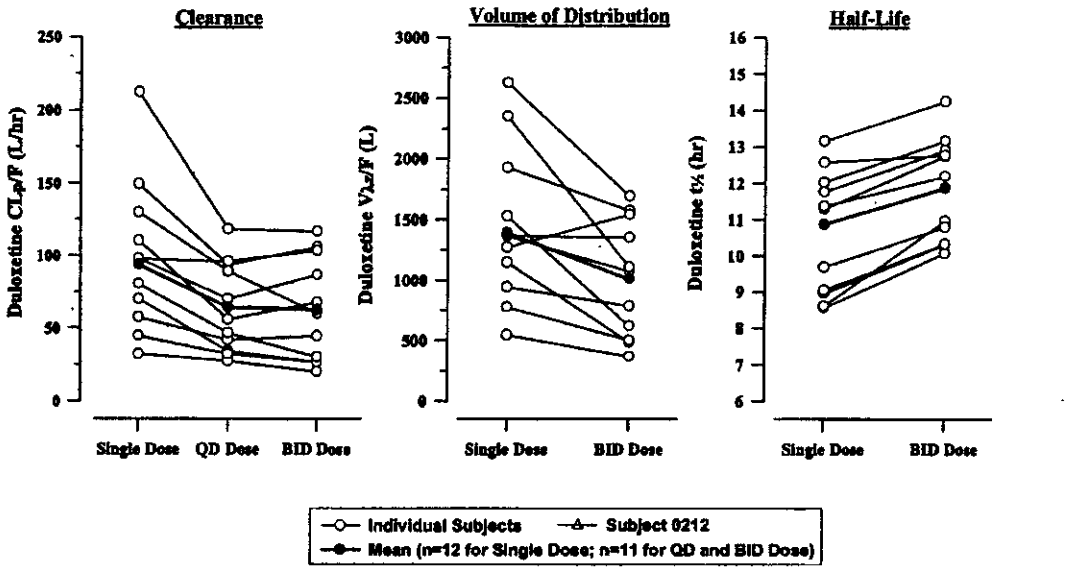


Table 17 Geometric Means and Comparisons of Duloxetine Pharmacokinetic Metrics Between 60 mg Single Dose and Multiple Dose Administration (Study HMBN).

Metrics	Dosing Regimen	QD or BID Dosing vs. a Single Dose				BID vs. QD Dosing		
		Geometric Mean	Ratio of Means	90% CI	p-Value	Ratio of Means	90% CI	p-Value
AUC (ng/ml x hr^{-1})	Single Dose	734.7						
	QD Dosing	1100.7	1.50	(1.33, 1.68)	0.0001			
	BID Dosing	1209.0	1.65	(1.37, 1.97)	0.0005	1.10	(0.96, 1.25)	0.22
CLp/F (L/hr)	Single Dose	81.7						
	QD Dosing	54.5	0.67	(0.59, 0.75)	0.0001			
	BID Dosing	49.6	0.61	(0.51, 0.73)	0.0005	0.91	(0.80, 1.04)	0.22
Vz/F (L)	Single Dose	1264.1						
	BID Dosing	864.8	0.68	(0.57, 0.83)	0.0045			
$t_{1/2}$ (hr)	Single Dose	10.7						
	BID Dosing	12.0	1.11	(1.08, 1.15)	0.0001			

Notes: AUC = AUC0-∞ or AUCτ,ss ;CLp/F=CLp/F; Vz/F = Vλz /F

Table 18 Duloxetine Pharmacokinetic Metrics for Single Rising Dose Studies

Study	Date	Design	Assay	N	Gender	Age (years)	Weight (Kg)	Race C/B/A/NatAmer	Tabacco (PPD)	2D6 Genotype	Formulation	Dose (mg) & Administration	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	AUC (ng/ml x hr)	t1/2 (hours)	CL/F (L/hr)	CL/F (L/hr x kg)	Vd/F (L)	Vd/F (L/kg)
HMAB	Mar – Apr 1992	SRD	NR	6	Male	37 5 ± 10 5 (28 1) 26 0 - 55 0	77 7 ± 8 4 (8 2) 67 7 - 85 0	NR	NR	NR	EC Tablets	—	—	—	—	—	—	—	—	—	—
				4	NR	NR	NR					10 mg	NR	4 15 ± 1 06 (25 5)	5 0 ± 1 41 (28 2)	76 8 ± 16 5 (21 5)	13 8 ± 1 5 (10 9)	NR	1 64 ± 0 47 (28 7)	NR	32 2 ± 5 8 (18 0)
				4	NR	NR	NR					20 mg	NR	17 6 ± 9 5 (54 0)	3 0 ± 0 0 (0 0)	247 ± 169 (68 4)	12 1 ± 5 3 (43 8)	NR	1 79 ± 1 75 (97 8)	NR	25 1 ± 16 9 (67 3)
				4	NR	NR	NR					40 mg	NR	38 8 ± 9 0 (23 2)	6 75 ± 3 77 (55 9)	632 ± 307 (48 6)	14 1 ± 6 2 (44 0)	NR	0 95 ± 0 40 (42 1)	NR	17 6 ± 6 1 (34 7)
				4	NR	NR	NR					60 mg	NR	46 3 ± 16 1 (34 8)	4 75 ± 1 5 (31 6)	789 ± 601 (76 2)	14 2 ± 8 6 (60 6)	NR	1 40 ± 0 75 (53 6)	NR	22 5 ± 4 7 (20 9)
				4	NR	NR	NR					80 mg	NR	43 3 ± 18 7 (43 2)	4 0 ± 1 41 (35 3)	622 ± 333 (53 5)	12 1 ± 1 2 (9 9)	NR	1 65 ± 0 79 (42 7)	NR	33 1 ± 15 3 (46 2)

Table 19 Pharmacokinetic Metrics of Duloxetine When Administered in To-Be-Marketed Enteric Coated Bead Capsule Formulation

Study	Date	Design	N	Sex M / F	Age (years)	Weight (Kg)	Race C/B/A/NatAmer	Tabacco (PPD)	2D6 Genotype	Formulation	Dose (mg) & Administration	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	AUC (ng/ml x hr)	Cmin (ng/ml)	C/F 3rd (ng/ml)	Fluctuation	t1/2 (hours)	CL/F (L/hr)	CL/F (L/hr x kg)	Vd/F (L)	Vd/F (L/kg)	Bioavailability (F)
HMBI a b	Aug-2000	SD Absolute BA	2	1 / 1	NR	NR	NR	NR	NR	60 mg Cap 20% EC pellets TBM	60 mg po	ND	59 3 ± 23 2 (39 1) [94 1]	5 ± 1 4 (28 3) [6 0]	910 5 ± 320 3 (35 2) [1080 5]	—	—	—	11 45 ± 0 2 (1 9) 10 1-	70 25 ± 24 7 (35 1) [60 1]	—	1157 5 ± 386 8 (33 4) [1071 8]	—	0 9745 ± 0 5 (55 9) [113 3]
HMBG a b	Jul 2001 BE	SD PK TBM	25	5 / 20	41 44 ± 10 6 (25 5) 22 - 65 [39]	70 37±13 64 (19 0) 53 1 – 100 2 [68 0]	19/4/2/0	NR	NR	60 mg caps 20% EC pellets TBM	60 mg po Fasted	2 0 ± 0 9 (45 3) 1 0 - 4 0 [2 0]	64 1 ± 23 1 (42 7) [46 5]	6 3 ± 1 1 (17 5) [6 0]	944 7 ± 448 7 (47 5) [897 2]	—	—	—	12 1 ± 1 9 (15 7) [12 0]	81 9 ± 51 2 (62 6) [68 9]	1 1 ± 0 6 (49 7) [0 9]	1362 1 ± 713 6 (52 4) [1254 1]	18 9 ± 8 3 (43 9) [16 0]	—
HMBN	Mar – Apr 2001	OL SD PK (First dose of MD Study)	12	6 / 6	38 9 ± 11 2 (28 7) [36 5] 23 0 - 61 0	80 3 ± 15 (19) 72 8 66 2 – 113 4	9/3/1/0	Mixed	11 EM 1 PM	60 mg caps 20% EC pellets TBM	60 mg po 2 hours after a light breakfast	2 4 ± 1 2 (51 3) 1 - 4 [2]	56 1 ± 28 6 (48) [45 2]	5 3 ± 1 3 (24 4) [5 0]	845 3 ± 473 6 (56) [680 7]	—	—	—	10 9 ± 1 8 (16 5) [11 3]	93 8 ± 51 7 (55) [89 0]	1 2 ± 0 7 (59 2) [1 1]	1390 9 ± 634 0 (45 7) [1318 6]	17 6 ± 8 2 (46 7) [15 2]	—
		MD qAM x 8 days	11	5 / 6	38 8 ± 11 7 (30 2) [36 0] 23 0 - 61 0	79 1 ± 15 1 (19 2) [71 2] 66 2 - 113 4	8/3/1/0/0	Mixed	EM	60 mg Caps 20% EC Pellets TBM	60 mg po qAM 2 hours after a light breakfast	2 7 ± 1 3 (46 6) 1 - 4 [2]	89 5 ± 35 6 (39 8) [94 1]	5 6 ± 1 2 (21 4) [6 0]	1175 6 ± 576 7 (49 1) [1080 5]	27 0 ± 17 3 (64 1) [24 4]	49 0 ± 24 0 (49 0) [45 0]	139 3 ± 34 6 (24 9) [143 2]	—	64 0 ± 31 0 (48 4) [55 5]	0 82 ± 0 4 (48 9) [0 70]	—	—	—
		MD q12h x 7 5 days (AM data)	11	5 / 6	38 8 ± 11 7 (30 2) [36 0] 23 0 - 61 0	79 1 ± 15 1 (19 2) [71 2] 66 2 - 113 4	8/3/1/0/0	Mixed	EM	60 mg Caps 20% EC Pellets TBM	60 mg po q12h 2 hours after a light breakfast	3 2 ± 1 2 (36 7) 1 - 4 [4]	144 0 ± 65 4 (59 3) [113 3]	6 0 ± 1 3 (21 1) [6 0]	1375 8 ± 869 2 (63 2) [998 1]	85 2 ± 59 7 (70 0) [64 9]	114 7 ± 72 4 (63 2) [63 2]	57 4 ± 17 3 (30 1) [61 7]	11 9 ± 1 4 (11 9) 10 1-	62 5 ± 35 9 (57 4) [60 1]	0 81 ± 0 49 (60 6) [0 67]	1009 4 ± 484 3 (48 0) [1071 8]	13 03 ± 6 62 (50 8) [11 74]	—

a AUC∞ for single dose data and AUCτ for multiple dose data
ND – Not determinable as raw data not provided
NR – Not reported

8.4 BIOAVAILABILITY

8.4.1 RELATIVE BIOAVAILABILITY

Relative bioavailability to a solution is not feasible, or advisable, as duloxetine is acid labile and hydrolyzes to produce naphthol. Thus an enteric-coated oral formulation is required.

Due to the need to maintain the enteric coating, patients should be advised not to crush the pellets.

8.4.2 ABSOLUTE BIOAVAILABILITY

The absolute bioavailability of duloxetine was examined in 2 subjects (male & female) in study HMBI. Unfortunately, the bioavailability varied considerably from 59% to 136%, (see Table 20). The bioavailability of greater than 1.0 may be due to duloxetine's nonlinear kinetics. However in mass balance study SAAZ the total radioactivity recovered in urine in combination with the identified and unidentified metabolites recovered in feces was approximately 88% indicating that duloxetine is well absorbed.

Table 20 Absolute Bioavailability of Duloxetine in TBM Formulation (Study HMBI)

Subjects	Tlag (hours)	Tmax[a] (hours)	Cmax[a] (ng/ml)	AUC_{0-t} (ng/ml x hr)	$AUC_{0-\infty}$ (ng/ml x hr)	$t_{1/2}$ (hours)	Cl[a] (L/hr)	Vd_β[a] (L)	F
1 M 1 F	**60 mg Capsule PO (TBM Formulation)**								
	NR	5 ± 1.4 (28.3)	59.3 ± 23.2 (39.1)	888 ± 330.9 (37.3)	910.5 ± 320.3 (35.2)	11.45 ± 0.2 (1.9)	70.25 ± 24.7 (35.1)	1157.5 ± 386.8 (33.4)	0.9745 ± 0.5 (55.9)
	0.8 mg IV over 0.5 Hours								
	NA	0.5 ± 0.0 (0.0)	2.05 ± 1.2 (58.6)	8.25 ± 1.9 (23.1)	13.35 ± 3.0 (22.8)	7.08 ± 2.4 (34.4)	61.6 ± 14.1 (23.0)	604 ± 72.1 (11.9)	NA

a – for oral administration metric/F
NR – not reported
NA – not applicable

8.5 BIOEQUIVALENCE

8.5.1 TO-BE-MARKETED FORMULATION (20% ENTERIC COATED CAPSULES) VS. CLINICAL TRIAL FORMULATION (10% ENTERIC COATED CAPSULES)

The to-be-marketed formulation, (a 20% enteric coated beaded capsule), is bioequivalent to the primary pivotal clinical trial formulation, (CTF-3, a 10% enteric coated beaded capsule), under single dose fasting conditions at the highest to be marketed strength (60 mg), (see Figure 8 and Table 21). Study HMBG was a single dose crossover study in 25 healthy males and females.

Figure 8 Comparison of Single Dose Mean Concentration vs. Time Profiles of Duloxetine (1 x 60 mg) To-Be-Marketed (20% w/w) and Primary Clinical Trials Formulations (10% w/w) (3 x 20 mg) Under Fasting Conditions - (Study HMBG)

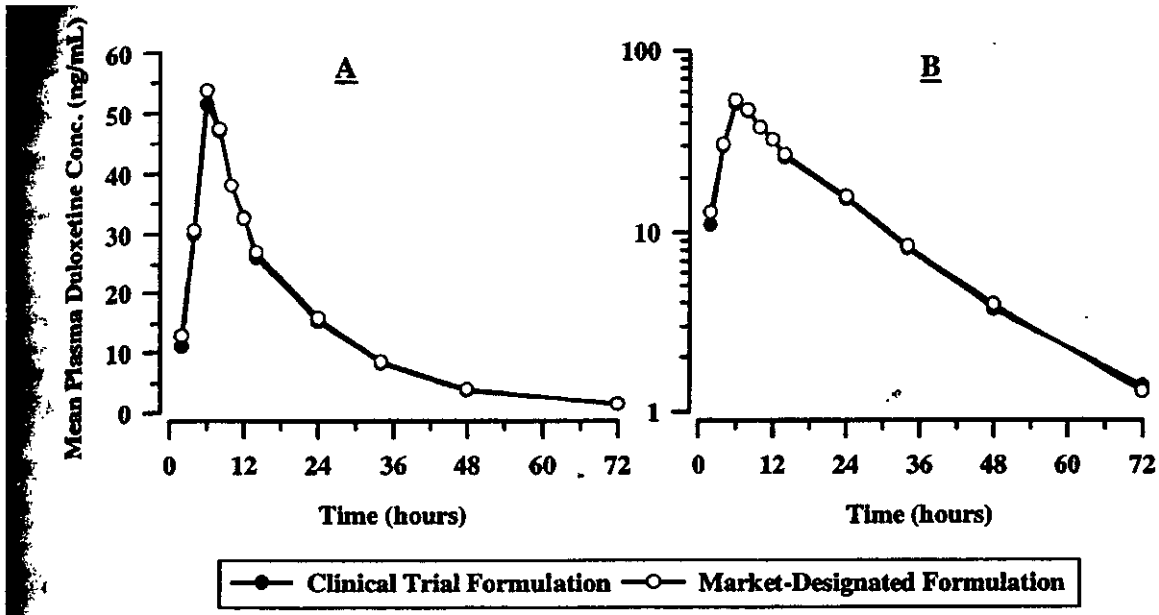


Figure HMBG.11.1. Mean plasma concentration-time curves of duloxetine after a single oral dose of 60 mg. Panel A: Linear scale; Panel B: Semilogarithmic scale.

Table 21 Bioequivalence of Duloxetine To-Be-Marketed Capsule Formulation to the Pivotal Clinical Trial Capsule Formulation Under Single Dose Fasting Conditions (Study HMBG)

Metric	Summary Statistics[a]		Geometric Means			
	Test (TBM) 1 x 60 mg Capsule	Reference (CTF) 3 x 20 mg Capsules	Test (TBM)	Reference (CTF)	Geometric Mean Ratio	90% Confidence Interval
Weight (kg)	71.7 ± 13.5 (18.8) 53.3 - 100.2 [68.7]					
Tlag (hours)	2.0 ± 0.9 (45.3) [2.0]	1.8 ± 0.8 (47.2) [2.0]				
Cmax (ng/ml)	54.1 ± 23.1 (42.7) [46.5]	52.8 ± 20.9 (39.7) [50.9]	49.60	48.65	**1.02**	**(0.96, 1.09)**
Tmax (hours)	6.3 ± 1.1 (17.5) [6.0]	6.5 ± 1.0 (16.1) [6.0]				
$AUC_{0-\infty}$ (ng/ml x hr^{-1})	944.7 ± 448.7 (47.5) [897.2]	921.4 ± 403.1 (43.8) [862.9]	846.5	835.0	**1.01**	**(0.95, 1.08)**
V_β/F (L)	1362.1 ± 713.6 (52.4) [1254.1]	1334.8 ± 674.8 (50.6) [1159.3]				
Cl/F (L/hr)	81.9 ± 51.2 (62.6) [66.9]	82.2 ± 51.7 (62.9) [69.5]				
$V_\beta/F^{Weight\ Normalized}$ (L/kg)	18.9 ± 8.3 (43.9) [16.0]	18.8 ± 8.9 (47.0) [17.1]				
$Cl/F^{Weight\ Normalized}$ (L/hr x kg^{-1})	1.1±0.6 (49.7) [0.9]	1.1 ± 0.6 (52.4) [0.9]				
$t_{1/2}$ (hours)	12.1 ± 1.9 (15.7) [12.0]	11.9 ± 2.3 (19.2) [11.7]				

a mean ± SD, (%CV), Range, [median]

8.5.2 CLINICAL TRIAL FORMULATION 3 (10% ENTERIC COATED CAPSULES) VS. CLINICAL TRIAL FORMULATION 2 (5% ENTERIC COATED CAPSULES)

8.5.2.1 Fasting Conditions

In addition, to the primary clinical trial formulation, (CTF-3 a 10% enteric coated beaded capsule), a second clinical trial formulation (CTF-2) was also used in the pivotal clinical trial. CTF-2 was a 5% enteric-coated beaded capsule formulation.

In a single dose crossover study under fasting conditions in 7 healthy males (study HMAO), CTF-3 had comparable pharmacokinetics to CTF-2 at a dose of 20 mg (see Figure 9 and Table 22). However, the highest dose was not used and formal statistical tests of bioequivalence were not performed, although the sponsor states that bioequivalence would likely not be demonstrated due to the high variability and small number of subjects.

Figure 9 Comparison of Single Dose Mean Concentration vs. Time Profiles of Duloxetine CTF-3 (10% w/w - 1 x 20 mg) and CTF-2 (5% w/w - 4 x 5 mg) - (Study HMAO)

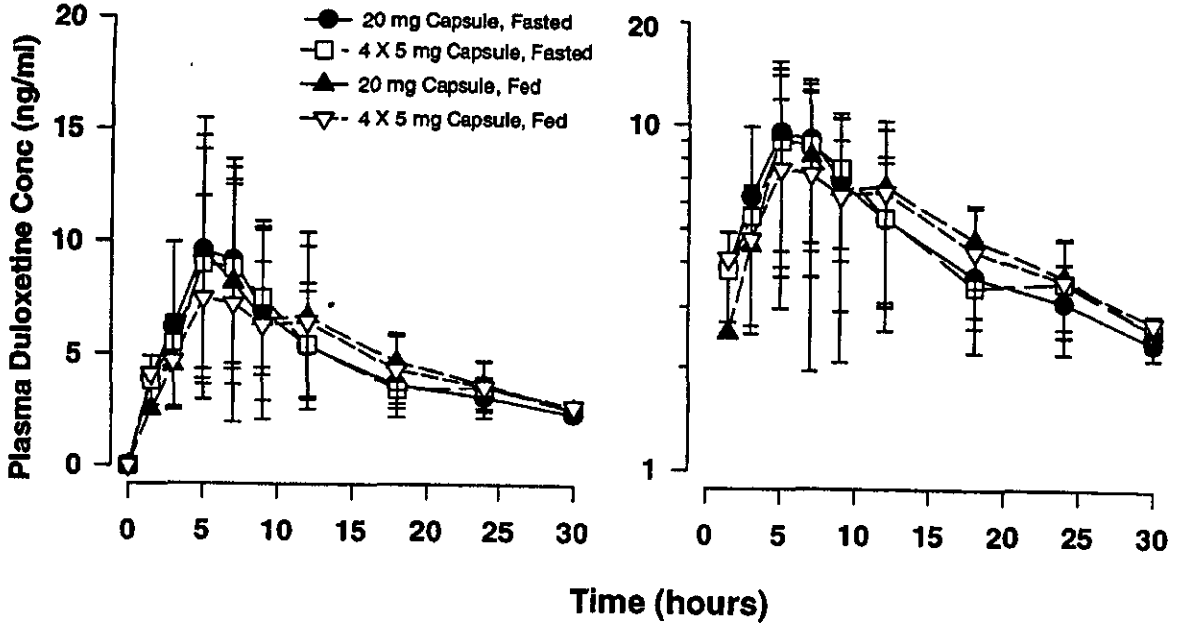


Table 22 Comparison of Pharmacokinetic Metrics[a] From Duloxetine CTF-3 (10% Duloxetine) and CTF-2 (5% Duloxetine) Under Single Dose Fasting Conditions - (Study HMAO)

Formulation	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	$t_{1/2}$ (hours)	AUC_{0-t} (ng/ml x hr^{-1})	$AUC_{0-\infty}$ (ng/ml x hr^{-1})	Cl/F (L/hr)	Cl/F Weight Normalized (L/hr x kg^{-1})	V_β/F (L)	V_β/F Weight Normalized (L/kg)
1 x 20 mg Capsule (CTF-3)	3.3 ± 1.2 (35.1)	10 7 ± 5.4 (50.7)	5.6 ± 1.0 (17.5)	9.0 ± 4.2 (46.7)	108.0 ± 76.3 (70.6)	142.0 ± 85.8 (60.4)	204.7 ± 146.3 (71.5)	2.9 ± 2.0 (70.7)	1999.0 ± 567.7 (28 4)	28.5 ± 9.9 (34 9)
[10%]	[3]	[9.2]	[5.0]	[9.3]	[88.1]	[110.9]	[180.3]	[2.4]	[1759.0]	[24.4]
4 x 5 mg Capsules (CTF-2)	3.1 ± 0.9 (30.8)	10 2 ± 4.3 (41.9)	4.7 ± 0.8 (16.0)	8.3 ± 3.2 (38.3)	89.2 ± 62.5 (70.1)	136.6 ± 75.6 (55.3)	190.9 ± 106.1 (55.6)	2.7 ± 1.5 (54.9)	1983.0 ± 709.5 (35.8)	27.8 ± 9.9 (35.7)
[5%]	[3]	[9.1]	[5.0]	[7.3]	[79.3]	[117.0]	[171.0]	[2.4]	[1808.0]	[23.1]

a mean ± SD, (%CV). Range, [median]

8.5.2.2 Fed Conditions

The pharmacokinetics of the primary clinical trial formulation, (CTF-3, a 10% enteric coated beaded capsule), and the second clinical trial formulation (CTF-2, a 5% enteric-coated beaded capsule formulation) were also compared under fed conditions in the same subjects in study HMAO. CTF-3 also had comparable pharmacokinetics to CTF-2 at 20 mg under fed conditions (see Figure 9 and Table 23). It should be noted that the highest dose was not used and formal statistical tests of bioequivalence were not performed, although the sponsor states that bioequivalence would likely not be demonstrated due to the high variability and limited number of subjects. The type of meal employed was also not reported in the abbreviated study report provided. Consequently, if a high-fat, high-caloric meal was not employed the results might be different with this type of meal.

Table 23 Comparison of Pharmacokinetic Metrics[a] From Duloxetine CTF-3 (10% Duloxetine) and CTF-2 (5% Duloxetine) Under Single Dose Fed Conditions - (Study HMAO)

Formulation	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	$t_{1/2}$ (hours)	AUC_{0-t} (ng/ml x hr^{-1})	$AUC_{0-\infty}$ (ng/ml x hr^{-1})	Cl/F (L/hr)	Cl/F Weight Normalized (L/hr x kg^{-1})	V_β/F (L)	V_β/F Weight Normalized (L/kg)
1 x 20 mg Capsule (CTF-3)	6.3 ± 2.5 (39.0)	9.0 ± 3.3 (36.0)	8.7 ± 2.4 (27.1)	10.3 ± 2.6 (25 3)	118.6 ± 69.1 (58.3)	167.6 ± 63.6 (37.9)	116.9 ± 61.8 (52.9)	1.7 ± 0.9 (55.7)	1890.3 ± 471.1 (24.9)	26.7 ± 6.8 (25.4)
[10%]	[7]	[7.4]	[7.0]	[9.3]	[98.8]	[164.6]	[121.5]	[1.6]	[1942.0]	[28.2]
4 x 5 mg Capsules (CTF-2)	5.6 ± 2.4 (43.9)	9.1 ± 4.0 (44.5)	8.6 ± 3.5 (40.9)	9.7 ± 1.3 (13.7)	127.9 ± 61.2 (47.9)	162.9 ± 60.1 (36.9)	136.6 ± 46.5 (34.0)	1.9 ± 0.7 (37.3)	1898.3 ± 627.0 (33.0)	26.7 ± 9.5 (35.6)
[5%]	[6]	[7.4]	[7.0]	[10.1]	[113.1]	[148.5]	[134.7]	[1.9]	[1901.0]	[24.7]

a mean ± SD, (%CV), Range, [median]

8.5.3 CLINICAL TRIAL FORMULATION 3 (10% ENTERIC COATED CAPSULES) VS. CLINICAL TRIAL FORMULATION 1 (ENTERIC COATED TABLETS)

Enteric-coated tablets from 5 mg to 60 mg were used in most of the early phase I studies single and multiple rising dose studies (see Table 108).

The pharmacokinetics of clinical trial formulation 3, (CTF-3, a 10% enteric coated beaded capsule), 20 mg, was compared to an enteric-coated tablet formulation, (CTF-1), 20 mg, in 6 healthy males under fasting conditions.

CTF-3 (the 10% enteric-coated beaded capsule) had comparable pharmacokinetics to the EC-tablet (CTF-1) at 20 mg under fasting condition. Although absorption was slightly faster with the tablets, as is frequently observed with enteric-coated products (see Figure 10and Table 24). In should be noted that the highest dose was not used and formal statistical tests of bioequivalence were not performed, although the sponsor states that bioequivalence would likely not be demonstrated due to the high variability and limited number of subjects.

Figure 10 Comparison of Single Dose Mean Concentration vs. Time Profiles of Duloxetine CTF-3 (10% w/w - 1 x 20 mg) and CTF-1 (Duloxetine EC Tablet 1 x 20 mg) - (Study HMAO)

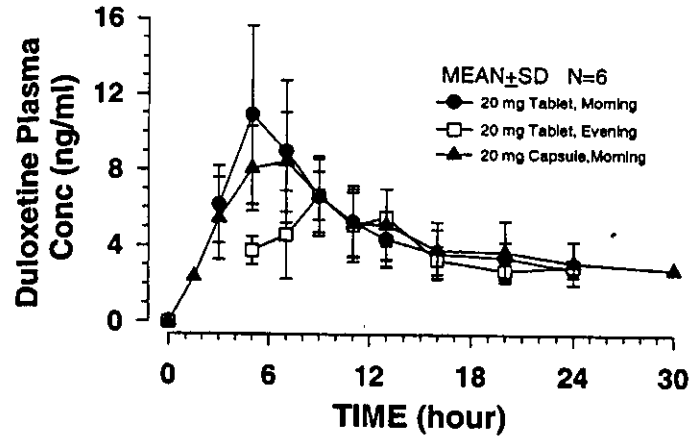


Table 24 Comparison of Pharmacokinetic Metrics[a] From Duloxetine CTF-3 (10% Duloxetine EC Capsules) and CTF-1 (Duloxetine EC Tablet) Under Single Dose Fasting Conditions in the Morning - (Study HMAO)

Formulation	Tlag (hours)	Cmax (ng/ml)	Tmax (hours)	$t_{1/2}$ (hours)	AUC_{0-t} (ng/ml x hr^{-1})	$AUC_{0-\infty}$ (ng/ml x hr^{-1})	Cl/F (L/hr)	Cl/F Weight Normalized (L/hr x kg^{-1})	V_z/F (L)	V_z/F Weight Normalized (L/kg)
20 mg Capsule (CTF-3) [10%]	3.4 ± 1.4 (39.7)	9.3 ± 2.2 (23.3)	6.0 ± 1.1 (18.3)	10.1 ± 1.5 (15.3)	113.8 ± 44.9 (39.5)	150.1 ± 55.3 (36.8)	150.1 ± 57.9 (38.6)	2.0 ± 0.8 (41.3)	2100.8 ± 531.0 (25.3)	27.6 ± 7.8 (28.2)
	[3]	6.7 - 11.6	[6.0]	7.8 - 11.6	55.9 - 184.3	81.7 - 234.7	85.2 - 245.6	1.2 - 3.3	1425.0 - 2771.0	20.4 - 37.6
20 mg EC Tablet (CTF-1)	3.7 ± 1.0 (28.2)	10.9 ± 4.7 (43.3)	5 ± 0 (0)	10.3 ± 5.8 (56.2)	106.1 ± 45.6 (43)	145.5 ± 58.1 (39.9)	158.7 ± 65.3 (41.1)	2.1 ± 0.9 (44.1)	2090 ± 840 (40.2)	27.5 ± 10.8 (39.3)
	[3]		[5]					1.1 - 3.3		17.0 - 44.8

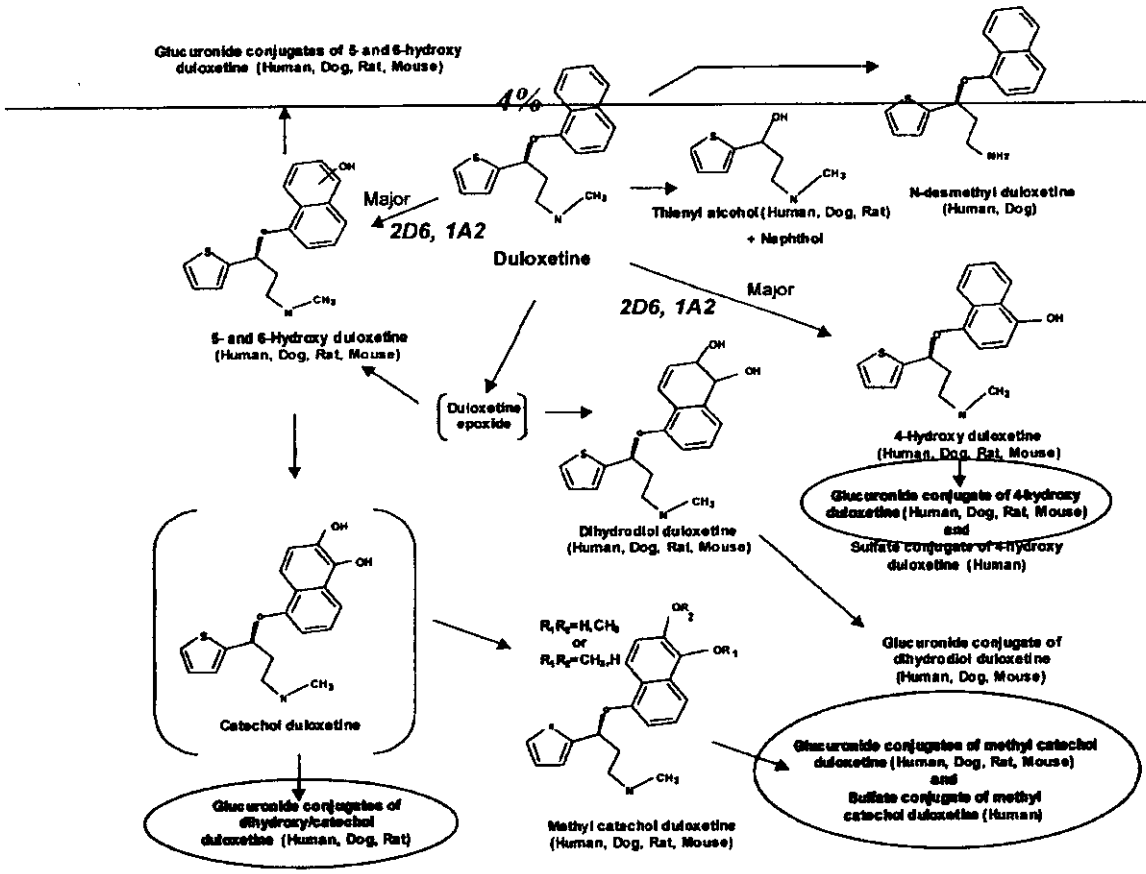
a mean ± SD, (%CV), Range, [median]

8.6 DRUG METABOLISM

8.6.1 METABOLIC SCHEME

The metabolic scheme for duloxetine as proposed by the sponsor is shown in Figure 11.

Figure 11 Proposed Metabolic Scheme for Duloxetine in Humans



N.B. Dihydrodiol-duloxetine cysteine conjugates were also observed in humans (reported in study HMBJ)

8.6.2 METABOLITE KINETICS

Two mass balance studies were conducted with radiolabeled ^{14}C-duloxetine, studies HMBF and SAAZ. In addition a multiple dose study that examined the metabolite kinetics of the quantitatively major circulating metabolites identified in the mass balance studies was also performed, (study HMBN). Plus desmethyl-duloxetine kinetics were examined in the temazepam interaction study HMAJ

Additional duloxetine metabolite kinetics in healthy volunteers can be found in the following studies (see Table 25):

Table 25 Non-Mass Balance Studies with Duloxetine Metabolite Kinetics

Study	Description	Compounds Quantified
HMBN	Multiple Dose Study of Duloxetine 60 mg SD, QD, and BID	Duloxetine 4-Hydroxy-Duloxetine Glucuronide 5-Hydroxy, 6-Methoxy Duloxetine Sulfate
HMBJ	Single Dose Study of Duloxetine 60 mg (ESRD Study)	
HMAX	Single Dose Study of Duloxetine 20 mg (Cirrhosis Study)	

8.6.2.1 Mass Balance Study HMBF

In this study 4 healthy males were administered a single dose of 20 mg of radiolabeled duloxetine as an enteric coated tablet. Subjects included 2 Caucasians, a "Black", and a Native American. Subjects were 30 or 40 years of age (mean 35 yo), one Caucasian was a non-smoker and the rest of the subjects were smokers. (Evidence will be presented in § 8.10.1 showing that smoking induces metabolism and decreases exposure to duloxetine.).

Results are shown in Table 26. It's readily apparent that the plasma exposure to metabolites is many times the exposure to duloxetine. This is due to elimination rate limited kinetics of at least some metabolites, with a net elimination half-life for total radioactivity of around 24 hours as compared to duloxetine's half-life of ~14 hours.

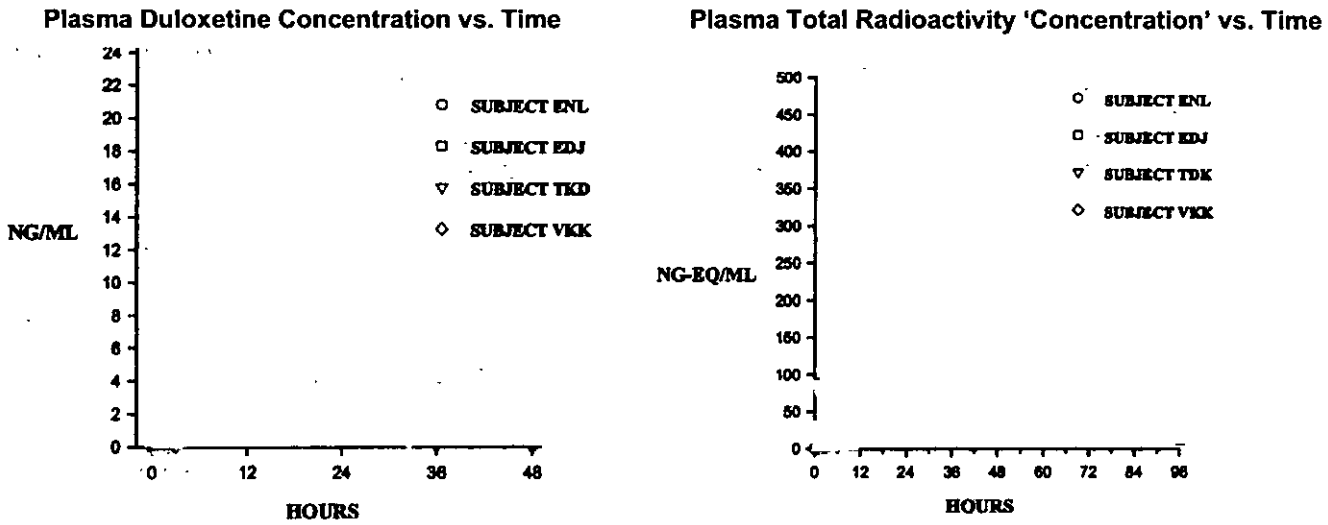
Table 26 Plasma Duloxetine and Total Radioactivity Pharmacokinetic Metrics after a single 20 mg EC tablet of 14C-Duloxetine (Study HMBF)

Metric	Total Radioactivity[a]	Metabolites[a]	Duloxetine	Ratio Metabolite Radioactivity to Duloxetine	Ratio Total Radioactivity to Duloxetine	Duloxetine as % of Total Radioactivity
n	4	4	4	4	4	4
Tlag (hours)	2.5 ± 1.0 (40.0)	—	2.8 ± 1.0 (34.8)	—	—	—
Cmax (ng/ml)	**358.3 ± 35.2 (9.8)**	344.7 ± 41.0 (11.9)	**13.5 ± 5.9 (43.6)**	31.4 ± 18.6 (59.1)	32.4 ± 18.6 (57.2)	3.9 ± 2.0 (51.8)
Tmax (hours)	5.5 ± 0.6 (10.5)	—	5.8 ± 1.0 (16.7)	—	—	—
AUC0-t (ng/ml x hr^{-1})	7785.2 ± 409.7 (5.3)	7591.5 ± 437.2 (5.8)	193.6 ± 119.8 (61.9)	48.6 ± 20.4 (42.0)	49.6 ± 20.4 (41.1)	2.5 ± 1.6 (63.6)
AUC∞ (ng/ml x hr^{-1})	8229.9 ± 450.3 (5.5)	8003.9 ± 490.8 (6.1)	226.0 ± 118.9 (52.6)	41.5 ± 15.5 (37.3)	42.5 ± 15.5 (36.4)	2.8 ± 1.5 (55.1)
t1/2 (hours)	24.7 ± 2.0 (8.2)	—	14.4 ± 5.3 (36.9)	—	—	—
Cl/F (L/hr)	2.4 ± 0.1 (5.3)	—	103.2 ± 38.5 (37.3)	—	—	—
Cl/F (L/hr x kg^{-1})	0.032 ± 0.004 (12.5)	—	1.3 ± 0.5 (37.7)	—	—	—
Vβ/F (L)	86.8 ± 9.4 (10.8)	—	2188.3 ± 1281.5 (58.6)	—	—	—
Vβ/F (L/kg)	1.1 ± 0.2 (15.6)	—	28.3 ± 17.0 (60.0)	—	—	—

a For total radioactivity and metabolites units are ng equivalents

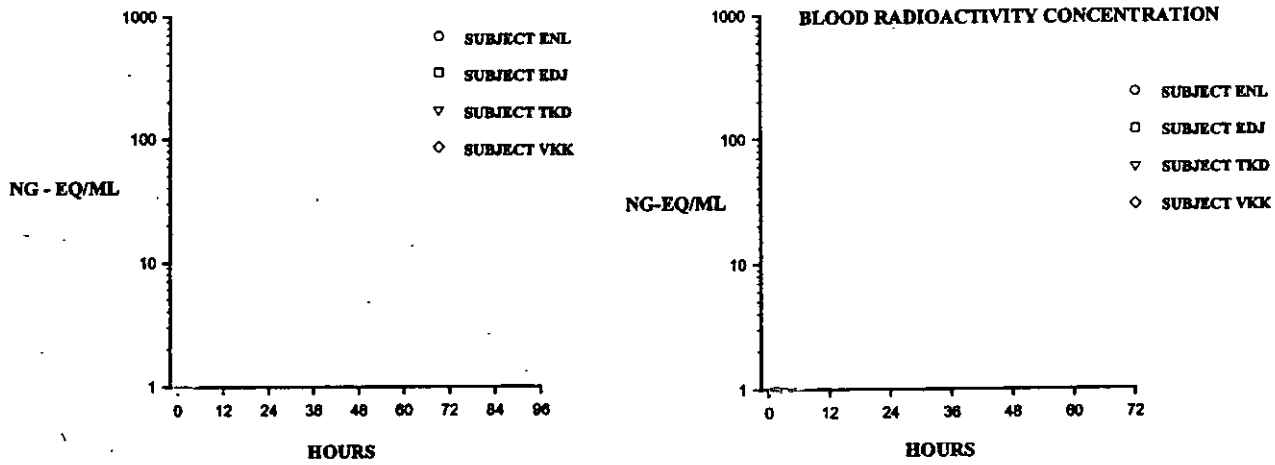
The relative plasma exposures and elimination rate limited kinetics are also seen in Figure 12, and in at least 2 of the subjects there appears to be potential enterohepatic recirculation.

Figure 12 Plasma Duloxetine and Total Radioactivity vs. Time (Study HMBF)



By comparing total plasma and blood radioactivity (see Figure 13), it's apparent that the circulating metabolites don't distribute into blood cells very well and by extension may or may not have good tissue penetration. This is supported by autoradiography in the rat where most of the radioactivity is concentrated in the liver, intestines, and kidney which are highly perfused organs which are involved in elimination, (ADME Report 55).

Figure 13 Total Plasma and Total Blood Radioactivity "Concentrations" vs. Time (Study HMBF)



The recovery of radioactivity was good with over 91% of the radioactivity administered recovered. All of this was in either urine or feces with no significant radioactivity detected in breath or saliva. Recovery of radioactivity in urine, (mean urinary recovery ~ 78%), indicates that absorption is relatively good (see Table 27).

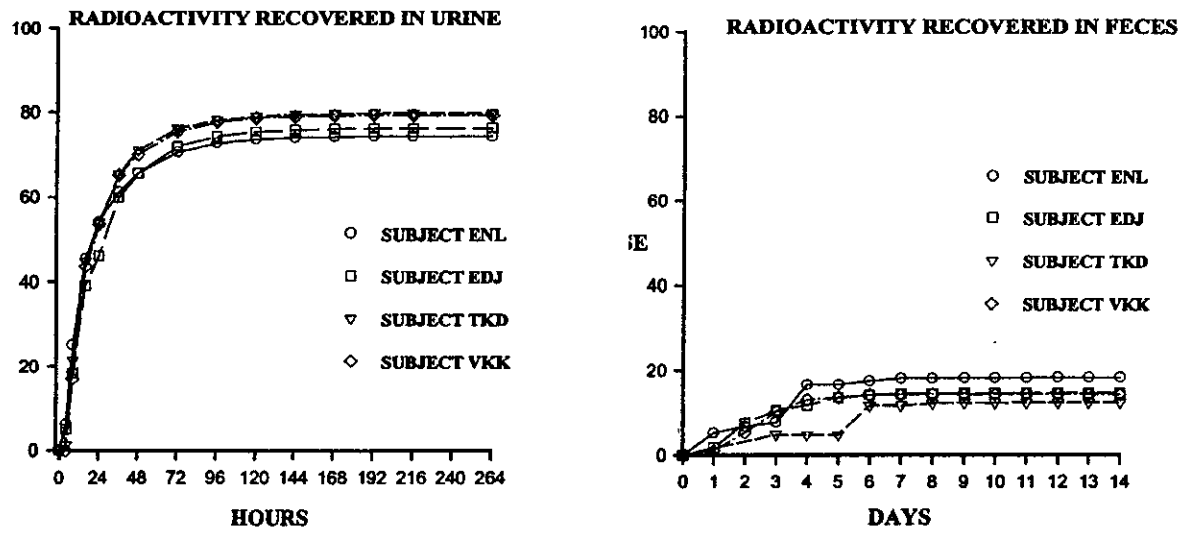
Table 27 Recovery of Radioactivity in Urine and Feces.

Study	% Recovery of Radioactivity[a]		
	Urine	Feces	Total (Urine & Feces)
HMBF	77.6 ± 2.6 (3.4)	14.9 ±2 .4 (16.1)	92.4 ± 1.1 (1.2)
SAAZ	72.0 ± 2.1 (3.0)	18.5 ± 1.7 (9.4)	90.5 ± 0.7 (0.8)

a Mean ± SD, (CV), range

Delayed recovery of approximately half of the radioactivity recovered in feces (up to 10%), (see Figure 14), is also indicative that a significant fraction of the recovery in feces is metabolites, thereby indicating that probably over 80% of the dose is absorbed.

Figure 14 Mean Percent of Duloxetine Dose Recovered in Urine and Feces vs. Time (Study HMBF)



Desmethyl-duloxetine was detected in the plasma of 2 subjects, but concentrations were too low to quantify. The following substances were identified in pooled urine samples:

Duloxetine
Desmethyl-duloxetine
naphthol
naphthol sulfate
naphthol glucuronide
a hydroxy (with hydoxylation on the naphthyl ring)
a hydroxy glucuronide (with hydoxylation on the naphthyl ring)
and a hydroxyl, methoxy analog

The sponsor reported that relatively little of this recovered radioactivity was duloxetine or desmethyl-duloxetine. However, the presence of naphthol and naphthol metabolites are worrisome as this is a potentially toxic compound. In addition, there is no identification of the circulating metabolites and the lack of reporting of fractional recoveries prevents estimation of exposure or relative contributions of different metabolic pathways. However an additional mass balance study was undertaken during development, (study SAAZ), that partially addresses some of these issues.

8.6.2.2 Mass Balance Study SAAZ

In study SAAZ 3 healthy males and 1 female were administered a single dose of 20 mg of radiolabeled duloxetine as an enteric coated tablet. Subjects included 3 Caucasians, and 1 "Black" male. Subjects ranged from 44 – 48 years of age. All subjects were genotypically CYP2D6 and CYP2C19 extensive metabolizers (EM), and all but 1 of the male Caucasians were CYP2C9 EMs. Tobacco use was not reported.

The duloxetine and total radioactivity plasma pharmacokinetic metrics are very similar to those reported in the previous mass balance study, (study HMBF), with some notable differences. In the present study duloxetine Cmax and AUCt are significantly higher, (mean 23.5 vs. 13.5 ng/ml and 236 vs. 193 ng/ml x hr^{-1}), in spite of Tmax occurring as late as 16 hours. Whereas Cmax for metabolites are lower, mean (250 vs. 345 ng/ml) with no difference in AUCt for metabolites. There is still rate-limited elimination of metabolites, although the terminal elimination half-life is now reported as 121 hours as compared with 25 hours in study HMBF. The reason for the longer half-life is readily apparent by comparing the plasma radioactivity vs. time profiles from the 2 studies. In the previous study, (HMBF), sampling was truncated at 96 hours, (see Figure 13), whereas in study SAAZ sampling was continued until 240 hours (see Figure 15). This accounts for the difference in half-life as well as the differences in AUC_{∞} between the 2 studies.

Recovery of radioactivity was similar to study HMBF with over 89.5% of the radioactivity administered recovered as compared with 91% in study HMBF (see Table 27). Urinary recovery was approximately 70% indicating good absorption, although the lack of a good IV comparison prohibits us from accurately determining the extent of the first pass effect.

The time course of recovery was also similar to study HMBF with delayed recovery of approximately half of the radioactivity that was recovered in feces (see Figure 14 and Figure 16). Indicating that a significant fraction of the recovery in feces is metabolites. However, recovery in urine is about 5.5% lower and recovery in feces is about 3.5% higher (see Table 27).

Four metabolites were identified in plasma samples pooled from the 4 individuals at the 10, 24, and 48 hour sampling times, (i.e. each sampling time was pooled individually across the four subjects). The 4-Hydroxy-Glucuronide, Methyl Catechol Sulfate Conjugate, Catechol Glucuronide, and Methyl Catechol Glucuronide, were identified as the circulating metabolites however, there were insufficient amounts to quantify them in plasma. In contrast, to study HMBF Desmethyl-duloxetine was not reported circulating in plasma.

Metabolites identified and fractional recoveries in urine and feces are shown in Table 29. Recoveries reported in Table 29 are less than recoveries reported in Table 27; as Table 29 only reports recovery through 72 hours whereas, Table 27 reports recoveries up through 2 weeks post dosing.

The compounds identified support the sponsor's proposed metabolic scheme as shown in Figure 11. The sponsor does report that the hydroxy-methoxy sulfate conjugate found in urine is the 5-Hydroxy, 6-Methoxy Sulfate, where as the 6-Hydroxy, 5-Methoxy Sulfate is produced by human liver slices (see Figure 17). The reason for this difference is not clear, but could be related to differences in concentrations, elimination in bile, or other reasons.

Table 28 Plasma Duloxetine and Total Radioactivity Pharmacokinetic Metrics after a single 20 mg EC tablet of 14C-Duloxetine (Study SAAZ)

Metric	Total Radioactivity[a]	Metabolites	Duloxetine	Ratio Metabolite Radioactivity to Duloxetine	Ratio Total Radioactivity to Duloxetine	Duloxetine as % of Total Radioactivity
Tlag (hours)	1.8 ± 1.5 (85.7)	—	2.5 ± 1.0 (40.0)	—	—	—
Cmax (ng/ml)	273.8 ± 15.5 (6.0)	250.3±18.7 7.5	23.5 ± 14.0 (60)	20.1 ± 22.3 (111.1)	21.1 ± 22.3 (105.8)	8.5 ± 5.2 (61.3)
Tmax (hours)	6.0	—	6.0	—	—	—
AUC0-t (ng/ml x hr^{-1})	7773.9 ± 1927.85 (25)	7537.7 ± 1770.2 23.5	236.2 ± 168.28 (71)	44.1 ± 25.8 (58.5)	45.1 ± 25.8 (57.2)	2.8 ± 1.4 (51.6)
AUC∞ (ng/ml x hr^{-1})	8770.2 ± 2213.43 (25)	8512.9 ± 2053.5 (24.1)	257.3 ± 181.8 (71)	45.0 ± 25.4 (56.5)	46.0 ± 25.4 (55.3)	2.7 ± 1.4 (52.0)
t1/2 (hours)	121.1 ± 15.9 (13.2)	—	11.2 ± 3.1 (24.4)	—	—	—
Cl/F (L/hr)	—	—	119.0 ± 80.7 (68)	—	—	—
Cl/F (L/hr x kg^{-1})	—	—	1.59 ± 1.08 (68)	—	—	—
Vβ/F (L)	—	—	1898.6 ± 1468.2 (77)	—	—	—
Vβ/F (L/kg)	—	—	25.9 ± 20.7 (80)	—	—	—

a For total radioactivity and metabolites units are ng equivalents

Figure 15 Duloxetine and Total Radioactivity in Plasma (mean ± SD) Following Oral Administration of ^{14}C-Duloxetine 20.2 mg EC Tablet (Study SAAZ)

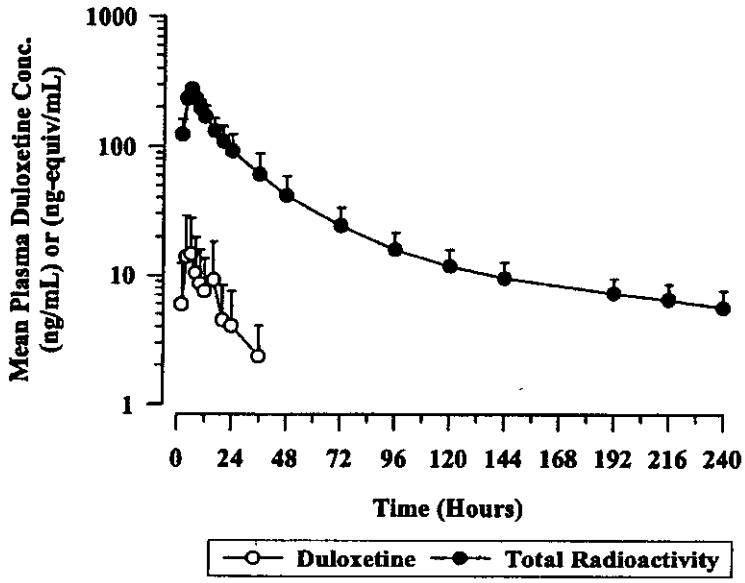


Figure 16 Cumulative Recovery of Radioactivity (mean ± SEM) Following Oral Administration of a 20.2 mg EC Tablet of ^{14}C-Duloxetine (Study SAAZ)

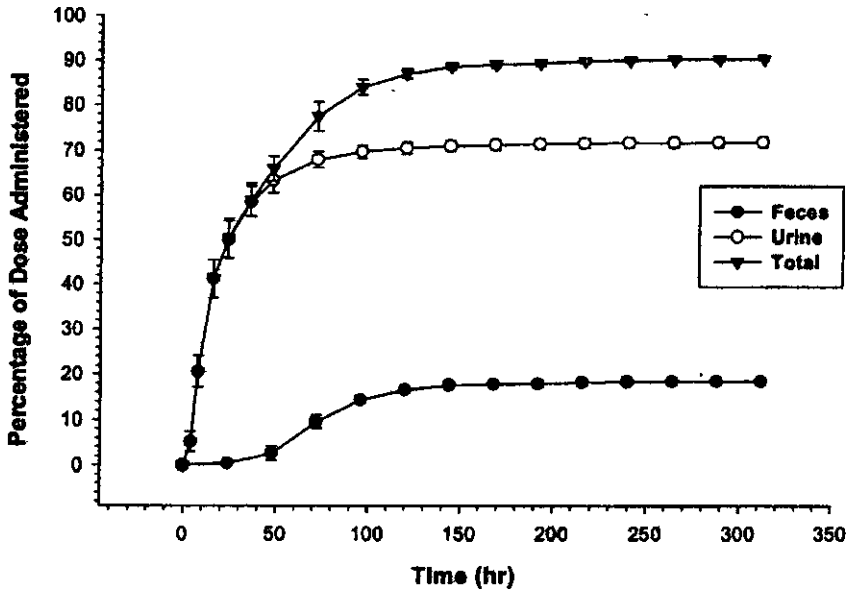


Table 29 Recovery 0-72 hours From Mass Balance Study SAAZ

Eliminated Species	Metabolite Peak #	Urine		Feces		U&F		Urine	Feces	U&F
		min	max	min	max	min	max	Average		
Duloxetine	—	—	—			—	—	0.0	2.4	2.4
Dihydrodiol Glucuronide	M1			—	—			0.9	—	0.9
Dihydrodiol	M2			—	—			2.3	—	2.3
5-OH, 6-MeOxy Glucuronide	M3			—	—			2.0	—	2.0
5-OH Glucuronide	M4			—	—			0.7	—	0.7
DiOH (Catechol) Glucuronide - #1	M5			—	—			2.8	—	2.8
4-OH Glucuronide	M6			—	—			20.1	—	20.1
5-OH, 6-MeOxy Sulfate	M7			—	—			14.8	—	14.8
6-OH Glucuronide	M8			—	—			2.4	—	2.4
DiOH (Catechol) Glucuronide - # 2	M9			—	—			5.1	—	5.1
6-OH, 5-MeOxy Glucuronide	M10			—	—			6.0	—	6.0
4-OH SO4	M11			—	—			6.0	—	6.0
4-OH	M14	—	—			—	—	0.0	1.5	1.5
Unknowns	—			NR	NR			4.9	0.0	4.9
Total	—	***65.2***	***73.2***	***0.6***	***8***	***65.2***	***73.2***	**68.0**	**3.9**	**71.9**

a n = 4
NR not reported

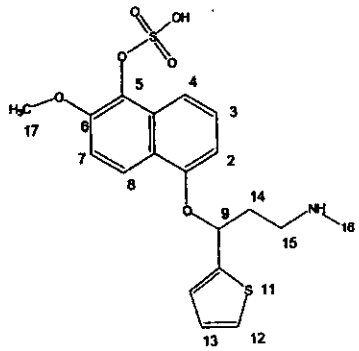
Based upon the fractional recoveries reported in Table 29, and the proposed scheme (see Figure 11), relative fractional metabolic clearances can be estimated and are shown in Table 30. However, since these numbers are only based upon recoveries through 72 hours and a significant fraction, most likely of the circulating elimination rate limited metabolites, are eliminated in feces after 72 hours these relative fractions are definitely off even in these individuals. In addition, since these subjects are all 2D6 extensive metabolizers, (which will later be shown to be a major pathway for eliminating), it should be noted that these relative fractional clearances will be significantly different from those of CYP2D6 poor metabolizers. In addition, these estimates are based upon single dose studies with 20 mg duloxetine tablets, thus we don't know what differences there may be with 60 mg bid steady-state dosing.

Table 30 Estimated Relative Fractional Clearances From Mass Balance Study SAAZ

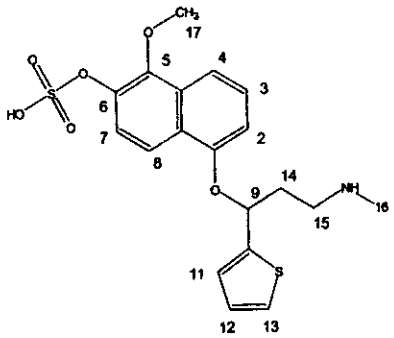
Subject	584			1522			1804			3017		
		Via CYP 1A2 or 2D6			Via CYP 1A2 or 2D6			Via CYP 1A2 or 2D6			Via CYP 1A2 or 2D6	
5-OH Gluc	1			1.2			0.5			0		
6-OH Gluc	1.9			2			3.1			2.6		
Subtotal Via 5-OH or 6-OH	**2.9**			**3.2**			**3.6**			**2.6**		
5-OH,6-MeOxy Sulfate	11.6			12.5			19.2			16		
5-OH,6-MeOxy Glucuronide	2.8			1.3			2 4			1.3		
6-OH,5-MeOxy Glucuronide	4.9			4.2			7.6			7.4		
Subtotal Via Methyl Catechol[a]	**19.3**			**18**			**29.2**			**24.7**		
		Subtotal Via 5-OH or 6-OH	2.9		Subtotal Via 5-OH or 6-OH	3.2		Subtotal Via 5-OH or 6-OH	3.6		Subtotal Via 5-OH or 6-OH	2.6
DiOH (Catechol) Glucuronide - #1 (Via Methyl Catechol)	3.1	Subtotal Via Methyl Catechol	19.3	1.8	Subtotal Via Methyl Catechol	18	2.9	Subtotal Via Methyl Catechol	29.2	3.2	Subtotal Via Methyl Catechol	24.7
DiOH (Catechol) Glucuronide - #2 (Via DiOH (Catechol))	6.8	Subtotal Via DiOH (Catechol)	9.9	3	Subtotal Via DiOH (Catechol)	4.8	6.1	Subtotal Via DiOH (Catechol)	9	4.4	Subtotal Via DiOH (Catechol)	7.6
Subtotal Via DiOH (Catechol)	**9.9**	Via 5-OH or 6-OH	32.1	**4.8**	Via 5-OH or 6-OH	26	**9**	Via 5-OH or 6-OH	41.8	**7.6**	Via 5-OH or 6-OH	34.9
4-OH Gluc	15.7			25.5			20.8			18.5		
4-OH SO4	4.9			4.2			7.6			7.4		
4-OH	0.4			0.6			2.9			2.1		
Subtotal Via 4-OH	**21**		21	**30.3**		30.3	**31.3**		31.3	**28**		28
Dihydrodiol Glucuronide	2.1			0			0.5			0.8		
Dihydrodiol[b]	4.5			1.5			0.7			2.6		
Subtotal Via Epoxide[b]	***6.6***			***1.5***			***1.2***			***3.4***		
Duloxetine	**0.2**			**0.1**			**5.1**			**4.2**		
Unknown - Urine	5.9			8.3			1.8			3.7		
Unknown - Feces												
Subtotal Unknowns	**5.9**			**8.3**			**1.8**			**3.7**		
Total Via CYP 1A2 or 2D6			53.1			56.3			73.1			62.9
Total Recovered	**65.8**			**66.2**			**81.2**			**74.2**		
Fraction of Recovered Dose Metabolized through CYP 1A2 or 2D6			0.81			0.85			0.90			0.85

a n.b. no MeCat reported as eliminated therefore this is likely an underestimate
b n.b. Could be higher as some epoxide could go to 5-OH or 6-OH

Figure 17 Structures of Sulfate Conjugates of Hydroxy, Methoxy-Duloxetine Found in Urine and Human Liver Slices



5-Hydroxy 6-Methoxy Duloxetine-O-Sulfate (Urinary Metabolite)



5- Methoxy 6-Hydroxy Duloxetine-O-Sulfate (Liver Slice Metabolite)

It should be noted that in contrast to study HBAF naphthol, naphthol sulfate, and naphthol glucuronide were not reported as detected. As naphthol is a potentially toxic compound this discrepancy should be clarified. Since both studies used the same enteric tablet formulation and have similar Tlags and Tmaxs the failure of the enteric coating in study HBAF does not seem to be the cause of this discrepancy. In addition, the high percent of the dose recovered in urine and feces as unidentified metabolites is troublesome; [(2.9 – 8.3% through 72 hours in urine with more anticipated if cumulative values were reported, and 12.2% ± 6.6% (range 4.3% – 17.8%) of the dose in feces that are unidentified metabolites]. In addition, in the urine radio-chromatograms provided there were some early unidentified (and unmarked albeit small) peaks. Naphthol and its conjugates would be expected to be elute early in comparison toother metabolites, and these peaks should have been pursued with at least the retention times compared to naphthol and naphthol conjugate standards.

Also worrisome is that with 66% - 81% of the dose recovered in CYP2D6 extensive metabolizers, as much as 6.6% of the dose (10% of 66%) appears to be eliminated via an expoxide. Epoxides can be highly reactive compounds, and have been implicated in the oro-facial terratogenicity of phenytoin and carbamazepine, and can also be considered a potential risk for hepatoxicity. The sponsor dismisses the potential risk of an epoxide by claiming that no circulating epoxide was found, and that it was too unstable chemically (hydrolyzing within minutes). This is not reassuring, as an epoxide with that degree of stability could still circulate and yet not be detected, as hydrolysis would likely occur before the sample is sufficiently processed. In addition, metabolic formation can occur within target tissues, i.e. fetal, hepatic, or other tissues. A potentially toxic epoxide also has to be sufficiently labile so that it can react, yet has to be sufficiently stable that it doesn't immediately fall apart within milliseconds prior to reacting with cellular proteins. Trapping experiments in human hepatocytes, and with glutathione depleted systems, could have helped establish the formation of a reactive epoxide intermediate. On the positive side based upon the doses and percent of the dose likely to go through an epoxide the degree of formation of an epoxide with duloxetine is likely to be quantitatively less than with phenytoin or carbamazepine and this would likely translate into a lower risk.

Animal reproduction studies are unlikely to be of any use in assessing the risk of an epoxide as the animals used in reproduction studies so far do not appear to form the epoxide. Even if the dog, which does form the expoxide to a significant degree is used, any terratogenicity found might be misleading and overestimate the quantitative risk to humans.

8.6.2.3 Additional Single Dose Metabolite Kinetic Studies

Additional single-dose studies with duloxetine metabolite kinetics in healthy volunteers can be found in studies examining pharmacokinetics in end stage renal disease and cirrhosis, (studies HMBJ and HMAX).

Selected metabolite kinetics from these studies are shown in Table 31 and Table 32.

Important to note is the approximately 10 fold exposure to both 4-Hydroxy Duloxetine Glucuronide, and 5-Hydroxy, 6-Methoxy-Duloxetine Sulfate (range approximately 1 to 30 fold) and the half-lives that are similar to duloxetine's half-life. This information indicates that both of these quantitatively major circulating metabolites are formation rate limited with volumes of distributions much smaller than duloxetines, thereby producing the high plasma exposures relative to duloxetine. It also indicates that the long half-life for radioactivity (>100 hours) is due to other unidentified, and likely more lipophilic metabolites, that are slowly coming out of tissues. As mentioned in § 8.6.2.2 these metabolites may be eliminated in bile and if identified and quantified the estimates of fractional clearances would likely change, as would possibly the risk assessment of the metabolic profile.

In study HMBJ in ESRD metabolites found in plasma included glucuronide conjugates of the 4-hydroxy duloxetine, methyl catechol duloxetine, and catechol duloxetine, and a sulfate conjugate of methyl catechol duloxetine. The glucuronide conjugate of 4-hydroxy duloxetine and the sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine were the major circulating metabolites. Other metabolites identified in the plasma of Study HMBJ ESRD subjects were the glucuronide conjugate of 6-hydroxy duloxetine and the glucuronide conjugate of 5-hydroxy, 6-methoxy duloxetine. The glucuronide conjugate of 6-hydroxy duloxetine and the glucuronide conjugate of 5-hydroxy, 6-methoxy duloxetine were not detected in the plasma from the healthy control subjects. The glucuronide conjugate of the dihydroxy and/or catechol metabolite that had been observed previously in Study F1J-LC-SAAZ was not observed in any of the analyzed plasma samples from Study HMBJ. In addition, the dihydrodiol of duloxetine but not the cysteine conjugate related metabolites were observed at trace, but detectable levels in plasma samples from both the ESRD subjects and the healthy control subjects.

The cysteine conjugate is a degradation product of glutathione conjugation of the reactive epoxide intermediate. It's interesting to note that the presence of this conjugate was reported in this study as occurring in mass balance study SAAZ, but was not reported in the study report for that study.

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Table 31 Duloxetine, 4-Hydroxy Duloxetine Glucuronide, and 5-Hydroxy, 6-Methoxy-Duloxetine Sulfate Pharmacokinetic Metrics following a Single 60 mg Dose in Healthy Volunteers (Study HMBJ – ESRD)

Metrics	Tlag (hours)	Tmax (hours)	Cmax (ng/ml)	AUC0-t (ng/ml x hr^{-1})	AUC0-∞ (ng/ml x hr^{-1})	t1/2 (hours)
Duloxetine	2.5 ± 0.9 (36.2) [2.0]	5.0 ± 1.3 (27.0) [4.0]	34.4 ± 18.3 (53.3) [33.9]	653 (92)	672.2 ± 615.9 (91.6) [469.5]	13.8 ± 4.6 (33.3) [13.1]
4-Hydroxy Duloxetine Glucuronide	2.3 ± 0.8 (33.4) [2.0]	5.3 ± 1.6 (29.2) [5.0]	304.7 ± 189.1 (62.1) [253.8]	5220 (71)	5267.8 ± 3732.1 (70.8) [4099.0]	13.7 ± 4.6 (33.4) [12.9]
5-Hydroxy, 6-Methoxy-Duloxetine Sulfate	2.5 ± 0.9 (36.2) [2.0]	4.8 ± 1.3 (27.7) [4.0]	227.2 ± 118.7 (52.2) [202.3]	2986 (43)	3025.2 ± 1269.5 (42.0) [2772.9]	12.7 ± 4.9 (38.7) [11.9]
Ratio 4-OH Gluc : Duloxetine	—	—	**11.1 ± 7.5 (67.6) [8.8]**	—	**10.6 ± 8.4 (79.3) [9.3]**	**1.0 ± 0.1 (13.0) [1.0]**
Ratio 5-OH, 6-MeOH SO_4: Duloxetine	—	—	**9.2 ± 8.4 (91.7) [6.9]**	—	**6.7 ± 5.2 (78.0) [5.3]**	**0.9 ± 0.1 (13.3) [0.9]**

Table 32 Duloxetine, 4-Hydroxy Duloxetine Glucuronide, and 5-Hydroxy, 6-Methoxy-Duloxetine Sulfate Pharmacokinetic Metrics following a Single 20 mg Dose in Healthy Volunteers (EMs) (Study HMAX – Cirrhosis)

Metrics	Tlag (hours)	Tmax (hours)	Cmax (ng/ml)	AUC0-t (ng/ml x hr^{-1})	AUC0-∞ (ng/ml x hr^{-1})	t1/2[a] (hours)
Duloxetine	2.2 ± 0.4 (18.8)	3.8 ± 1.2 (30.5)	13.8 ± 10.9 (79.1)	267.9 ± 392 0 (146 3)	370.1 ± 605.2 (163.5)	18.3 ± 15.2 (82.9)
	[2]	[3.5]	[12.0]	[115.3]	[126.0]	[12.9]
4-Hydroxy Duloxetine Glucuronide	2 ± 0.6 (31.6)	5.0 ± 1.1 (21.9)	118.1 ± 58.2 (49.3)	1955.9 ± 896 8 (45.8)	2115.2 ± 1114.5 (52.7)	14.0 ± 8.2 (59.1)
	[2]	[5.0]	[102.5]	[2000.0]	[2040.7]	[11.2]
5-Hydroxy, 6-Methoxy-Duloxetine Sulfate	2.2 ± 0.4 (18.8)	4.3 ± 0.8 (18.8)	96.7 ± 48.9 (50.5)	1117.9 ± 363.2 (32.5)	1172.6 ± 389.7 (33.2)	12.9 ± 5.9 (45.7)
	[2]	[4.0]	[98.1]	[1122.7]	[1162.0]	[10.4]
Ratio 4-OH Gluc : Duloxetine	—	—	**13.1 ± 9.0 (68.9)**	**15.9 ± 10.7 (67.5)**	**14.0 ± 9.9 (70.4)**	**0.9 ± 0.3 (32.3)**
			[12.1]	**[15.2]**	**[12.6]**	**[0.8]**
Ratio 5-OH, 6-MeOH SO_4: Duloxetine	—	—	**10.4 ± 5.8 (56.1)**	**9.5 ± 5.3 (55.6)**	**8.3 ± 4.6 (55.7)**	**0.8 ± 0.3 (39.6)**
			[11.6]	**[10.3]**	**[8.3]**	**[0.8]**

a all but one subject had metabolic half-lives less than parent.

8.6.3 MULTIPLE DOSE METABOLITE KINETICS

Multiple dose metabolite kinetics were examined in studies HMBN and HMAJ.

8.6.3.1 Study HMBN

In study HMBN plasma duloxetine, 4-hydoxy-duloxetine glucuronide and 5-hydroxy, 6-methoxy-duloxetine sulfate metabolite kinetics were examined after single doses, and QAM, and BID (both AM and PM) dosing of 60 mg of duloxetine administered 2 hours after meals. As shown in § 8.3 upon multiple dosing duloxetine exhibits nonlinear kinetics, whereas in Table 33 we see that although exposure to 5-hydroxy, 6-methoxy-duloxetine sulfate increases upon multiple dosing, it is less than we would expect given the degree of increase in duloxetine seen in § 8.3. In addition there is possibly even a slight decrease in exposure to 4-hydoxy-duloxetine glucuronide upon multiple dosing (see Table 33). Indicating saturation of one of the isozymes metabolizing duloxetine to both of these metabolites. Although for both metabolites the half-life increases as a reflection of their being formation rate limited, with the apparent half-life really reflecting duloxetine's half-life.

Table 33 Single and Multiple Duloxetine 60 mg Dose Plasma 4-Hydoxy-Duloxetine Glucuronide and 5-Hydroxy, 6-Methoxy-Duloxetine Sulfate Metabolite Exposures (Study HMBN)

4-Hydroxy-Duloxetine Glucuronide						5-Hydroxy, 6-Methoxy-Duloxetine Sulfate					
SD	QD	BID (AM)	Ratios			SD	QD	BID (AM)	Ratios		
			QD:SD	BID:QD	BID:SD				QD:SD	BID:QD	BID:SD
Cmax (ng/ml)											
459.6 ± 131.9 (28.7) [411.7]	482.5 ± 156.3 (32.4) [452.9]	656.3 ± 241.7 (36.8) [615.9]	1.1 ± 0.22 (21.1) [1.0]	1.4 ± 0.33 (23.5) [1.3]	1.3 ± 0.15 (10.8) [1.3]	284.4 ± 107.8 (37.9) [253.6]	278.0 ± 72.2 (26.0) [278.3]	386.2 ± 109.1 (28.3) [375.2]	1.0 ± 0.2 (21.2) [1.0]	1.4 ± 0.3 (22.6) [1.5]	1.4 ± 0.2 (14.6) [1.4]
AUC (ng/ml x hr)											
7852.9 ± 4025.2 (51.3) [6117.5]	6944.6 ± 3119.5 (44.9) [6117.5]	6383.1 ± 2971.5 (46.5) [5948.0]	0.9 ± 0.16 (17.9) [1.0]	0.8 ± 0.21 (24.7) [0.9]	0.9 ± 0.11 (12.3) [0.9]	3388.7 ± 1301.5 (38.4) [2884.0]	3169.3 ± 870.8 (27.5) [2800.1]	3759.5 ± 1126.6 (30.0) [3741.6]	1.0 ± 0.1 (11.7) [1.0]	1.2 ± 0.5 (44.7) [1.2]	1.2 ± 0.4 (33.5) [1.2]
t1/2 (hours)											
11.8 ± 2.3 (19.2) [10.8]	—	14.2 ± 2.7 (19.2) [14.6]	—	1.2 ± 0.13 (10.6) [1.2]	—	10.1 ± 1.2 (11.5) [10.2]	—	13.2 ± 2.9 (21.8) [14.0]	—	1.3 ± 0.2 (18.8) [1.2]	—

8.6.3.2 Study HMAJ

Study HMAJ was a multiple dose pharmacodynamic drug interaction study with temazepam, however, pharmacokinetics were also examined to confirm the lack of pharmacokinetic interaction. Although, there was no effect on duloxetine pharmacokinetics there was decrease in desmethy-lduloxetine exposure in the presence of temazepam. This indicates that dexmethyl-duloxetine may be formed via CYP2C11. Although based upon the mass balance study this pathway probably accounts for less than 20% of total clearance, and desmethyl-duloxetine plasma exposures upon multiple dosing were approximately 1% to total plasma exposure to duloxetine and all metabolites after a single 20 mg radiolabeled dose, (see Table 26 and Table 34).

Table 34 Effect of Temazepam on Desmethyl-duloxetine Pharmacokinetic Metrics (Study HMAJ)

Pharmacokinetic Metric	Test Duloxetine + Temazepam	Reference Duloxetine 20 mg	Geometric Mean Ratios [90% CI]
Cmax ng/ml	4.2 ± 2.87 (68.4)	5.02 ± 2.93 (58.4)	83.6 [65.3, 107]
Tmax hours	13 ± 5 (40)	12 ± 8 (66)	—
AUCτ ng/ml x hr^{-1}	62.56 ± 49.5 (79.1)	78.27 ± 44.79 (57.2)	69.2 [56.8, 84.2]
Cav ng/ml	2.606 ± 2.063 (79.1)	3.261 ± 1.866 (57.2)	69.2 [56.8, 84.5]
Cmin ng/ml	1.44 ± 1.25 (86.9)	2 01 ± 1.3 (64.7)	79.2 [66.2, 94.7]
Fluctuation Index	1.82 ± 1.935 (106.3)	1.006 ± 0.63 (62.6)	—

APPEARS THIS WAY
ON ORIGINAL

8.6.4 IN VITRO METABOLISM STUDIES

8.6.4.1 Isozyme Identification and Relative Contributions to Primary Metabolism of Duloxetine

In vitro studies with human liver microsomes and expressed isozymes indicate that both 4-hydroxy and 5-hydroxy duloxetine are primarily formed by CY2D6 and CYP1A2, (see Table 35, Table 36, and Figure 18). In addition, it was reported in study HMAZ (the desipramine interaction study; vol. 44 page 246) that Japanese studies with CYP selective antibodies inhibited duloxetine metabolism by 2C19, although details were not reported, so the contribution of 2C19 to overall metabolism cannot be assessed.

Table 35 In Vitro Enzyme Kinetic Parameters for Formation of Hydroxy-Duloxetine Metabolites and Relative Isozyme Activities in Microsomes from Selected Human Livers (ADME Report 72)

Human Liver	Product Formation when Incubated with Isozyme Selective Substrate (pMol/min x mg protein^{-1})			Initial Rate Enzyme Kinetic Parameters when Incubated with Duloxetine 2.5 µM[a] (pMol/min x mg protein^{-1})											
				4-OH Duloxetine				5-OH Duloxetine				6-OH Duloxetine			
				Km[1]	Vmax[1]	Clint[1]	Clint[2]	Km[1]	Vmax[1]	Clint[1]	Clint[2]	Km[1]	Vmax[1]	Clint[1]	Clint[2]
	1A2	2D6	2C9	(µM/L)	(pMol/min x mg prot^{-1})	(µL/min x mg prot^{-1})	(µL/min x mg prot^{-1})	(µM/L)	(pMol/min x mg prot^{-1})	(µL/min x mg prot^{-1})	(µL/min x mg prot^{-1})	(µM)	(pMol/min x mg prot^{-1})	(µL/min x mg prot^{-1})	(µL/min x mg prot^{-1})
HLG	***595***	**44**	373	2.2 ± 0.2	24 ± 1	**10.9**	0.14 ± 0 02	3.6 ± 0.2	34 ± 1	**9.4**	0.16 ± 0.02	5.6 ± 0.3	3.1 ± 0.1	**0.55**	0.02 ± 0.0
HLH	**970**	***24.9***	546	4.9 ± 0 7	15 ± 1	3.1	0 09 ± 0 01	8.2 ± 1.1	26 ± 2	3.1	0 11 ± 0.02	19 ± 1	5.0 ± 0.3	0.26	0.01 ± 0.0
HLP	***159***	**44.3**	292	2.4 ± 0.2	11 ± 1	4.7	0.08 ± 0.01	3 1 ± 0.4	9.2 ± 0.7	3.0	0.08 ± 0.02	22 ± 4	0.6 ± 0.0	0.03	NA[b]
HLN[d]	**877**	***13.9***	463	6.4 ± 1.1	54 ± 6	**8.4**	0.41 ± 0.06	8.0 ± 0.9	134 ± 11	**16.9**	0.63 ± 0.10	8.0 ± 1.0	21 ± 2	**2.6**	0 11 ± 0.02

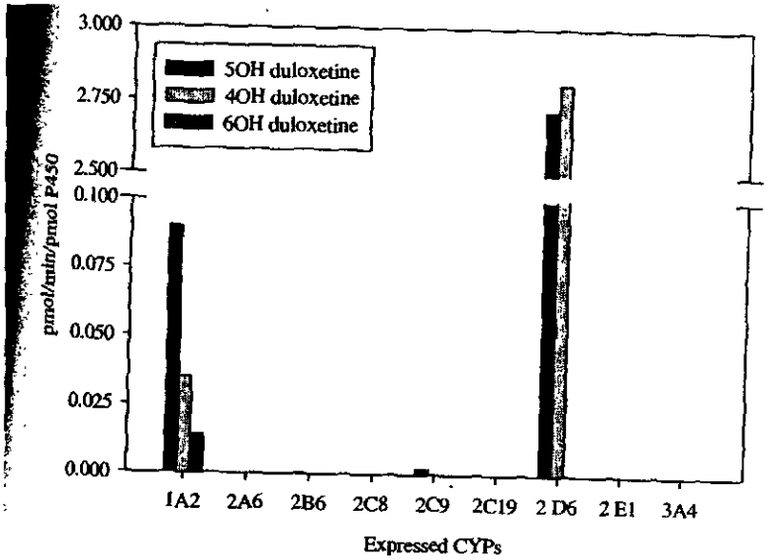
a Superscripts on enzyme kinetic parameters refer to apparent high and low affinity enzymes
b NA – not applicable
c CYP2D6 deficient by immunoblot

Table 36 *In Vitro* **Duloxetine Metabolism and Isozyme Selective Metabolism and Inhibition (ADME Report 72)**

Human Liver	Product Formation when Incubated with Isozyme Selective Substrate (pMol/min x mg protein^{-1})			Product Formation when Incubated with Duloxetine 2.5 µM (pMol/min x mg protein^{-1})			Product Measured	% Inhibition		
	Isozyme							Isozyme		
	1A2	2D6	2C9					1A2	2D6	2C9
	Product Measured							Inhibitor		
	O-Deethyl-Phenacetin	1'-OH Bufuralol	4'-OH Diclofenac	4-OH Duloxetine	5-OH Duloxetine	6-OH Duloxetine		Furafylline	Quinidine	Sulfaphenazole
HLA	**1490**	***17.3***	597	28.8	48.9	7	4-OH	**76**	***23***	8.3
							5-OH	**89**	***2.4***	-4.8
							6-OH	NQ	***-3.3***	-3.3
HLG	595	**44**	373	nd	104.2	7.5	4-OH	25	**72**	-20
							5-OH	***39***	***47***	-21
							6-OH	NQ	-16	-32
HLN[a]	877	***13.9***	463	22.1	49	8.2	4-OH	NQ	***9***	19
							5-OH	NQ	***-0.4***	7.9
							6-OH	NQ	***0***	7.3
HLO	862	**91.8**	298	100.7	95.6	9.4	4-OH	28	**74**	5.8
							5-OH	***50***	***45***	-1.5
							6-OH	NQ	2.1	4.2
HLQ	293	**50.4**	677	87.9	83.5	3.1	4-OH	16	**91**	29
							5-OH	23	**80**	8.3
							6-OH	NQ	13	19

a 2D6 Deficient by Western Blotting
NQ Not quantifiable

Figure 18 Relative Formation of Hydroxy Duloxetine Metabolites in Expressed CYP Isozymes



Enzyme kinetic parameters for CYP formation of duloxetine mono-hydroxy metabolites are shown in Table 37.

Table 37 Mean (± SEM) Enzyme Kinetic Parameters for the Formation of 4-OH, 5-OH, and 6-OH Duloxetine by Expressed CYP1A2 and CYP2D6

Expressed CYP	Sponsor's Values		Reviewer's Calculations		
	Km (µM)	Vmax (pmol/min/pmol P450)	Mean Clint ml/min /µMol P450	Adjusted for Hepatic CYP Content as per Sponsor[b]	Predicted Relative Contribution
4-OH Duloxetine					
CYP1A2	22 ± 1	0.35 ± 0.01	15.9	159	
CYP2D6	1.1 ± 0.1	5.6 ± 0.1	5090	5090	32
5-OH Duloxetine					
CYP1A2	16 ± 2	0.62 ± 0.08	38.75	387.5	
CYP2D6	0.9 ± 0.1	4.8 ± 0.1	5333	5333	13.76
6-OH Duloxetine					
CYP1A2	25 ± 1	0.15 ± 0.01	6	60	
CYP2D6	na[a]	na[a]	—		

a na = not applicable due to no detectable formation of 6-OH duloxetine.
b Hepatic CYP1A2 content is 10 fold CYP2D6

The sponsor claims that based upon the relative Km's of CYP2D6 and CYP1A2 and that CYP1A2 is 10 fold more abundant in human liver that the relative contribution of each isozyme to the elimination of duloxetine is approximately equal. Consequently as per the sponsor: *"since these 2 isozymes are responsible for "the two dominant routes of duloxetine metabolism. Should the activity of one of CYP1A2*

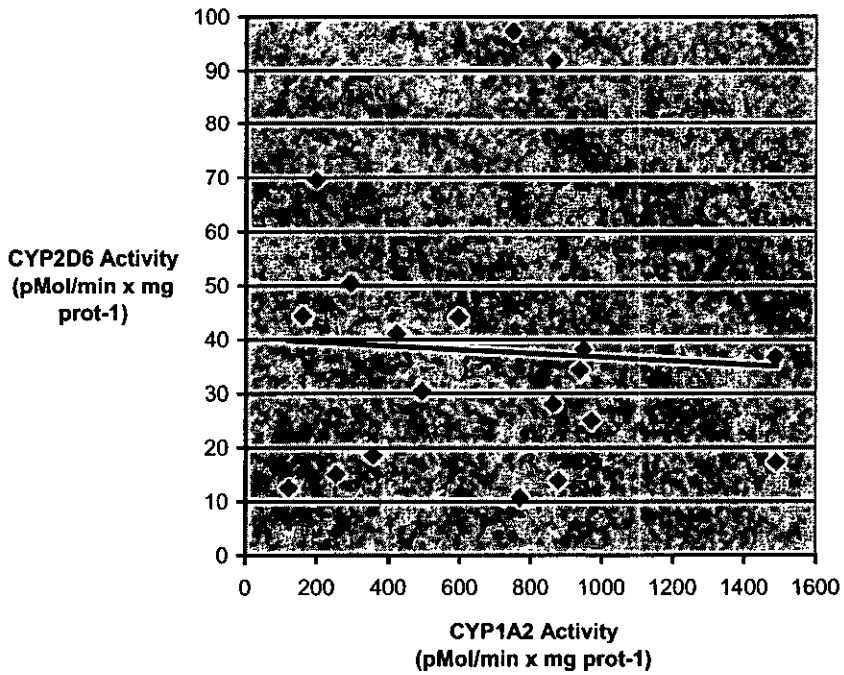
and CYP2D6 be absent or decreased in a subject, the other enzyme would be available to efficiently metabolize duloxetine (ADME Report 72)."

First, even using the sponsor's number of a 10 fold greater amount of CYP1A2 relative to CYP2D6, based upon the sponsor's enzyme kinetic parameters 2D6 would be expected to contribute to more to the overall metabolism than CYP1A2 under linear conditions, (see Table 37).

Second the human liver microsomal data shows that in most of the human livers CYP2D6 is responsible for most of the metabolism, although in an occasional liver CYP1A2 is primarily responsible (see Table 35 and Table 19).

Third, looking at the CYP1A2 vs. CYP2D6 activity across 20 human livers, (data provided by sponsor in ADME study 77), we see that the CYP1A2 activity varies 12.3 fold, the activity of CYP2D6 varies 9.1 fold, and that activity of each isozyme is independent (see Figure 19).

Figure 19 Lack of Covariance of CYP2D6 Activity vs. CYP1A2 Activity in Human Liver Microsomes (ADME Report 77)



As a final note the data indicate that 6-hydroxy-duloxetine is formed to a minor extent relative to the other mono-hydroxy duloxetine metabolites by CYPs 1A2, 2D6, and 2C9 and is thus formed by a different isozyme, or 5-OH duloxetine is the primary substrate for 6-hydroxylation.