8.6.4.2 *In Vitro* Inhibition

In vitro inhibition studies were conducted with human cytochromes P-450, CYP3A, CYP2D6 and CYP1A2. A summary of the results is shown in Table 38. No data was presented to support the proposed non-competitive mechanism for 2C9 and 3A4. In addition, from the description of the methodology used it would not be possible to tell the mechanism. It seems that the mechanism of non-competitive inhibition is based upon the relative lack of metabolism of duloxetine by 2C9 or 3A at clinically achieved concentrations. However, there was some metabolism of duloxetine by CYP2C9 in vitro, (see § 8.6.4.1). Consequently, mechanism of inhibition for either of these and especially for 2C9 could be competitive.

Table 38 *In Vitro* Cytochrome P450 Inhibition by Duloxetine (ADME45 & ADME64)

Report	CYP Isozyme	Probe Substrate	Probe Reaction	Mechanism	Ki (μM)
ADME 64	2C9	Diclofenac	4'-Hydroxylation	Non-Competitive	306 ± 31
ADME 45	3A	Midazolam	1'-Hydroxylation	Non-Competitive	133 ± 10
ADME 64	1A2	Phenacetin	O-Deethylation	Competitive	17.7±1.0
ADME 45	2D6	Bufuralol	1'-Hydroxylation	Competitive	2.4 ± 0.1

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8.6.4.2.1 CYP2D6

According to the sponsor: *"the form-selective biotransformation for CYP2D6, 1'-hydroxylation of bufuralol was inhibited competitively by duloxetine (Ki =2.4μM or approximately 800 ng/mL). This Ki value is similar to that obtained for other selective serotonin reuptake inhibitors. Concentrations of duloxetine approaching 2.4 μM at the active site of CYP2D6 would be predicted to inhibit CYP2D6-mediated metabolism by 50 %."*

The following are the highest duloxetine Cmaxs reported in multiple dose studies with duloxetine (see Table 39). As shown, Cmaxs in nonsmoking females average 200 ng/ml, (μM), with maximum reported peaks of ng/ml, (uM). This would correspond to 30% and 22% peak inhibition respectively, with associated increases of 43% and 22% for drugs that are metabolized exclusively by 2D6 with linear kinetics. It should be noted that these are approximations as true peaks are likely higher than the measured peak concentrations, this is a limited sample of subjects and individuals in a population could have higher exposures, although these are maximal concentrations and mean concentrations over a dosage interval would be lower.

Table 39 Steady-State Duloxetine Cmax Concentrations

Study	Subjects	Dosage Regimen	Cmax (excluding PM) (ng/ml)	Highest Reported Cmax (ng/ml)	2D6 Genotype of Subject with Highest Cmax
HMAZ	Male and Female EM (Smoking Status Not Reported)	60 mg q12h	128.5 ± 68.9 (53.6) [117.1]		EM
HMBN	Female Nonsmoking EM	60 mg q12h	200.6 ± 74.6 37.2 [215.1]		EM
HMAR	Females of Mixed Smoking Status	60 mg q12h	105.8 ± 51.1 (48)		NR
		80 mg q12h	184.5 ± 93.3 (51)		

These peak concentrations and *in vitro* Kms are consistent with the nonlinear kinetics seen in study HBMN.

8.6.4.2.2 CYP1A2

According to the sponsor: *"The form-selective biotransformation for CYP1A2 was investigated using the in vitro metabolism of phenacetin to acetaminophen. These studies showed that the metabolism of phenacetin was competitively inhibited by duloxetine with a Ki of 17.7 μM. The plasma concentration of duloxetine after 60 mg BID administration of duloxetine ranged from μM. Assuming a conservative estimate of the concentration of μM at the active site of the enzyme, these in vitro studies would predict that duloxetine has very low potential to inhibit metabolism of concomitantly administered drugs biotransformed by CYP1A2."*

As mentioned in the section above, (§ 8.6.4.2.1), the concentrations seen with clinical dosing are higher than claimed by the sponsor, (i.e. μM as compared with μM as claimed by the sponsor). (See section 8.6.4.2.3 below for basis of sponsor's claimed clinically achieved concentrations). If there is active transport into the hepatocyte and protein binding is ignored it's possible based upon the in vitro data that there's a potential for inhibition of CYP1A2 *in vivo*, (albeit in this reviewer's opinion a low likelihood).

8.6.4.2.3 CYP3A

According to the sponsor: *"Duloxetine was found to inhibit noncompetitively 1'-hydroxy midazolam formation, the form-selective catalytic activity for CYP3A, yielding a Ki value of 133 µM. This Ki value would predict that duloxetine must be present at the active site of CYP3A approaching a concentration of 133 µM to inhibit the catalytic activity of this enzyme by 50 %. However, such interaction is unlikely to occur in vivo since average plasma concentrations obtained with 60 mg b.i.d. (HMAR study) were in the range — ng/ml (or — µM)."*

Although in other clinical studies the clinically achieved concentrations are higher, especially in women (see Table 39 and § 8.6.4.2.2), the maximally achieved concentrations are still 1/100th of the Ki for inhibition of CYP3A4 formation of 4-hydroxy-midazolam. Thus duloxetine is unlikely to inhibit the site on CYP3A4 responsible for midazolam metabolism *in vivo*. However, there is information suggesting that there are multiple substrate binding sites on 3A4 and this experiment does not probe the potential to effect metabolism of compounds that bind to other binding sites on 3A4.

N.B.: In addition to being rough estimates, all of these *in vitro* predictions ignore the effect of any inhibition by duloxetine metabolites. Although the 4-OH glucuronide and 5-OH, 6-MeO sulfate metabolites would not be expected to be likely competitive inhibitors, the effects of other metabolites are unknown. Of special interest would be the unidentified circulating metabolites that are slowly eliminated. Consequently, *in vivo* interaction studies need to be considered (see § 8.10.3).

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8.6.4.3 Metabolic Induction

In human hepatocyte cultures duloxetine did not induce either CYP1A2 or CYP 3A4 (see Table 40 and Table 41). The sponsor claims that these are the only isozymes that are readily inducible, whereas others are not. This is incorrect. In addition, to 1A2 and 3A4, 2C9, 2C19, 2E1, and 2A6 are also inducible. Of these 2C9, 2C19, and 2A6 metabolize drugs and 2E1 metabolizes ethanol.

CYP2C9 is the primary isozyme responsible for the metabolism of coumarin, phenytoin, and tolbutamide.

CYP2C19 metabolizes valproate.

CYP2A6 is involved in the 7-hydroxylation of coumarin, C-oxidation of nicotine, and the metabolism of tobacco specific nitroso-amines. It has been proposed that 2A6 activates pro-carcinogens.

Table 40 Test of Induction of CYP1A2 in Cultured Human Hepatocytes (ADME 77)

Incubate	Duloxetine (µM)				3-MC (Positive Control)
	0.01	0.1	1	10	
7-Ethoxyresorufin O-deethylase Activity					
Human Hepatocyte #	% of Baseline				Multiple of Baseline
HH868	~70	~60	~50	NT	116
HH870	~80	~105	~90	NT	196
HH914	~135*	~185*	~130	~175	92

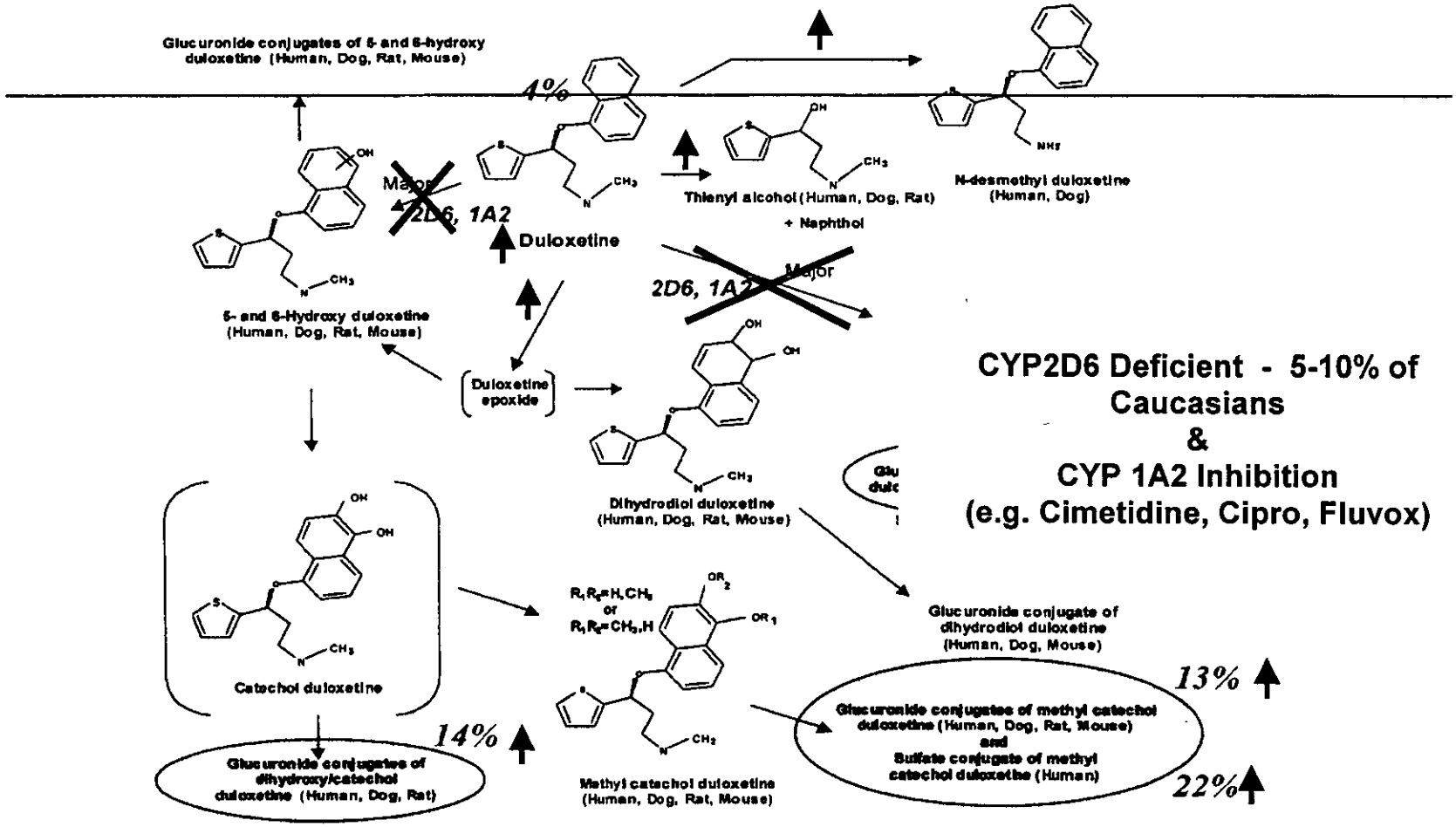
* $p < 0.05$
NT not tested

Table 41 Test of Induction of CYP3A in Cultured Human Hepatocytes (ADME 77)

Incubate	Duloxetine (µM)					Rifampicin (Positive Control)
	0.01	0.1	1	10	100	
Midazolam 1' Hydroxylase Activity						
Human Hepatocyte #	% of Baseline					Multiple of Baseline
HH868	NT	~85	~90	~40*	0*	3.6
HH870	NT	~65*	~70	~40*	0*	10.1
HH914	~90	~110	~125	~75	NT	2.4

* $p < 0.05$
NT not tested

Biotransformation of Duloxetine in Humans



Metabolites which have been detected circulating in human plasma indicated in blue 9

8.7 PROTEIN BINDING

Protein binding was determined in a number of different experiments, many of these with protein obtained from subjects from various phase 1 and 2 studies, representing various subpopulations. Initial studies showed plasma protein binding of around 80%, however this appears to be spuriously low due to bias with the experimental method. A number of later experiments showed protein binding of 90% or greater to plasma proteins, albumin, and α1-acid glycoprotein, and there is a statistically significant difference in binding with sex and a trend was seen with age, (see Figure 20, Table 42, and § 10.5).

Mean protein binding for 'metabolites' was 65%, (see § 10.5).

Due to the large volume of distribution increases in free fraction due to changes in protein binding will increase the volume of distribution.

However, there will likely be significant differences in bioavailability with changes in protein binding, with decreases in bioavailability with lower protein binding. However, this will be compensated to some degree by the higher free fraction, and the shape of the concentration time profile may change.

Table 42 Statistical Comparison, by Category, of *In Vitro* Protein Binding of ^{14}C-Duloxetine in Plasma from American and Japanese Subjects

Comparison Groups	Ratio of Means (90% Confidence Interval)	Category	p value
Japanese / American	0.9986 (0.9887, 1.0086)	Race	0.938
		Age	0.253
Female / Male	1.0110 (1.0000, 1.0220)	Sex	0.054

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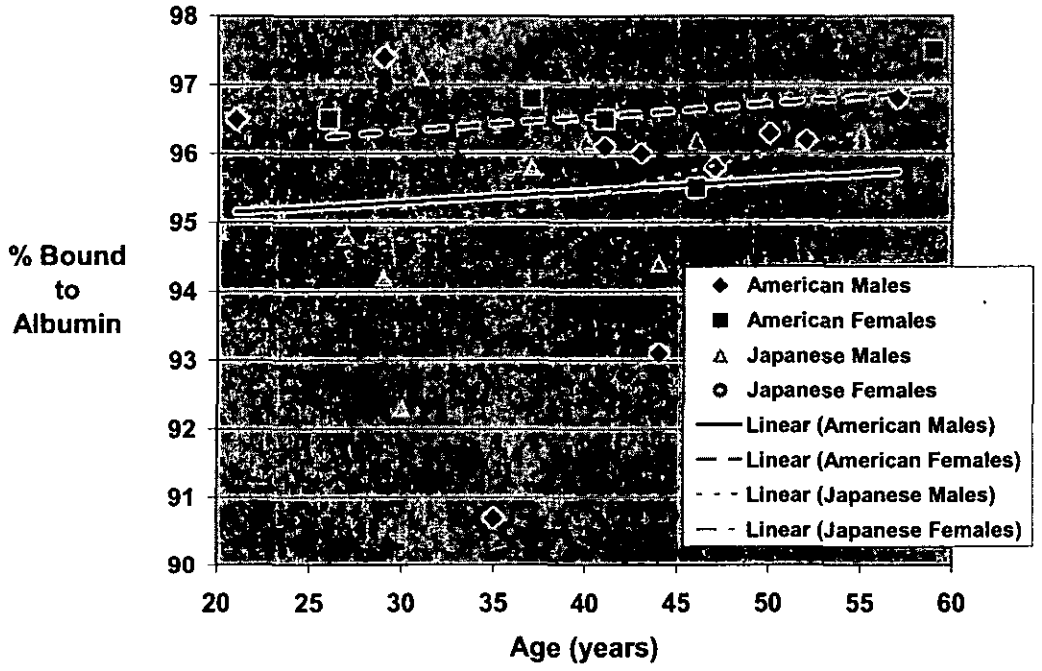
Figure 20 Duloxetine Albumin Binding vs. Age in American and Japanese Males and Females



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8.8 PHARMACODYNAMICS

8.8.1 IN VITRO PHARMACODYNAMICS

For duloxetine and its metabolites, *in vitro* Kis for the proposed active sites are shown in Table 43. For the quantitatively important circulating metabolites the Ki for inhibition of the human transporters of 5HT and NE are greater than 50 times the Ki of duloxetine, therefore the sponsor claims they are inactive. However, quantitatively less important metabolites that are much more active, (see Table 43), and when in vivo concentrations are examined the conclusion is that they might be active *in vivo,* (see Table 44).

Table 43 Inhibition of Neuronal Receptor Binding by Duloxetine and Its Potential Human Metabolites - Values are Expressed as K_i in nM

Compound	5HT Transporter	Norepinephrine Transporter	Dopamine Transporter	α1, α2, β1, β2, D1, D2, H1, 5HT2, Muscarinic Receptors
	[^{3}H]-Paroxetine	[^{3}H]-Nisoxetine	[^{3}H]-Mazindol	NR
Duloxetine	0.8 ± 0.04[a] 0.87	7.5 ± 0.3 14.1	240 ± 23 241	'do not bind'
Metabolites				
Glucuronide Conjugate of 4-OH Duloxetine	>10000	>10000	3509	'do not bind'
Sulfate Conjugate of 5-OH 6-OCH_3 Duloxetine	3118	>10000	>10000	
Glucuronide Conjugate of 5-OH 6-OCH_3 Duloxetine[b]	>10000	>10000	>10000	
Glucuronide Conjugate of Dihydroxy/Catechol Duloxetine	>10000	>10000	>10000	
Glucuronide Conjugate of 6-OH Duloxetine	1459	5454	>10000	
Dihydrodiol of Duloxetine-Isomer I	120	695	7295	
Dihydrodiol of Duloxetine-Isomer II	32	554	>10000	
Metabolites Found Only After Hydrolysis of Urine				
5-OH Duloxetine	9.6	18.4	240	
6-OH Duloxetine	1.06	4.7	164	
4-OH Duloxetine[c]	64	97	130	
5-OH 6-OCH_3 Duloxetine	266	920	2814	
6-OH 5-OCH_3 Duloxetine	3.66	235	353	

a Ki – in vivo – < 0.34 μM (100 ng/ml – $Cmax^{SS}_{ave}$)
b Isomer of the glucuronide conjugate of the methyl catechol found in humans.
c The value for this compound may not be accurate since the compound is unstable.
NR – not reported

Table 44 Summary of Single Dose Mass Balance Study, Multiple Dose PK Study, *In Vitro* Metabolism and Receptor Binding Studies

	Analytes	Found in Non-Human Species	Fraction of circulating radioactivity (%)	(AUCm / AUCp) Ratio	Enzymes Forming	Km formation µM/L	Major (Sponsor Defined)	Conc.* ng/ml	Max Conc µM/L (60 mg BID)	Fraction of Duloxetine Conc. ^{14}C study	Activity S, NE, DA ® Ki (µM)	Active
1	Duloxetine	EC Tab 20 mg SD	3%	—	—	—		23.5 ± 14				
		EC Cap 60 mg BID		—	—	—	NA	316	1.1	NA	0 001, 0.0075, 0.240	Y – Y - Y
2	4-OH	DRM			2D6* 1A2	1.1 22		'usually detectable'	*0.11a*	1 - <10%	0.064, 0.097, 0.13	M - M - M
3	4-OH-Gluc	DRM	47%	15.7			X	NR	16.8-?		>10, >10, 3.5	M – M - Y
4	4-OH SO4	—										
5	5-OH	DRM			2D6* 1A2 2C9 minor	0.9 22		Usually — ng/ml	*0.11a*	1 - <10%	0.01, 0.018, 0.24	Y – Y- M
6	6-OH	DRM			1A2	25		Usually — ng/ml	*0.11a*	1 - <10%	0.001, 0.005, 0.164	Y – Y- M
7	5-O-Gluc	DRM									NR	
8	6-O-Gluc	DRM									1.5, 5.5, >10	? - ? - ?
9	(Catechol) Intermediate	DRM										
10	5-O-Gluc 6-OH	DRM	13%	4.3				NR	4.8		>10, >10, >10	M - M - M
11	5-OH 6-O-Gluc	DRM									>10, >10, >10	? - ? - ?
12	***Me Catechol (M15)***	***DRM***									***0.27, 0.92, 2.8***	
13	***Me Catechol (M16)***	***DRM***						***Usually — ng/ml***	***0.11a***	***1 - <10%***	***0.004, 0.24, 0.35***	***Y – M - M***
14	***Me Catechol Gluc 1 (M3)***	***DRM***	***14%***	***4.7***				***NR***	***5.1***		***>10, >10, >10***	***? - ? - ?***
15	***Me Catechol Gluc 2 (M10)***	***DRM***										
16	Me Catechol SO4 (M7)	—	22%	7.3			X	NR	8.1		> 3.1, >10, >10	Y – M - M
17	(epoxide) Intermediate	DRM										
18	Dihydrodiol	DRM			EH - ?						0.12, 0.7, 7.3 0.032, 0.55, >10	? - ? - ? ? - ? - ?
19	Dihydrodiol Gluc	Dog, Mouse										
20	N-Desmethyl	Dog	1%		2C11?			?		NR	?	
21	Thienyl Alcohol & Napthol	Dog, Rat			?			?			?	
	Total		100%									

- Meaning of 'Usually — ng/ml' unclear but may mean BLQ.
- N.B. SD & low dose therefore relative circulating exposures under clinical conditions could be much different
- Do not know concentrations
- DRM – Dog, Rat, Mouse

8.8.2 IN VIVO & EX VIVO

8.8.2.1 Serotonin Reuptake Blockade

In study HMAA, after a single 60 mg immediate release capsule dose of duloxetine *ex vivo* platelet serotonin uptake was inhibited by over 85% at 3 hours post-dosing under both fed and fasting conditions, (see Table 45).

Pharmacokinetic sampling was also performed and the sponsor claimed that this information could be found in appendix 2, however appendix 2 was not provided. Therefore a PK/PD relationship could not be established. However, as this was an immediate release formulation the concentrations were likely much higher than would be achieved by the to-be-marketed formulation.

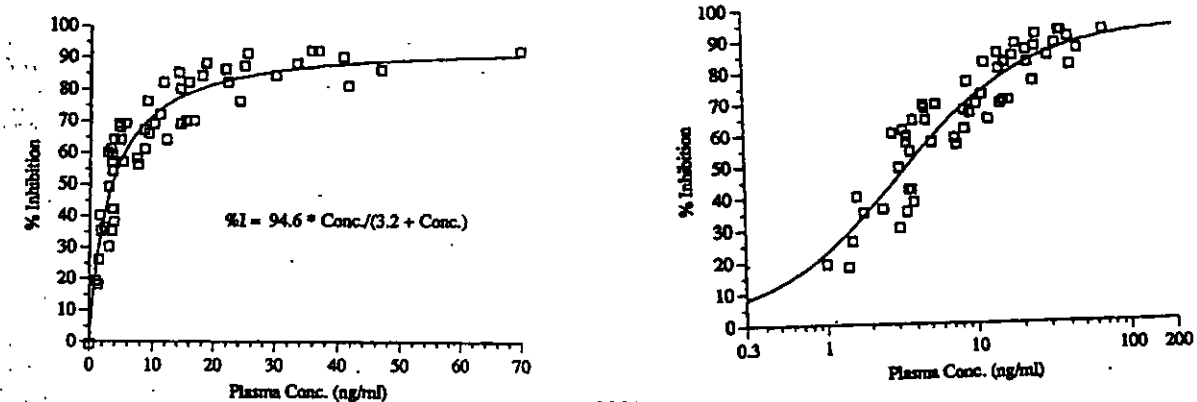
Table 45 *Ex Vivo* Platelet Serotonin Uptake Inhibition After a Single 60 mg Dose of Duloxetine Under Fasted Conditions (Study HMAA)

Subject	Baseline (Placebo)	60 mg						
		Fasting				Fed		
		0 hour	1.5 hour post dosing			3.0 hour post dosing		
	pMol 5-HT/ minute per 10^9 platelets	pMol 5-HT/ minute per 10^9 platelets	pMol 5-HT/ minute per 10^9 platelets	% Inhibition	pMol 5-HT/ minute per 10^9 platelets	% Inhibition	pMol 5-HT/ minute per 10^9 platelets	% Inhibition
816	7.65	11.3	1.04	90.8	1.04	90.8	0.65	91.5
567	10.25	13.85	4.77	65.6	1.8	87.0	1.26	87.7
671	10.1	—	—	—	—	—	—	—
506	9.74	9.64	0.75	92.2	0.97	89.9	0.58	94.0
Mean ± SD (CV%)	9.44 ± 1.21 (12.81)	11.60 ± 2.12 (18.29)	2.19 ± 2.24 (102.53)	82.86 ± 15.00 (18.10)	1.27 ± 0.46 (36.25)	89.25 ± 1.99 (2.23)	0.83 ± 0.37 (45.1)	91.1 ± 3.2 (3.5)
Range [Median]	[9.92]	[11.30]	[1.04]	[90.80]	[1.04]	[89.94]	[0.65]	[91.5]

In study HMAB, *ex vivo* platelet serotonin uptake was measured prior to and 3, 8, and 24, hours after 10 mg, 20 mg, 40 mg, and 60 mg single doses of duloxetine enteric coated tablets and the percent inhibition was calculated. Plasma concentrations were determined after doses of 40 mg and 60 mg.

Emax was 94.6% inhibition and the EC_{50} was 3.2 ng/ml, with approximately 80% inhibition achieved at 20 ng/ml, (see Figure 21).

Figure 21 *Ex Vivo* Platelet Serotonin Reuptake Inhibition vs. Duloxetine Plasma Concentration (Study HMAB)



In study O001, whole blood 5-HT concentrations were significantly lower after duloxetine 60 mg BID as compared to placebo, and there was a trend at 80 mg qd that did not reach statistical significance. In addition, the norepinephrine reuptake inhibitor, desipramine did not effect 5-HT concentrations. Surprisingly, 48 hour 5-HIAA was not significantly altered by any regimen, (see Table 46).

Table 46 Effect of Duloxetine and Desipramine on Whole Blood 5-HT and 48 hour Urinary 5-HIAA Excretion (Study O001)

Whole Blood 5-HT Concentration (nMol/ml)				
Treatment	Placebo	Duloxetine 80 mg QD	60 mg BID	Desipramine
n	12	5	6	11
Baseline Day -1	1.151 ± 0.438 (38.1) [1.058]	1.111 ± 0.362 (32.6) [0.913]	1.226 ± 0.438 (35.7) [1.144]	1.045 ± 0.404 (38.7) [1.156]
n	9	5	6	11
Day 6	1.099 ± 0.544 (49.5) [1.015]	0.761 ± 0.516 (67.8) [0.605]	0.474 ± 0.114 (24.1) [0.492]	0.963 ± 0.46 (47.8) [0.854]
GMR	{1.059}	{0.617}	{0.525}	{1.049}

p-Value row(s) vs. col.	Placebo	Duloxetine 80 mg QD	Duloxetine 60 mg BID	Desipramine	
Placebo					
Duloxetine 80 mg QD	0.0728			0.0769	0.0122
Duloxetine 60 mg BID	0.0244			0.0247	
Desipramine	0.9549				

48 Hour Urinary 5-HIAA Excretion (µMol)				
Treatment	Placebo	Duloxetine 80 mg QD	60 mg BID	Desipramine
n	11	5	6	11
Day 5-6	48.73 ± 9.733 (20.0) [47.1] {48.51}	46.44 ± 9.761 (21.0) [42.9] {45.71}	45.23 ± 8.767 (19.4) [48.35] {44.94}	46.92 ± 11.88 (25.3) [44.9] {46.69}

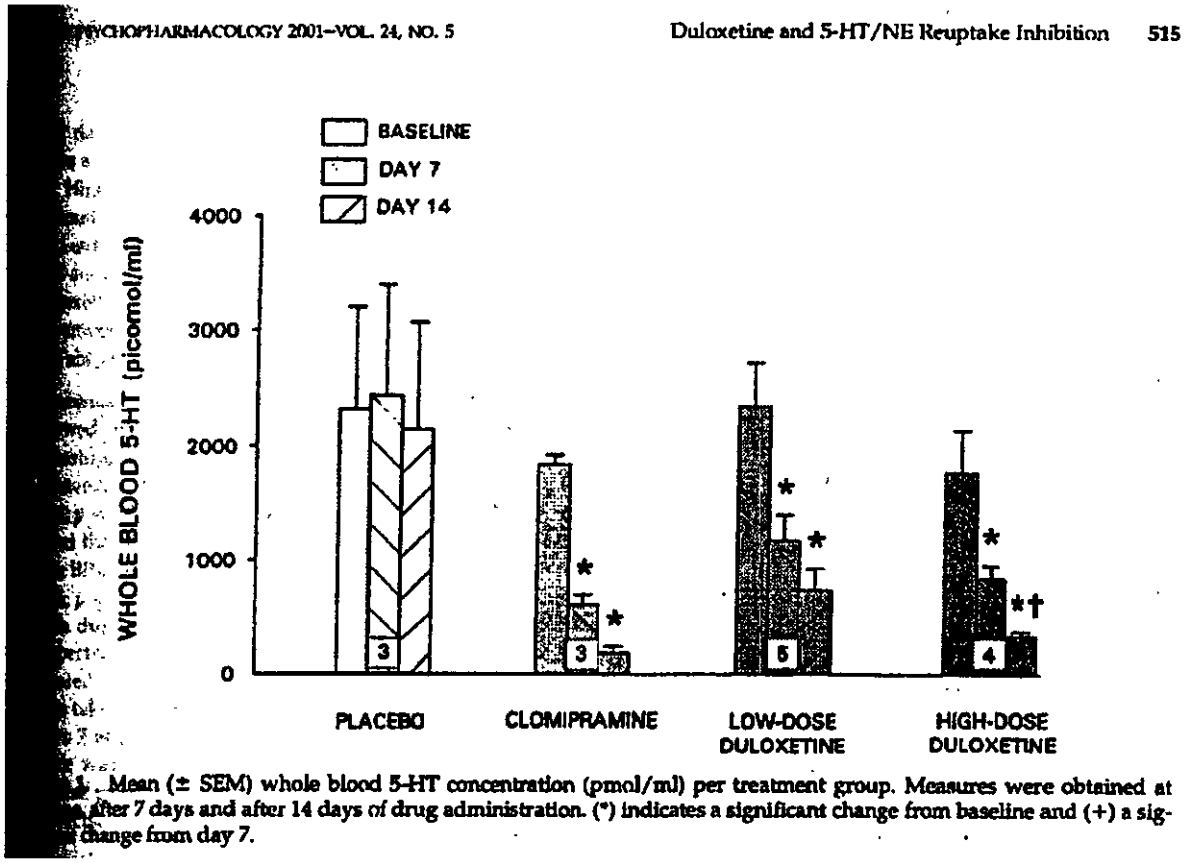
p-Value row(s) vs. col.	Placebo	Duloxetine 80 mg QD	Duloxetine 60 mg BID	Desipramine	
Placebo					
Duloxetine 80 mg QD	0.6394			0.8692	0.7519
Duloxetine 60 mg BID	0.5159			0.7487	
Desipramine	0.6732				

GMR – geometric mean ratio

Also as reported in study SAAN in Neuropsychopharmacology 2001 Vol 24 No. 5 (511 – 521), clomipramine 100 mg qd, a 5-HT/NE reuptake inhibitor, and duloxetine 20 mg and 60 mg qd, all significantly decreased whole blood 5-HT after 7 days with a greater effect seen at 14 days.

A dose effect is also seen with duloxetine, with the degree of effect with duloxetine 60 mg closer to the degree seen with clomipramine than the degree of effect seen with duloxetine 20 mg, (see Figure 22).

Figure 22 Whole Blood 5-HT Concentration at Baseline and After 7 and 14 days of Treatment



Mean (± SEM) whole blood 5-HT concentration (pmol/ml) per treatment group. Measures were obtained at after 7 days and after 14 days of drug administration. (*) indicates a significant change from baseline and (+) a significant change from day 7.

8.8.2.2 Norepinephrine Reuptake Blockade

8.8.2.2.1 Pupilscans

In study HMAA, after single doses of an immediate release capsule of 35 mg – 60 mg, consistent effects were seen on pupil size and response with pupilscan, indicating potential inhibition of norepinephrine uptake. However, as this was an immediate release formulation the concentrations were likely much higher than would be achieved by the to-be-marketed formulation.

In study HMAB pupil scans were conducted pre-dose and at 2.5 and 7 hours post-dose with an effect seen only at 7 hours. The effect was maximal after 20 mg, and was not dose related.

Pupilscans were also conducted in study HMAD with no effect seen at doses up to 40 mg qd.

8.8.2.2.2 Plasma Norepinephrine Concentrations

In study HMAP plasma norepinephrine concentrations were determined in young healthy males after dosing for 6 days with duloxetine 40 mg bid or placebo. No statistical difference was found, however there was no information provided on sampling times and the lack of difference might be due to the small number of subjects.

Table 47 Plasma Norepinephrine Concentrations After Duloxetine 40 mg BID and Placebo (Study HMAP)

	Plasma Norepinephrine Concentration (pg/ml)			Group Comparison p-value
	40 mg BID	PBO	Difference	
N	8	3		
Mean ± SD (CV%) Range [Median]	213.2 ± 80.1 (37.6) [220]	189.6 ± 87.6 (46.2) [175]	23.5 ± 74.0 (314.3) [24.0]	0.316116
Average Difference	-14.6	-47.3		0.543
Nullity p-Value	0.311	0.601		

8.8.2.2.3 Effect on Heart Rate

In study HMAR, an Emax model was fit to the effect of duloxetine concentration vs. heart rate, (see Figure 23). This effect may be an indication of norepinephrine reuptake blockade.

Figure 23 Emax Model of the Effect of Duloxetine Concentration vs. Heart Rate (Study HMAR)

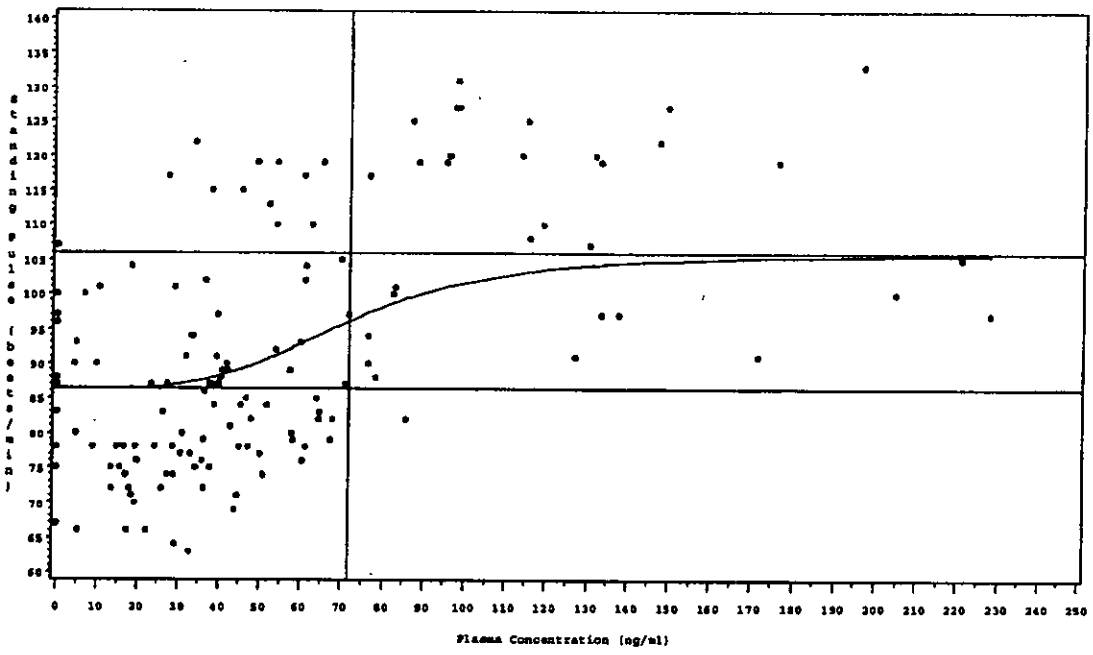


Figure HMAR.12.1. Standing pulse versus duloxetine plasma concentration recorded pre-morning dose for F1J-BD-HMAR. Mean predicted profile (mean E_{max} = 19.6 beats/minute; mean EC_{50} = 71.8 ng/mL).

8.8.2.2.4 Tyramine Pressor Response

Note the following is paraphrased from the sponsor:

Based upon the presumed mechanism of tyramine as an indirect NE agonist requiring uptake in the neuron to exert a pressor effect, if duloxetine inhibits NE reuptake then it should potentially decrease the hypertensive response to tyramine.

In study SAAN, at duloxetine doses of 20 mg and 60 mg qd, a fixed dose of tyramine failed to demonstrate a statistically significant decrease in blood pressure.

In addition, in study O001 when a tyramine dose necessary to produce a fixed increase (30 mm Hg) in systolic blood pressure under control conditions was administered in combination with duloxetine doses of 80 mg QD and 60 mg BID. Again there was no significant change in the mean pressor effect of tyramine compared to placebo.

However, changes in the 48 hour urinary excretion of NE and its metabolites show that both regimens of duloxetine were associated with a significant decrease in whole body NE turnover. A comparison of urinary ratios reflecting the influence of the study drugs on NE metabolism showed a similar pattern with duloxetine 80 mg and desipramine, a known NE reuptake inhibitor. Furthermore, polygraphic sleep recordings showed that both duloxetine and desipramine induced a significant increase in mean REM sleep latency and a decrease in mean REM time. Thus, while the tyramine test was again unsuccessful in demonstrating a NE reuptake effect, the urinary NE turnover and sleep data provide pharmacological evidence that support NE reuptake as a likely effect of duloxetine at these doses. Studies with venlafaxine and sertraline suggest the possibility that the tyramine pressor challenge test may not be a reliable measure of NE reuptake inhibition in the setting of concurrent 5-HT reuptake inhibition (Harvey et al. 2000). In addition, results in duloxetine clinical studies provide considerable indirect evidence suggesting the presence of NE reuptake inhibition in vivo. For example, hemodynamic data from clinical pharmacology and phase 2/3 studies consistently indicate a modest but statistically significant increase in systemic blood pressure (ISS Section 10.1.2.4). Such changes in blood pressure are consistent with pharmacological actions resulting from systemic NE effects. This hypothesized action specifically includes at least one drug approved for the treatment of MDD that also has dual reuptake (5-HT and NE) properties.

8.8.2.3 Effect on Mood in Healthy Volunteers

Conclusions:

In study HMAE duloxetine did not systematically affect mood in healthy normal volunteers at doses of up to 20 mg. Higher doses that will be used clinically (40 mg bid and 60 mg QD) were not studied. The lack of a finding of an effect of mood elevation does not preclude the possibility that duloxetine may induce switching from depression to mania in susceptible patients.

Comments:

In early studies on healthy volunteers adverse effects on mood were reported, (see Table 48). Euphoria was also reported in study HMAZ in a single male subject receiving duloxetine EC capsules 40 mg bid.

Table 48 Reported Adverse Effects on Mood

Study	Population	Formulation	Dose & Regimen	Reported Effect Related to Mood
HMAA	Healthy male volunteers	IR Tablets	SD: 1 mg to 60 mg fasted	weird feeling high feeling
HMAB	Healthy male volunteers	EC Tablets	SD: 5 mg to 80 mg fasted	weird feeling high feeling hyperactivity
HMAD	Healthy male volunteers	EC Tablets	MD: 2.5 mg to 40 mg qAM before breakfast	mood swings irritability hyperkinesia at doses up to 20 mg
HMAZ	Healthy male volunteer	EC Capsule	MD: 40 mg bid	Euphoria

In study HMAE the effects of duloxetine on mood in normal volunteers was examined. Baseline tests included a general health questionairre (GHQ), (Goldberg et al. 1970), Buss Durkee Hostility Inventory (Buss and Durkee, 1957) and the MMPI (excluding the depression and psychomotor acceleration subsets), and the Profile of Moods Scores (Lorr and McNair, 1988), to rule out any psychopathology. The study was a 3-way cross over study with a 5 day baseline run-in period and 1 week inter-period washouts in 12 healthy male volunteers. Duloxetine 5 mg, 20 mg, or placebo, as EC tablets were administered qAM before breakfast x 14 days. Profile of Moods Scores (Lorr and McNair, 1988), and trough duloxetine concentrations were examined every 3-4 days during the 5 day baseline run-in period, during treatment, and during the inter-period washouts. Data was analyzed by ANOVA.

There was no effect observed on POMS score (see Table 49). Of 63 LS means measured 5 were above the upper limit of the 95% CI and 4 were below the lower limit. This is approximately 15% of the measurements and is slightly high. However, since scores were evenly distributed divided between changes in opposite directions without any discernable pattern it's likely that these were random deviations.

The sponsor also claimed that there was no association with duloxetine trough concentrations. According to the sponsor: 'Only 1 subject (Subject 0742 reported irritability during the study (event terms agitation and hostility). This subject had previously reported irritability during the multiple-dose safety study (study HMAD). During the current study, he reported feeling irritable while receiving all treatment regimens, including placebo.' (Note – subject received 5mg, then 20 mg, and placebo last. Subject was irritable during entire placebo phase (2 weeks)).' One other subject (Subject 0913) became angry with a dietary staff member for a brief time while receiving placebo as his third experimental treatment regimen (event term agitation).'

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Table 49 Profile of Moods Scores on Duloxetine (Study HMAE)

Factor	Baseline		Dose Level	Least Squares Means Treatment Period			Direction outside of 95% CI
				First	Second	Third	
TMD[a]	LL 95% CI	32.05	High	**47.19**	33.58	40.60	↑
	Mean	38.73	Low	43.67	39.81	**30.31**	↓
	UL 95% CI	45.51	PBO	36.56	41.25	43.40	
Tension	LL 95% CI	10.67	High	**13.44**	**10.25**	11.15	↑, ↓
	Mean	11.64	Low	11.50	11.25	12.19	
	UL 95% CI	12.60	PBO	11.81	11.55	10.92	
Depression	LL 95% CI	15.03	High	18.19	15.25	16.35	
	Mean	16.71	Low	16.44	17.88	15.50	
	UL 95% CI	18.38	PBO	17.25	16.25	18.00	
Anger	LL 95% CI	12.16	High	13.88	13.17	12.60	
	Mean	12.93	Low	**14.06**	12.50	**12.00**	↑, ↓
	UL 95% CI	13.69	PBO	12.75	12.80	**14.08**	↑
Vigor	LL 95% CI	15.82	High	17.25	21.50	17.05	
	Mean	19.46	Low	17.81	17.31	**26.00**	↑
	UL 95% CI	23.10	PBO	21.81	17.70	**15.00**	↓
Fatigue	LL 95% CI	6.43	High	8.94	7.58	9.10	
	Mean	8.16	Low	9.80	7.63	7.00	
	UL 95% CI	9.88	PBO	7.56	8.90	7.45	
Confusion	LL 95% CI	7.81	High	10.00	8.83	8.45	
	Mean	8.93	Low	9.44	7.88	9.63	
	UL 95% CI	10.05	PBO	9.00	9.45	9.18	

a Total Mood Disturbance Score

8.8.2.4 Sedation

As mentioned under tyramine in § 8.8.2.2.4. In study O001, polygraphic sleep recordings showed that both duloxetine and desipramine induced a significant increase in mean REM sleep latency and a decrease in mean REM time.

8.8.2.5 Urinary Retention

In study HMAB, which was a single rising dose study, decreases in urine output was noticed during the first 6 hours after dosing in most subjects.

In study HMAP the sponsor reported the following: Urine flow variables (including void time, flow time, maximum flow rate, time to maximum flow rate, average flow rate, and void volume) were measured and the results were analyzed statistically. In the duloxetine group, when examining the mean treatment changes from baseline, isolated changes were noted, as were isolated trends in dose response. Specifically, duloxetine 30 mg BID was associated with small decreases in maximum flow rate and average flow rate. Duloxetine administration was also associated with a trend towards increased flow time and void time. However, in examining the pattern of mean responses across periods in the duloxetine and placebo-only treatment groups, no significant differences between groups were observed. Thus, the above-described effects on urine flow are not clearly a consequence of duloxetine dosing. Thus, duloxetine did not have major effects on urine flow in this study. This conclusion should be interpreted cautiously for several reasons. First, the number of urine flow measurements in each subject was relatively small. Second, the subjects in this study were healthy and major effects on urine flow were not

expected in healthy subjects, and should not infer a lack of potential beneficial effects on urine flow in patients with urinary dysfunction.

8.8.3 TOXICITY IN PHASE I/II STUDIES

According to the sponsor the highest dose utilized in phase I/II studies was 80 mg BID in study HMAR. This was a multiple rising dose safety and tolerability study in 12 healthy subjects (six males and six females). The highest duloxetine concentration observed in this study was approximately 300 ng/mL.

8.8.3.1 Cardiovascular Effects

Summaries of effects on cardiovascular vital signs and ECGs in phase I/II studies are shown in Table 50 and Table 51, respectively. There may be minor increases in HR and occasional orthostatic hypotension. Possible pharmacodynamic drug interactions are questionable.

Table 50 Summary of Effects on Cardiovascular Vital Signs in Clinical Pharmacology Studies

Study	Effect	Comments
HMBN	BP, HR	Occasional orthostatic hypotension in individuals. Can't tell by mean data.
HMAR	HR standing	Sigmoid Emax **Vmax 19.6 bpm Km 71.8 ng/ml** Exploratory data – not designed to assess, so concentrations are not high enough to clearly determine Emax
	SBP DBP standing & supine	Minor increases on average – dose related 3 cases of orthostatic hypotension
	HR standing	sigmoid Emax
	HR – Standing	Ave increase 5 bpm
HMAA	SBP DBP	Minor increases (4 mmHG at 50 & 60 mg) in ¾ of subjects Possible increase in DBP with dose (minor)
HMAB	BP	No discernable effects
HMBJ - ESRD	SBP supine	Elevated especially in 1 healthy control with elevations at baseline and in 4 patients with ESRD with a history of HTN – according to sponsor a history of HTN may be a relative contraindication
HMAX – (Cirrhosis)	BP supine	no change
	SBP standing	mild increase
	HR supine	mild increase
HMAZ	HR standing	increased when desipramine added
	DBP standing	decreased in combination with desipramine 1 case of orthostatic hypotension in combination with
	SBP & DBP Supine	increased in combination with desipramine
HMBF	HR	Possible synergistic PD interaction with theophylline 3 subjects with tachycardia on the combination only
HMBN	BP	day 1 – 1 subj 26 mmHg dep in DBP day 1 – average 8.5 mmHg dec DBP day 19 – 1 subject with - 22 mmHg decrease in SBP & 14 mmHg decrease in DBP day 19 – 1 subject with 32 mmHg decrease in SBP No associated orthostatic symptoms
	HR	some orthostatic changes day 1 approximately double the change at baseline (mean as high as 15) but it's just as large after discontinuation
HMAD	DBP	7 – 11 mmHg increase in DBP @ 40 mg
SBAG	HR	slight increase in the presence of paroxetine

Table 51 Summary of ECG Effects in Clinical Pharmacology Studies

Study	Comments
HMAR	Sponsor claimed all ECGs were normal No change in metric means
HMAP	QTc average increase of ≤5% with means of 400 – 410 mSec
HMAA	2 subjects with borderline minor ST segment elevations and prominent Q waves
HMAB	3 subjects with sinus bradycardia
HMBJ (ESRD)	No change in QT or QTc at 6 hrs (~Tmax)
HMAX (Cirrhosis)	QT no change in mean QTc no change in mean
HMAZ	QTc trend for decrease; p = 0.08 PR decreased; p = 0.003
HMBB	
HMBG	1 subject with ST segment depression 1 subject with sinus bradycardia with PVCs 1 subject with inverted T waves (no symptoms)
HMBN	Slight lengthening of QTc but highest mean < 400 mSec and only a 1 subject with QTc > 430 mSec (one subject had a baseline QTc of 427 mSec but I can't tell if this is the same subject)
HMAD	2 subjects with sinus bradycardia

In study HMAA in subjects with tricuspid regurgitation there was no effect on cardiac blood flow velocity.

8.8.3.2 Changes in Laboratory Values

8.8.3.2.1 Increased LFTs

In study SBAG, there were no obvious abnormal laboratory values attributable to duloxetine alone, although there was a slight increase in LFTs in 2 subjects in the presence of paroxetine, a CYP2D6 inhibitor & duloxetine.

There are also other sporadic cases of increased LFTs reported in other studies. One case in study HMAB, 2 subjects in study HMAZ, and one in study HMAA. One of the subjects in HMAA was subsequently shown to have hepatitis C.

8.8.3.2.2 Hematology

Table 52 Summary of Hematology Changes Noted

Lab	Change	# Subjects	Study	Comments
WBC	Increased	9	HMAD	
	Increased	several	HMBG	
	Decreased	3	HMAX	
RBC	Decreased	several	HMBG	claimed possibly due to venepunction, this was also in the face of increased WBCs
Platelets			HMAX	
Platelets	Thrombocytopenia	1	HMAP	~ 50 K plts about 2 months after d/c of duloxetine

Echymoses was also noted in one subject. Inhibition of platelet serotonin uptake might inhibit aggregation.

8.8.3.2.3 Cholesterol

Study HMBG 5 subjects had increased cholesterol

8.8.3.3 Other AEs

In study HMAD 2 subjects reported decreased deep tendon reflexes.

A summary of other AEs commonly seen across the phase I/II studies is tabulated in § 10.6.

It's noteworthy that AEs are higher in females as compared to males, and in end-stage renal disease and cirrhosis, and all are covariates associated with increase plasma concentrations of duloxetine.

8.9 EFFECT OF INTRINSIC FACTORS

8.9.1 GENDER

Women have significantly higher exposures to duloxetine than men, with mean Cmaxs 160% or greater as compared with men and mean AUCs approximately 2 fold higher. This is presumably due to the lower expression of CYP1A2 in women resulting in lower clearance and greater bioavailability, (See § 8.11.1, § 10.5, § 10.8, and § 10.10). It may also be partially due to the higher protein binding in women.

8.9.2 CYP 2D6 GENOTYPE

There is limited pharmacokinetic data on the effect of CYP2D6 phenotype on duloxetine pharmacokinetics as most studies either did not genotype or phenotype subjects or limited enrollment to CYP2D6 extensive metabolizers. Consequently, there's only a few subjects identifiable as CYP2D6 PMs from any of the PK studies even when the data is combined. However, based upon these few subjects, the information from subjects with end-stage renal disease, the *in vitro* information, and the non-linear pharmacokinetics, CYP2D6 phenotype appears to be the primary determinant of inter-subject variability in duloxetine exposure. Thus, 2 fold or greater increases in AUCs are expected in poor metabolizers as compared with extensive metabolizers. (See § 8.11.1, § 10.5, § 10.8, § 0, and § 8.9.8).

8.9.3 RACE / ETHNICITY

Except for the population pharmacokinetic analyses there were no formal examinations of the effect of race or ethnicity on duloxetine pharmacokinetics. In one population PK analysis, there were sufficient numbers of Caucasians and Hispanics to determine that ethnicity was not an important covariate in duloxetine exposure. This is consistent with inspection of data from the traditional descriptive pharmacokinetic studies. As compared to Caucasians were either insufficient numbers of subjects with different ethnic backgrounds, i.e. Native Americans, or inspection of the data did not reveal any striking differences between Caucasian EMs 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), (see § 10.5, § 10.8, § 0).

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.

8.9.4 GASTRIC PH

In study HMAA, gastric pH was measured in 4 healthy subjects on 4 to 8 occasions over a 5 hour period. Table 53 shows the average of the mean 5 hour gastric pH in these subjects and the highest single pH measured. Gastric pH tended to be similar within each subject across occasions. What is noteworthy is that the measured pH's tend to be much higher than is usually quoted as normal gastric pH (median pH 1.7).

The enteric coating material, hydroxypropyl methylcellulose acetate succinate (HPMCAS), dissolves at pH 5.5. Therefore, these reported gastric pHs raise the question of whether the enteric coating may dissolve in some individuals and release duloxetine in the stomach. Subsequent acid secretion would then be of concern.

Table 53 Mean and Maximum Gastric pH in 4 Volunteers (Study HMAA)

	Subject #			
	671	816	597	506
Average pH	2.5	4.0	2.7	6.2
Maximum Measured pH	5.2	12.4	6.2	7.6

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8.9.5 DIURNAL VARIATION

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, a decrease in Cmax and AUC 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 napthol. This issue has not been addressed. Data from these studies are shown in the following sections.

8.9.5.1 HMAO

Table 54 Diurnal Variation of Duloxetine in Study HMAO

Sampling Scheme	N	wt	Tlag	Cmax	Tmax	t1/2	AUCt	AUCinf	CL/F	CL/kg	Vb/F	Vd/kg
20 mg Tablet AM	6	76.3 ± 6.8 (8.9) 68 - 87.2	3.7 ± 1.0 (28.2) [3]	10.9 ± 4.7 (43.3)	5 ± 0 (0) 5 - 5	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) 1.1 - 3.3	2090 ± 840 (40.2)	27.5 ± 10.8 (39.3) 17.0 - 44.8
20 mg Tablet PM	6	76.2 ± 5.7 (7.5) 75.9 69.1 - 85.1	6.3 ± 1.6 (25.8) [6]	6.2 ± 1.9 (31 1) 2.9 - 8.7	8.3 ± 2.1 (24.8) 5.0 - 11.0	9.8 ± 3.9 (39 5) 6 1 - 16.5	68.4 ± 30.7 (44 9) 22.3 - 116.9	104.9 ± 44.4 (42 4) 54.0 - 185.8	218.5 ± 87.5 (40 0) 107.7 - 370.7	2.9 ± 1.2 (40 8) 1.6 - 4.9	2944.8 ± 1451.8 (49.3) 1859.0 - 5810.0	38.9 ± 19.6 (50.4) 24.2 - 77 6
20 mg Capsule AM	6	76.6 ± 5.9 (7.7) 75.6 69.8 - 86.2	3.4 ± 1.4 (39 7) [3]	9.3 ± 2.2 (23.3) 6.7 - 11.6	6.0 ± 1.1 (18.3) 5.0 - 7.0	10.1 ± 1.5 (15.3) 7.8 - 11.6	113.8 ± 44.9 (39.5) 55.9 - 184.3	150.1 ± 55.3 (36.8) 81.7 - 234.7	150 1 ± 57.9 (38.6) 85.2 - 245.6	2.0 ± 0.8 (41.3) 1.2 - 3.3	2100.8 ± 531.0 (25 3) 1425.0 - 2771.0	27.6 ± 7.8 (28 2) 20.4 - 37.6

Figure 24 Mean Duloxetine Concentration vs. Time Profiles showing Diurnal Variation (Study HMAO)

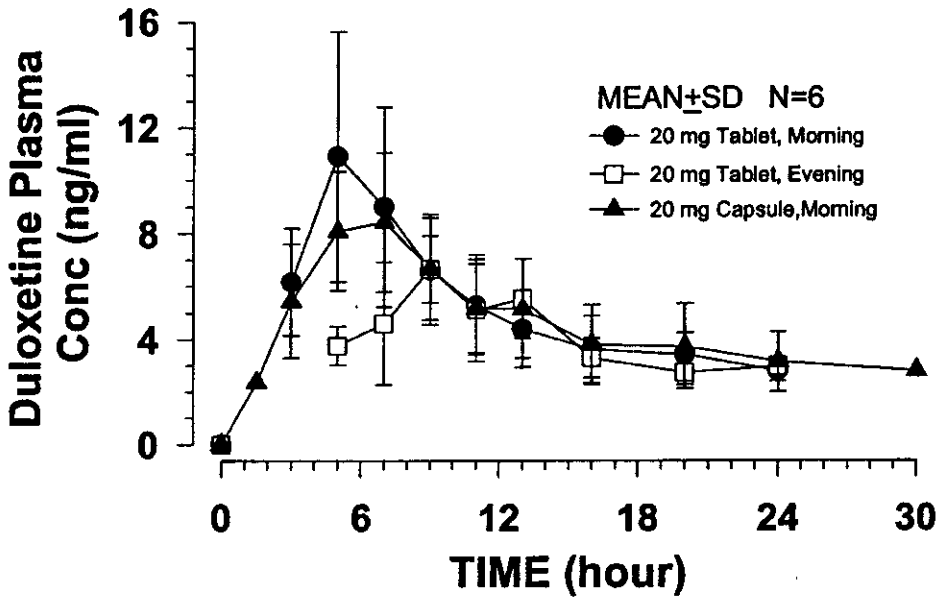

Figure HMAO.1 Part I mean plasma concentration results.

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8.9.5.2 HMBN

Table 55 Diurnal Variation of Duloxetine in Study HMBN

Sampling Scheme	N	wt	Cmin	Cmax	Tmax	AUCtau	Cav	% Fluc	CL/F
BID AM	11	79.1±15.1 (19.2) [71.2]	85.2±59.7 (70.0) [64.9]	144.0±85.4 59.3 [113.3]	6.0±1.3 (21.1) [6.0]	1375.8±869.2 (63.2) [998.1]	114.7±72.4 (63.2) [83.2]	57.4±17.3 (30.1) [61.7]	62.5±35.9 (57.4) [60.1]
BID PM	11	79.1±15.1 (19.2) [71.2]	79.3±53.4 (67.4) [49.0]	120.0±76.6 (63.8) [77.4]	6.0±1.3 (21.1) [6.0]	1136.5±884.4 (77.8) [748.4]	103.4±68.2 (66.0) [64.5]	41.9±11.9 (28.3) [47.1]	63.2±45.1 (71.3) [47.0]

Figure 25 Mean Duloxetine Concentration vs. Time Profiles showing Diurnal Variation (Study HMBN)

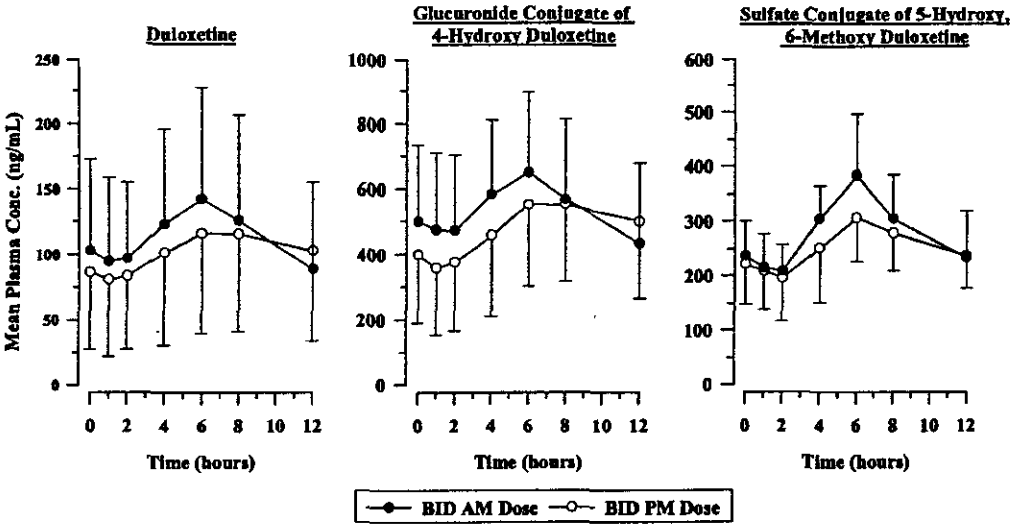

Figure HMBN.11.6. Mean (SD) plasma concentration-time curves of duloxetine and its major metabolites in healthy subjects receiving a 60-mg dose in the morning and evening at steady state on BID regimens.

8.9.5.3 SBAA

Table 56 Effect of AM and HS dosing on Duloxetine 20 mg Pharmacokinetics (Study SBAA)

Metrics	Bed	Fasted	Fasted 2	% Change	p-Value
n M/F					
Age		36.2 ± 10.7 (29.6) 18 - 50 [37]			
Weight		67.1 ± 10.2 (15.2) 53.5 - 84.8 [63.95]			
Tlag	4.3 ± 1.4 (33.1) [4]	2.9 ± 1.2 (39.9) [3]	2.3 ± 1.4 (63.2) [2]	~1.5 – 2 hours	
Tmax	9 8 ± 3.1 (31.5) [10]	6.7 ± 1.6 (23.4) [6]	5.4 ± 2.3 (42.0) [6]	3.4 hr	<0.001
Cmax	19.6 ± 6.8 (34 7) [21.85]	27.5 ± 8.3 (30 3) [27 75]	26.7 ± 9.3 (34 9) [28.55	-26%	<0.001
AUCt	364.2 (42)	448.1 ± 150.7 (33 6) [458.5]	457.0 ± 185.1 (40.5) [535.56]		
AUCinf	381.7 ± 154.4 (40.4) [424.38]	464.3 ± 148.9 (32.1) [470.505]		-17%	0.005
Cl/F	142.3 ± 119.6 (84.1) [94.7]	97.8 ± 44.0 (45.0) [85.02]			
Cl/kg	2.41 ± 2.52 (104.59) [1.29]	1.61 ± 0.99 (61.58) [1.35]	2.03 ± 2.11 (103.90) [1.20]		
Vss/F	3078.1 ± 2844.0 (92.4) [2013.175]	1935.4 ± 1222.1 (63.1) [1629.95]	2262.7 ± 2028.2 (89.6) [1633.28]		
V/kg	52.4 ± 59.9 (114.3) [30.8]	32.3 ± 26.7 (82.6) [27.0]	38.5 ± 42.9 (111.4) [24.2]		
t1/2	11.2 ± 2.1 (18.6) [11.1]	12.5 ± 2.9 (23.4) [12.05]	11.7 ± 2.3 (19.8) [11.4]		

Table 57 Mean Duloxetine Concentration vs. Time Profiles showing Diurnal Variation (Study SBAA)

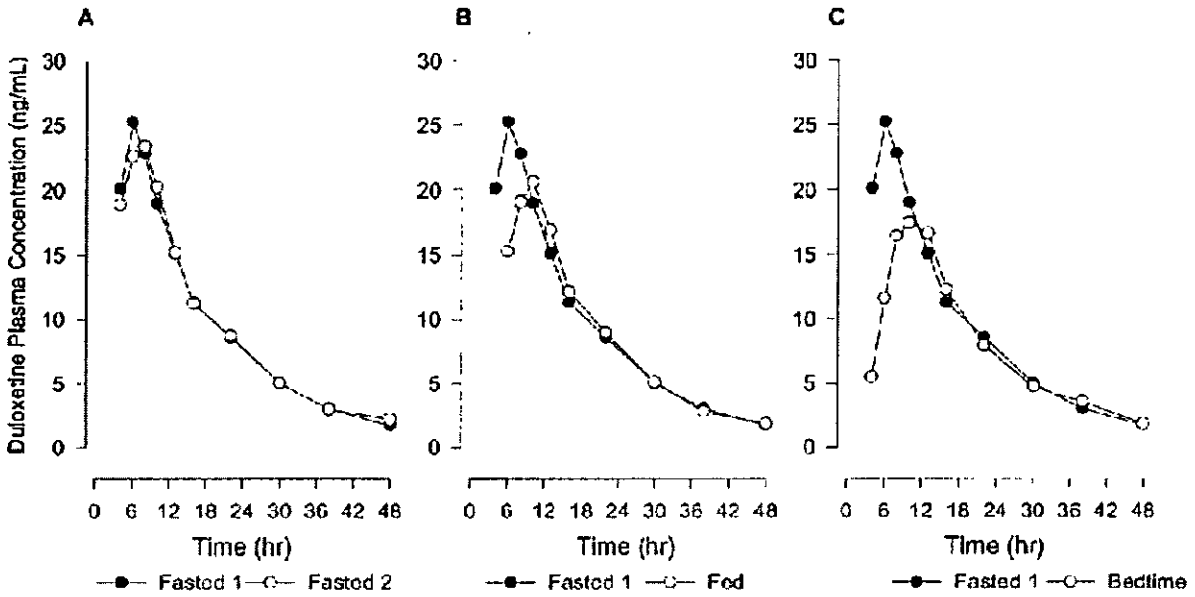

Figure SBAA.11.1. Mean plasma concentration versus time profiles of duloxetine in healthy female subjects after an oral dose of 40 mg administered twice in a fasting state (A), with food (B) and at bedtime (C).

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8.9.6 AGE

8.9.6.1 Elderly

Clearance was 25% lower and AUC was 24% higher in elderly (mean age 69 yo) as compared with middle aged (mean age 42 yo) women in Study SAAY, although these differences did not reach statistically significance, (see Table 58). However, a statistically significant correlation of clearance with age was found in the population pharmacokinetic analysis SAAB, (see Table 59). The difference in statistical results is presumed due to the difference in the ages and numbers of subjects in the 2 studies.

Table 58 Effect of Age Duloxetine 40 mg (2x 20 mg) Study SAAY

Metrics	n	Age	Weight	Tlag	Tmax	Cmax	AUCt	AUCinf	Cl/F	Cl/kg	V/F	V/kg	Vss	Vss/kg	t1/2
Elderly	12 F	68 6 ± 4 1 (6 0) 67 0 65 0 - 77 0	66 0 ± 7 6 (11 6) 66 0 52 2 - 80 7	2 2 ± 1 2 (55 1) 2 0 1 0 - 4 0	4 8 ± 1 5 (32.5) 5.0 1 0 - 6 0	49 4 ± 15 9 (32 2) 52 6 20 0 – 75 0	824 5 (37)	866.9 ± 335 2 (38 7) 912 4 464 6 - 1594.5	52 9 ± 20 2 (38 2) 44 1 25.1 - 86 1	0.82 ± 0 4 (45.6) 0 7 0 4 - 1 6	1077 9 ± 349.2 (32.4) 1007 9 655 8 - 1914 7	18 9 ± 7 4 (44.0) 15.2 10 0 - 36 7	1099 9 ± 377.5 (34.3) 1033 8 645 0 - 2050 5	17 2 ± 8 0 (46.6) 15 2 9 8 - 39 3	15 0 ± 4 6 (30 7) 13 3 9.8 - 26 7
Middle Aged	12 F	41 6 ± 5 7 (13 7) 41 0 32.0 - 50.0	71 4 ± 11 7 (16.3) 71 5 44 5 - 85 7	1 8 ± 0 8 (45 5) 2.0 1 0 - 4 0	3 7 ± 0.8 (21 2) 4 0 2 0 - 4.0	49 8 ± 18 9 (37 9) 47 7 26 5 - 94.7	677 7 (49)	699 3 ± 341 9 (48 9) 631.0 294.2 - 1490 5	70 3 ± 33.9 (48 3) 63 4 26.8 - 136 0	1 0 ± 0 5 (51 6) 0.9 0 4 - 2 2	962 0 ± 322 4 (33 5) 883.7 554.3 - 1586 5	13.7 ± 4.8 (35 2) 12.3 7.7 - 25 9	1083 5 ± 364 9 (33.7) 982.2 585.0 - 1766 4	15 5 ± 5 8 (37 4) 13.7 8.2 - 28 9	10 4 ± 2 8 (27 2) 10.1 6 9 - 14 7
% Difference Elderly – Middle Aged				0 4 hr	1 hr	-0 8%	21 7%	24 0%	-24 8%	-22%	12 0%	23 4%	15 1%	11 0%	44 2%
p-Value					0 139	0.958	0.272	0 238	0.141		0.407				

Table 59 Table SAAB.8.5. Effect of Age on Oral Clearance of Duloxetine

Age (yr)	Estimate of CL/F (L/hr)
23.5	95.6
55.5	62.3
76.8	40.1

8.9.6.2 Children

Pediatric data were not submitted.

At the End of Phase II Meeting on December 16, 1999 and at the pre-NDA meeting it was agreed that a deferral of pediatric studies is appropriate.

[

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8.9.7 HEPATIC INSUFFICIENCY

The effect of hepatic insufficiency on duloxetine pharmacokinetics was examined in study HMAX.

This was a parallel single dose study in 6 patients with moderate cirrhosis, (Child-Pugh scores 7-8), and healthy controls matched by age and sex. All subjects were caucasian and genotypically 2D6 and 2C19 EMs. There was 1 female in each group both of whom were non-smokers. Two cirrhotics were smokers, whereas 3 controls were smokers.

All cirrhotic subjects had low serum albumin, three had elevated serum bilirubin, two had elevated prothrombin times, one had mild ascites, and one had mild encephalopathy. All subjects, except one, had a normal serum creatinine at screening. One cirrhotic subject (3995) had a slightly elevated serum creatinine at screening (1.6 mg/dL).

8.9.7.1 Effects on Duloxetine Exposure

Mean Duloxetine Cmax was similar in cirrhotics and controls, however the upper 90% confidence limit on the geometric mean ratio was almost 2 fold. Tlag was shorter in cirrhotics, even in the face of discontinuance of laxatives, and Tmax was significantly delay. Based upon AUC and other metrics it's apparent that the delay is at least partly due to delayed elimination (see Table 60 and Table 61). However, absorption rates were not determined so without further analysis we can't say whether absorption rate is also delayed or not.

It should be noted that sampling was only conducted to 72 hours in controls, whereas it was extended to 120 hours in cirrhotics. In spite of the extended sampling, comparison of AUC_{0-t} underestimates the degree of exposure in cirrhotics relative to duloxetine exposure in controls. 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 (see Table 60, Table 61, Figure 26, and Figure 27).

Table 60 Pharmacokinetic Metrics of Duloxetine and Selected Metabolites after Duloxetine 20 mg SD in Cirrhotics and Healthy Controls (EMs) Matched for Age and Genoder (Study HMAX)

Metrics	Duloxetine			4-Hydroxy Duloxetine Glucuronide			5-Hydroxy, 6-Methoxy-Duloxetine Sulfate		
	Healthy Volunteers	Cirrhotics	Ratio of Means (C/HV)	Healthy Volunteers	Cirrhotics	Ratio of Means (C/HV)	Healthy Volunteers	Cirrhotics	Ratio of Means (C/HV)
n M / F	6 5 / 1	6 5 / 1	—	—	—	—	—	—	—
Age (years)	45.7 ± 15.7 (34.5) 24 - 63	44.3 ± 15.2 (34.2) 20 - 60	—	—	—	—	—	—	—
Weight (kg)	80.4 ± 10.5 (13.1) 62.8 - 93.9	82.2 ± 7.0 (8.5) 73.9 - 93	—	—	—	—	—	—	—
Child-Pugh Score	NA	7.5 ± 0.5 (7.3) 7 - 8	—	—	—	—	—	—	—
Tlag (hours)	2.2 ± 0.4 (18.8) [2.0]	1.2 ± 0.4 (35.0) [1.0]							
Tmax (hours)	3.8 ± 1.2 (30.5) [3.5]	7.5 ± 5.4 (72.1) [6.0]	**1.97**	5.0 ± 1.1 (21.9) [5.0]	16.3 ± 17.0 (104.3) [7.0]	**3.26**	4.3 ± 0.8 (18.8) [4.0]	11.0 ± 8.0 (72.5) [6.0]	**2.56**
Cmax (ng/ml)	13.8 ± 10.9 (79.1) [12.0]	14.6 ± 4.0 (27.5) [13.6]	**1.06**	118.1 ± 58.2 (49.3) [102.5]	35.0 ± 40.6 (115.9) [19.8]		96.7 ± 48.9 (50.5) [98.1]	19.6 ± 24.8 (126.8) [10.7]	**0.20**
AUCt[a] (ng/ml x hr^{-1})	267.9 ± 392.0 (146.3) [115.3]	774.7 ± 228.0 (29.4) [847.5]	**2.89**	1955.9 ± 896.8 (45.8) [2000.0]	1338.6 ± 790.0 (59.0) [1068.4]	**0.68**	1117.9 ± 363.2 (32.5) [1122.7]	673.4 ± 355.3 (52.8) [584.4]	**0.60**
Ratio $AUCt^{metab}$ / $AUCt^{dulox}$	—	—	—	15.9 ± 10.7 (67.5) [15.2]	2.25 ± 2.46 (109.47) [1.39]	—	9.5 ± 5.3 (55.6) [10.3]	1.13 ± 1.19 (105.70) [0.68]	—
AUC_∞ (ng/ml x hr^{-1})	370.1 ± 605.2 (163.5) [126.0]	1027.1 ± 429.2 (41.8) [1064.9]	**2.78**	2115.2 ± 1114.5 (52.7) [2040.7]	1643.9 ± 777.9 (47.3) [1432.3]	**0.78**	1172.6 ± 389.7 (33.2) [1162.0]	816.0 ± 362.2 (44.4) [814.7]	**0.70**
Ratio AUC_∞^{metab} / AUC_∞^{dulox}	—	—	—	14.0 ± 9.9 (70.4) [12.6]	2.33 ± 2.55 (109.44) [1.48]	—	8.3 ± 4.6 (55.7) [8.3]	1.16 ± 1.28 (109.97) [0.81]	—
% Extrap	17.2 ± 11.7 (67.9) [11.7]	23.8 ± 14.7 (61.9) [25.5]	1.38	5.0 ± 7.8 (155.8) [2.0]	17.7 ± 15.1 (85.3) [14.3]	3.54	5.1 ± 4.3 (82.7) [3.6]	15.6 ± 9.5 (60.7) [17.1]	3.06
Cl/F (L/hr)	160.2 ± 100.6 (62.8) [159.7]	24.1 ± 15.1 (62.7) [18.8]	**0.15**	—	—	—	—	—	—
Cl/kg (L/hr x kg^{-1})	1.9 ± 1.2 (61.6) [2.1]	0.3 ± 0.2 (72.4) [0.2]	**0.16**	—	—	—	—	—	—
V/F (L)	2908.6 ± 1714.8 (59.0) [2298.0]	1703.9 ± 417.6 (24.5) [1770.7]	**0.59**	—	—	—	—	—	—
V/kg (L/kg)	35.3 ± 19.3 (54.8) [29.5]	20.7 ± 5.9 (28.7) [19.3]	**0.59**	—	—	—	—	—	—
$t_{1/2}$ (hours)	18.3 ± 15.2 (82.9) [12.9]	59.8 ± 28.4 (47.6) [60.7]	**3.27**	14.0 ± 8.2 (59.1) [11.2]	48.9 ± 26.8 (54.9) [41.8]	**3.49**	12.9 ± 5.9 (45.7) [10.4]	40.7 ± 14.3 (35.1) [36.7]	**3.16**

a **For AUCt, t is 72 hours for controls and 120 hours for cirrhotics**

Table 61 Statistical Analysis of Exposure to Duloxetine and Selected Metabolites in Cirrhotics and Healthy Controls (Study HMAX)

Metrics	Summary Statistics		Geometric Means		GM Ratio (90% CI)	p Value
	Healthy Volunteers	Cirrhotics	Healthy Volunteers	Cirrhotics		
	Duloxetine					
Cmax (ng/ml)	13.8 ± 10.9 (79.1) [12.0]	14.6 ± 4.0 (27.5) [13.6]	11.92	14.17	1.19 (0.72, 1.97)	0.5569
AUCt[a] (ng/ml x hr^{-1})	267.9 ± 392.0 (146.3) [115.3]	774.7 ± 228.0 (29.4) [847.5]	**167.33**	**738.27**	**4.41 (2.10, 9.29)**	**0.0037**
AUC∞ (ng/ml x hr^{-1})	370.1 ± 605.2 (163.5) [126.0]	1027.1 ± 429.2 (41.8) [1064.9]	**199.53**	**943.09**	**4.73 (1.99, 11.22)**	**0.0124**
Cl/F (L/hr)	160.2 ± 100.6 (62.8) [159.7]	24.1 ± 15.1 (62.7) [18.8]	**100.24**	**21.21**	**0.21 (0.09, 0.50)**	**0.0124**
V/F (L)	2908.6 ± 1714.8 (59.0) [2298.0]	1703.9 ± 417.6 (24.5) [1770.7]	2220.06	1657.75	0.75 (0.45, 1.25)	0.3310
$t_{1/2}$ (hours)	18.3 ± 15.2 (82.9) [12.9]	59.8 ± 28.4 (47.6) [60.7]	15.35	51.33	**3.34 (2.2, 5.08)**	**0.0015**
	4-Hydroxy Duloxetine Glucuronide					
Cmax (ng/ml)	118.1 ± 58.2 (49.3) [102.5]	35.0 ± 40.6 (115.9) [19.8]	**87.97**	**22.66**	**0.26 (0.12, 0.54)**	**0.006**
AUCt[a] (ng/ml x hr^{-1})	1955.9 ± 896.8 (45.8) [2000.0]	1338.6 ± 790.0 (59.0) [1068.4]	1498.6	1167.8	0.78 (0.45, 1.36)	0.4405
AUC∞ (ng/ml x hr^{-1})	2115.2 ± 1114.5 (52.7) [2040.7]	1643.9 ± 777.9 (47.3) [1432.3]	1580.7	1490.2	0.94 (0.52, 1.70)	0.8620
	5-Hydroxy,6-Methoxy-Duloxetine Sulfate					
Cmax (ng/ml)	96.7 ± 48.9 (50.5) [98.1]	19.6 ± 24.8 (126.8) [10.7]	**73.29**	**11.91**	**0.16 (0.08, 0.33)**	**0.0021**
AUCt[a] (ng/ml x hr^{-1})	1117.9 ± 363.2 (32.5) [1122.7]	673.4 ± 355.3 (52.8) [584.4]	946.8	598.63	**0.63 (0.40, 0.99)**	**0.0945**
AUC∞ (ng/ml x hr^{-1})	1172.6 ± 389.7 (33.2) [1162.0]	816.0 ± 362.2 (44.4) [814.7]	1005.7	738.75	0.73 (0.47, 1.15)	0.2308

a **For AUCt, t is 72 hours for controls and 120 hours for cirrhotics**

Figure 26 Duloxetine Plasma Concentration Time Profiles in Cirrhotics and Healthy Controls after a Single 20 mg Dose (Study HMAX)

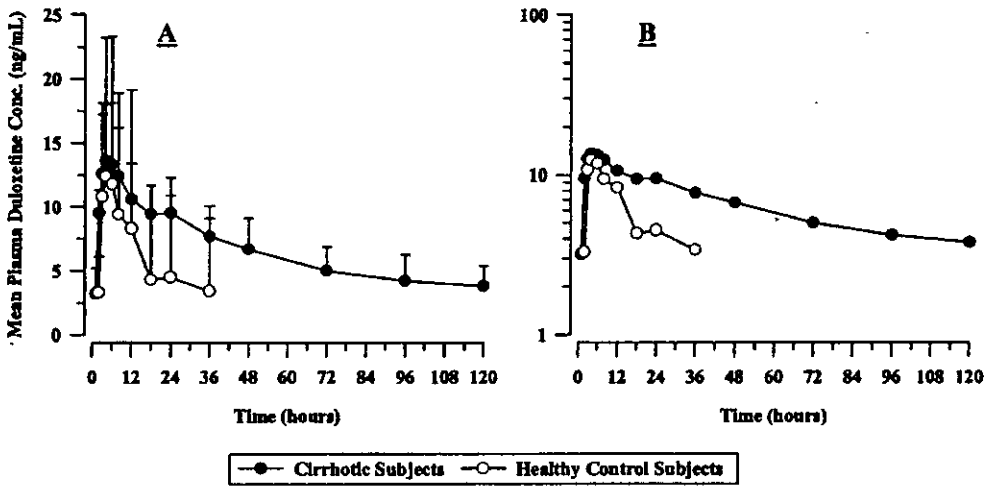

Figure HMAX.11.1. Mean (±SD) duloxetine plasma concentration-time curves following a single 20-mg dose given to cirrhotic and healthy subjects. Panel A: Linear scale; Panel B: Semilogarithmic scale.

Figure 27 Comparison of Duloxetine Cmax and AUCt in Cirrhotics (t = 120 h) and Healthy Controls (t = 72 h) after a Single 20 mg Dose (Study HMAX)

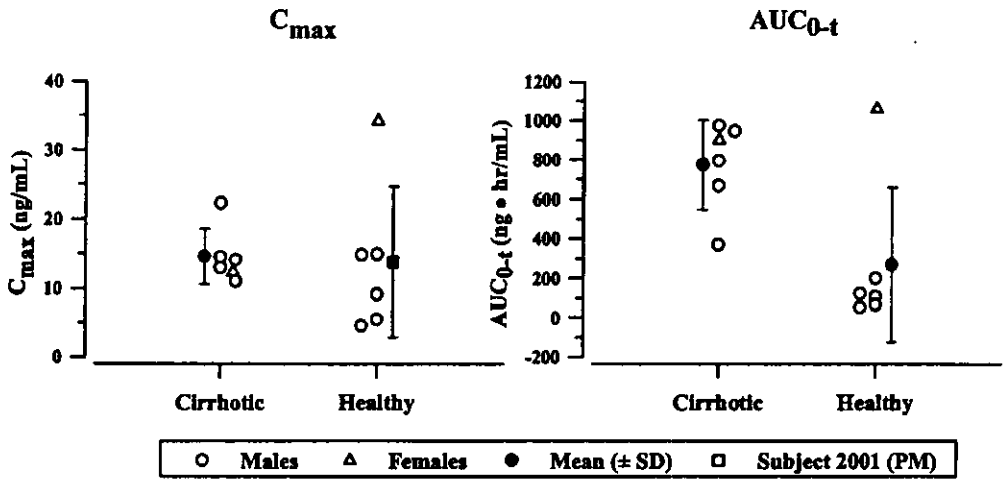

Figure HMAX.11.2. Individual and mean (±SD) pharmacokinetic parameters (C_{max} and AUC_{0-t}) of duloxetine following a single 20-mg dose given to cirrhotic and healthy subjects (Subject 2001 was not used in the mean calculations).

8.9.7.2 Effects on 4-Hydroxy-Duloxetine Glucuronide and 5-Hydroxy, 6-Methoxy-Duloxetine Sulfate Exposure

In contrast to the increased exposure to duloxetine, concentrations and exposures to 4-hydroxy-duloxetine glucuronide and 5-hydroxy, 6-methoxy-duloxetine sulfate tend to be decreased in most cirrhotics (see Table 60, Table 61, and Figure 28).

Figure 28 Comparison of 4-Hydroxy-Duloxetine Glucuronide, and 5-Hydroxy, 6-Methoxy-Duloxetine Sulfate Cmax and AUCt in Cirrhotics (t = 120 h) and Healthy Controls (t = 72 h) after a Single 20 mg Dose (Study HMAX)

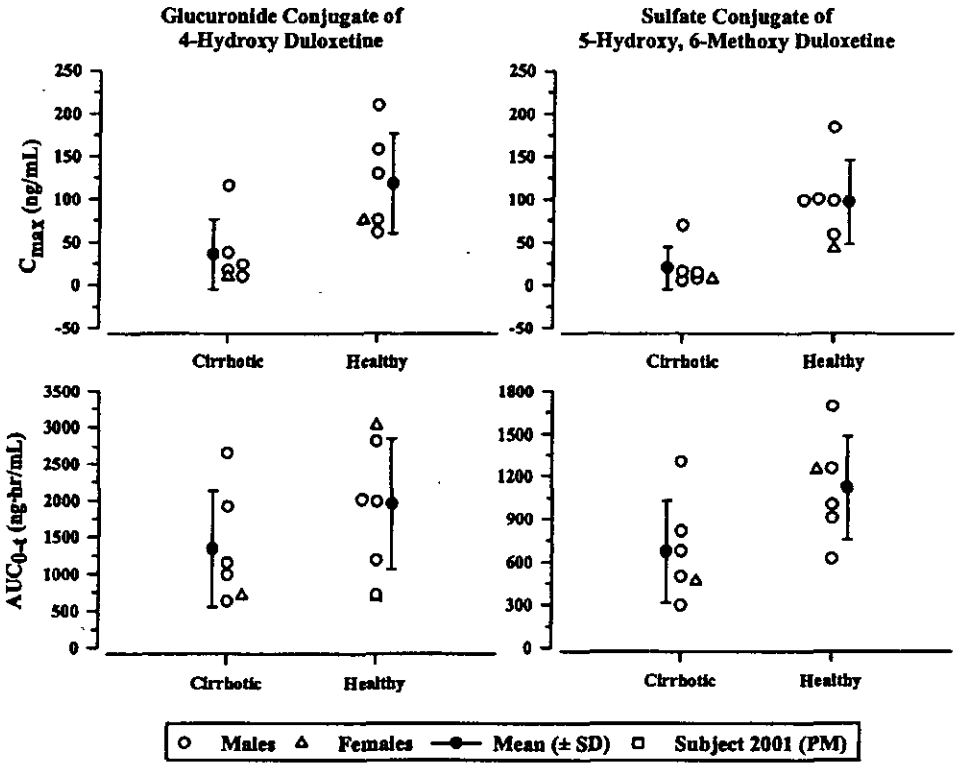

Figure HMAX.11.4. Individual and mean (±SD) pharmacokinetic parameters(C_{max} and AUC_{0-t}) of the glucuronide conjugate of 4-hydroxy duloxetine and the sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine following a single 20-mg dose of duloxetine in cirrhotic and healthy subjects (Subject 2001 was not used in the mean calculations).

This is due to at least in part to decreased formation by CYP2D6, the cirrhotics are phenotypically CYP2D6 poor metabolizers (see Table 62)), and probably decreased formation by CYP1A2 as well, and is evidenced by the continued formation rate limited kinetics of both of these metabolites (see Figure 29).

Whether there is also decreased elimination of these compounds can't be determined from this study, however, if elimination is decreased, the relative degree has to be less than the degree of decrease in the formation rates.

Table 62 Urinary Dextromethorphan (DM) and Dextrorphan (DP) Ratio, CYP2D6 Phenotype (PT) and Duloxetine Exposures in Cirrhotics (Study HMAX)

Subject	Ratio DM/DP	Phenotype based on Urinary Dextromethorphan/ Dextrorphan Ratio[a]	Duloxetine Exposure	
			AUCt	AUC∞
3884	0.0	EM	369.7	395.0
3958	0.39	PM	666.6	965.3
3972	1.36	PM	901.4	1596.6
3995	24.59	PM	944.8	c
4042	0.23	EM	972.1	1114.0
2002[b]	0.33	PM	793.5	1064.9

a EM designates CYP2D6 extensive metabolizer; PM designates poor metabolizer
b Pre-dose control sample showed measurable amounts of DM and DP
c Could not be determined

Figure 29 Duloxetine, 4-Hydroxy-Duloxetine Glucuronide, and 5-Hydroxy, 6-Methoxy-Duloxetine Sulfate Plasma Concentration Time Profiles in Cirrhotics and Healthy Controls after a Single 20 mg Dose (Study HMAX)

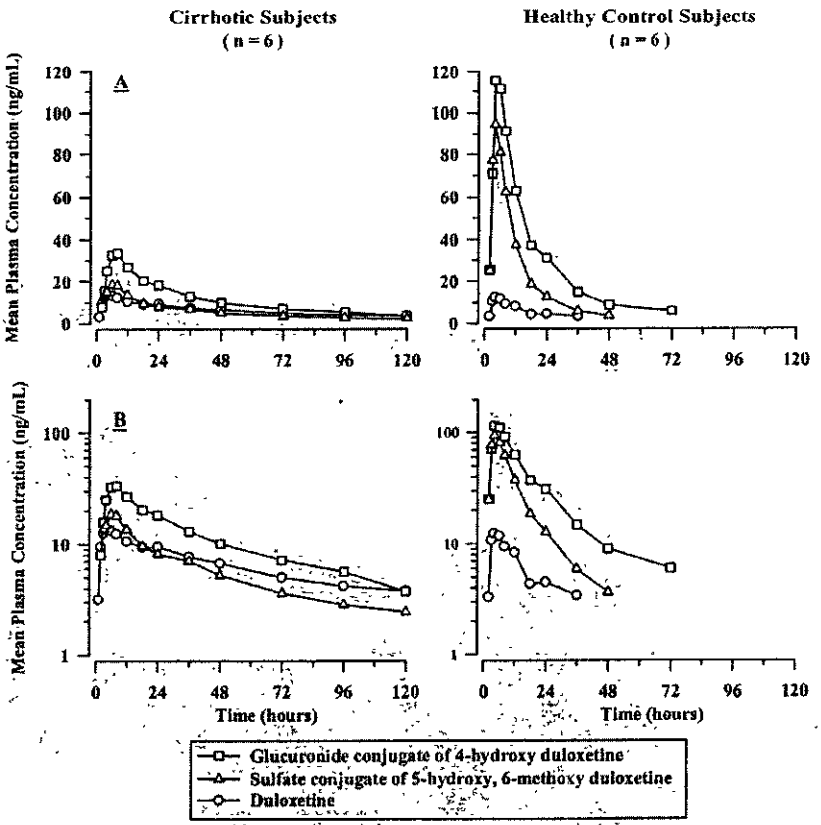

Figure HMAX.11.3. Mean plasma concentration-time curves of duloxetine, the glucuronide conjugate of 4-hydroxy duloxetine, and the sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine for cirrhotic and healthy subjects given a single 20-mg dose of duloxetine. Panel A: Linear scale; Panel B: Semilogarithmic scale.

8.9.7.3 Sponsor's Assessment

The sponsor attempts to show that peak concentrations are no worse than in the single poor metabolizer that was erroneously included in this study (see Figure 30). (n.b. values of summary pharmacokinetic parameters in tables in this review exclude data from this individual.)

Figure 30 Sponsor's Comparison of Mean Duloxetine Concentration Time Profiles in Cirrhotics and Healthy Controls and in a Single Poor Metabolizer (Study HMAX)

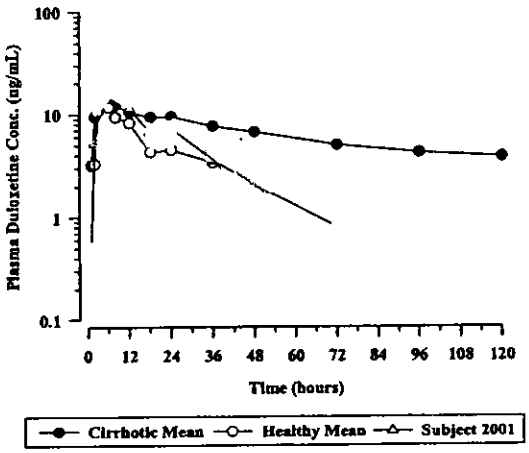

Figure HMAX.13.1. Duloxetine plasma concentration-time profile for Subject 2001 compared to the mean plasma concentration-time curves following a single 20-mg dose given to cirrhotic and healthy subjects.

Simulations were also performed to estimate what dose of duloxetine might provide an equivalent concentration vs. time profile in patients with cirrhosis as compared with healthy controls. The sponsor only simulated duloxetine concentrations, using the rationale that the conjugated metabolites are not pharmacologically active. The proposed labeled dosage and the dosages used in the simulations were as follows:

Table 63 Proposed Labeled Dosages and Dosages Used Simulations with Healthy Controls and Cirrhotics (Study HMAX)

Subject Profile	Description	Dosage Regimen	Dose Relative to Proposed Labeled Dose
Healthy Controls	Proposed Labeled Regimen	60 mg QD	—
Healthy Controls	Simulation	20 mg QD	1/3
Cirrhotics	Simulation A	6.7 mg QD	~1/11
Cirrhotics	Simulation B	10 mg QD	1/6
Cirrhotics	Simulation C	20 mg QD	1/3
Cirrhotics	Proposed Regimen as per Sponsor's Proposed Labeling	30 mg QD	1/2

The results of these simulations are shown in Figure 31. N.B. that the sponsor's labeled relative dose is not in comparison to the proposed labeled regimen.

Figure 31 Sponsor's Simulations of Duloxetine Plasma Concentrations Upon Multiple Dosing in Cirrhotics and Healthy Controls (Study HMAX)

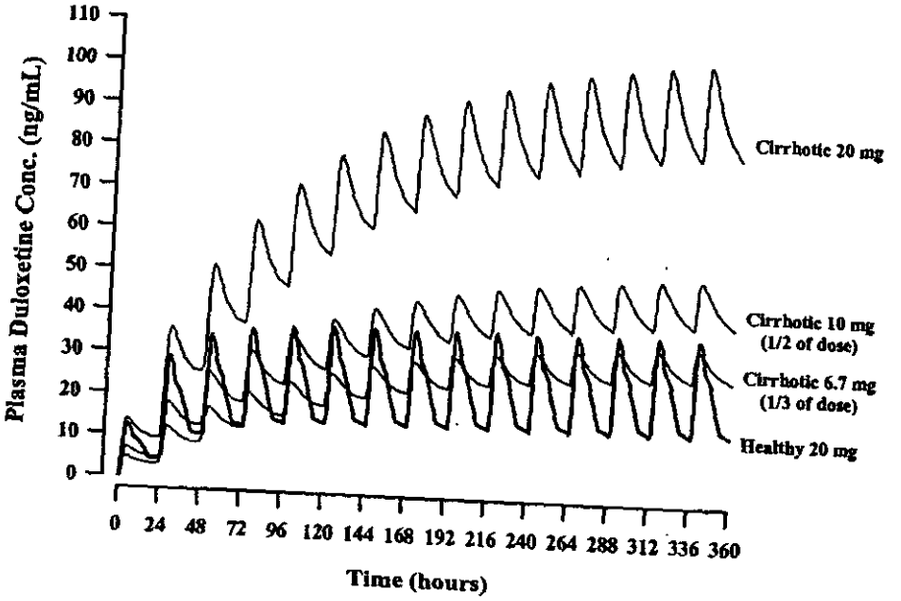

Figure HMAX.13.2. Simulations of duloxetine plasma concentration-time curves following QD administration of full (20 mg), half (10 mg), and one-third (6.7 mg) duloxetine dose for a typical cirrhotic subject compared to a 20 mg QD concentration profile for a typical healthy subject.

8.9.7.4 Reviewer's Assessment

First, the simulations underestimate the degree of accumulation for both healthy controls as well as cirrhotics as they fail to take into account the nonlinear kinetics of duloxetine.

Second, the simulations use mean parameters, although it's not clear if arithmetic or geometric means were used. In either case, if we use the upper limit of the 90% CI, the true mean concentrations in cirrhotics could be more than 1.75 fold or 2.3 fold greater.

Third, the lower exposures to 4-hydroxy-duloxetine glucuronide and 5-hydroxy, 6-methoxy-duloxetine sulfate are troubling. Even if metabolites are not active, the much lower total exposures to these 2 metabolites in spite of the elevated total duloxetine exposure 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 noncirrhotics, on average at least 6 times as much epoxide and other metabolites are being formed as compared to normals. This is especially in 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 expoxide could have dire consequences.

In addition, all of the cirrhotic patients experienced adverse events (35 total events) as compared to none of the controls. (see Table 64)

Even if not all the AEs are due to duloxetine, these observations still raise concerns especially in face of the low doses and concentrations achieved in this study as compared to the concentrations and

exposures that will be achieved in patients. Consequently, without additional clinical data in patients with hepatic insufficiency, this reviewer does not believe that there is sufficient information to determine if the potential benefit out-weighs the potentially significant risks, nor to make a quantitative dosage recommendation.

Table 64 Adverse Events Occurring on, or after Duloxetine Administration in Cirrhotics and Healthy Controls (Study HMAX)

Event Class Term	Cirrhosis Subjects (n=6)		Healthy Subjects (n=7)	
	Total Subjects with Events	Total Occurrences	Total Subjects with Events	Total Occurrences
Abdominal Pain	1	1	0	0
Asthenia	2	2	0	0
Diarrhea	2	4	0	0
Dizziness	3	5	0	0
Dyspepsia	2	2	0	0
Epistaxis	1	1	0	0
Headache	3	3	0	0
Nausea	5	7	0	0
Somnolence	1	1	0	0
Vomiting	3	9	0	0
Totals	6[a]	35[b]	0[a]	0[b]

a Total subjects reporting at least 1 adverse event
b Total events reported by all subjects

8.9.8 RENAL INSUFFICIENCY

The effect of end stage renal disease, (ESRD) and hemodialysis on duloxetine pharmacokinetics was examined in study HMBJ. A study in ESRD was specifically requested by this reviewer, as duloxetine is metabolized by CYP2D6 and since the metabolism of other CYP2D6 substrates, (e.g. propranolol), are known to known to be inhibited in ESRD, presumably by non-dialyzable endogenous compounds.

This was a parallel single dose study in 12 patients with ESRD on hemodialysis, and 12 healthy controls matched by age and sex. Eleven patients with ESRD were 'Black' and 1 was Caucasian. Five of the subjects were 'Black' and 6 were Caucasian. No subject was genotyped or phenotyped for any polymorphism for drug metabolism, (e.g. CYP2D6). There were 2 females in each group. One male patient with ESRD was a smoker, whereas 3 controls were smokers, 1 female and 2 males, (one Black and one Caucasian).

Ten of the control subjects had creatinine clearances (Clcr) of >74 ml/min. 8 subjects had Clcr of 115 – 171 ml/min. Two additional subjects had Clcr of 89 ml/min and 32 ml/min. The subject with a Clcr of 89 ml/min had a low total urinary creatinine (<15 mg/kg), whereas the second subject probably has a spuriously low estimate of Clcr due to inadequate urine collection (24 hour urine volume 250 ml).

Subjects with ESRD were dosed with duloxetine during their longest weekly between dialysis interval. Subjects received a duloxetine 60 mg as a single dose of three 20 mg capsules following a 3 hour fast. After dosing subjects continued to fast for 2-hours (except for water) followed by a light snack or light breakfast. All healthy controls received their duloxetine dose between 6:00 am and 9:15 am, whereas 8 of

the ESRD patients received the duloxetine dose between approximately 5 PM and 7 PM, while the other 4 ESRD subjects received their doses between 5:30 AM and 7:45 AM.

Subjects took the following concomitant medications:

Subjects with ESRD			Healthy Controls
BABY ASPIRIN	x	1	ASA x 2
CALCIJEX	x	2	VITAMIN E x 2
CARDIZEM CD	x	1	MULTIVITAMIN x 1
PROCARDIA	x	3	CALCIUM x 1
CLONIDINE	x	3	TYLENOL x 2
LOPRESSOR	x	2	
LOTENSIN	x	1	
VASOTEC	x	2	
MINOXIDIL	x	2	
COZAAR	x	1	
COLACE	x	1	
EPOGEN	x	11	
HUMALOG	x	1	
HUMULIN	x	1	
HUMULIN N	x	1	
MULTIVITAMIN	x	2	
NEPHRO VITE	x	1	
NEPHROCAPS	x	4	
OSCAL or CALCIUM	x	2	
TUMS	x	4	
PEPCID	x	1	
ZANTAC	x	1	
PRILOSEC	x	1	
PHOSLO	x	2	
AMPHOJEL	x	1	
RENAGEL	x	3	
FERRLECIT	x	6	
CALCITRIOL	x	1	
ROCALTROL	x	2	
ZEMPLAR	x	2	

Post-dosing plasma concentrations of duloxetine and selected metabolites were determined at intervals over a 144-hour period. Sampling times were as follows: prior to dosing, then, 2, 4, 6, 8, 14, 24, 36, 54 (pre-dialysis), 58-ESRD only (post-dialysis), 72, 102 (pre-dialysis), 106-ESRD only (post-dialysis), 120, and 144 hours post dose; (ESRD 15 samples; controls 13 samples). Samples from both ESRD and healthy control subjects were also analyzed by LC/MS to identify other potential metabolites of duloxetine.

Matched individuals formed a couplet that was analyzed with a linear mixed effect model using PROC MIXED of the SAS System.

8.9.8.1 Effects of ESRD and Hemodialysis on Duloxetine Exposure

Mean Duloxetine Cmax, was approximately 2 fold higher in subjects with ESRD as compared to controls. However Tlag and Tmax were similar. AUCt and AUC∞ were both approximately 2 fold higher, with Cl/F and V/F both decreased by approximately half and half-life was relatively unchanged (see Table 65 and Table 66).

All of the above findings are consistent with what would be expected with a drug with approximately 50% of the elimination via CYP2D6. In addition, hemodialysis had no effect on parent duloxetine plasma pharmacokinetics, as is expected for a drug with a large volume of distribution (V/F in ESRD of ~1000 L i.e. 15 L/kg), (see Figure 32).

8.9.8.2 Effects of ESRD and Hemodialysis on 4-Hydroxy-Duloxetine Glucuronide and 5-Hydroxy, 6-Methoxy-Duloxetine Sulfate Exposure and Other Metabolites

Mean 4-hydroxy-duloxetine glucuronide and 5-hydroxy, 6-methoxy-duloxetine sulfate Cmaxs, were approximately 2½ and 2 ⅓ fold higher respectively in subjects with ESRD as compared to controls. Tlags were similar for both compounds in subjects with ESRD and controls, whereas Tmax was delayed by 3 - 4 fold. AUCt and AUC∞ were both approximately 7- 9 fold higher, with average half-lives increased from ~13 and ~14 hours to ~20 and ~29 hours respectively (see Table 65 and Table 66).

The increase in half-lives in face of the lack of increase in duloxetine's half-life changes these metabolites from being formation rate limited (FRL) to elimination rate limited (ERL) in ESRD. Superficially it appears that 7-9 fold increase in AUC is inconsistent with only a doubling of half-life. However, since these compounds are normally formation rate limited, the original half-life is simply reflecting duloxetine's half-life (see Table 65 and Table 66).

Assuming no change in volume of distribution, which is a poor assumption in ESRD, we can deduce that the elimination half-lives in normals are approximately 3 – 4 hours, or less, which is reasonable for compounds that are eliminated by glomerular filtration. Plus, the true half-lives are probably shorter, since these metabolites are largely formed via CYP2D6. Consequently, the formation of these metabolites may be decreased. Otherwise the increase in AUCs would be greater.

As these compounds are hydrophilic with much smaller volumes of distribution and are renally eliminated we expected that they would be eliminated by hemodialysis. Consequently, we see large drops in plasma concentrations of these metabolites due to hemodialysis without rebound, indicating that a substantial portion of the amount of these metabolites that are in the body are being eliminated by hemodialysis (see Figure 33).

8.9.8.3 Effects of ESRD on Other Metabolites

With regards to other metabolites, according to the sponsor: *"Metabolites identified in the plasma of ESRD subjects besides the glucuronide conjugate of 4-hydroxy duloxetine and the sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine 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 mention of cysteine conjugates is noteworthy. These were not mentioned in the report of study SAAZ, and may be part of the large percentage of 'unidentified metabolites' mentioned in that report. Cysteine conjugates are a result of glutathione conjugation and are usually a consequence of detoxification of a reactive nucleophilic species. From the wording it appears that these were cysteine conjugates of dihydrodiol duloxetine, which is consistent with the formation of an epoxide with sufficient longevity such that it may react with cellular components.

The increase in duloxetine, presumably due to inhibition of CYP2D6, forces the shunting of duloxetine metabolism to other pathways. Consequently, the degree of formation of the expoxide would be expected to increase even if the dosage of duloxetine is adjusted. However, the degree of shunting and formation of alternative metabolites should be no greater than in CYP2D6 poor metabolizers.

Table 65 Pharmacokinetic Metrics of Duloxetine and Selected Metabolites after Duloxetine 60 mg SD in Patients with ESRD on Hemodialysis and Healthy Controls Matched for Age and Gender (Study HMBJ)

Metrics	Duloxetine			4-Hydroxy Duloxetine Glucuronide			5-Hydroxy, 6-Methoxy-Duloxetine Sulfate		
	Healthy Volunteers	ESRD	Ratio of Means RD/HV	Healthy Volunteers	ESRD	Ratio Of Means RD/HV	Healthy Volunteers	ESRD	Ratio of Means RD/HV
n M / F	12 10 M / 2 F	12 10 M / 2 F	—	—	—	—	—	—	—
Age (years)	38.9 ± 13.2 (33.8) 19.0 - 61.0 [39.5]	41.0 ± 10.8 (26.5) 26.0 - 55.0 [40.5]	—	—	—	—	—	—	—
Weight (kg)	81.3 ± 16.5 (20.2) 62.1 - 112.9 [74.6]	77.4 ± 27.3 (35.2) 42.6 - 151.0 [74.4]	—	—	—	—	—	—	—
Clcr (ml/min)	124.2 ± 42.1 (33.9) [133.0]	—	—	—	—	—	—	—	—
Tlag (hours)	2.5 ± 0.9 (36.2) [2.0]	2.8 ± 1.0 (36.3) [2.0]	1.1	2.3 ± 0.8 (33.4) [2.0]	2.8 ± 1.0 (36.3) [2.0]	1.2	2.5 ± 0.9 (36.2) [2.0]	2.8 ± 1.0 (36.3) [4.0]	1.2
Tmax (hours)	5.0 ± 1.3 (27.0) [4.0]	5.8 ± 2.0 (34.2) [5.0]	1.2	5.3 ± 1.6 (29.2) [5.0]	21.2 ± 14.8 (70.0) [14.0]	4.0	4.8 ± 1.3 (27.7) [4.0]	14.3 ± 6.5 (45.6) [24.0]	3.0
Cmax (ng/ml)	34.4 ± 18.3 (53.3) [33.9]	73.4 ± 37.8 (51.5) [69.9]		304.7 ± 189.1 (62.1) [253.8]	656.3 ± 347.9 (53.0) [552.1]		227.2 ± 118.7 (52.2) [202.3]	484.5 ± 232.4 (48.0) [997.3]	2.1
AUCt (ng/ml x hr^{-1})	653 (92)	1448 (81)	2.2	5220 (71)	40057 (61)	7.7	2986 (43)	21117 (43)	7.1
AUC_∞ (ng/ml x hr^{-1})	672.2 ± 615.9 (91.6) [469.5]	1482.6 ± 1203.3 (81.2) [1121.3]	2.2	5267.8 ± 3732.1 (70.8) [4099.0]	37756.3 ± 22519.4 (59.6) [29273.8]	7.2	3025.2 ± 1269.5 (42.0) [2772.9]	21307.8 ± 9142.4 (42.9) [39469.7]	7.0
Ratio AUC_∞^{metab} / AUC_∞^{dulox}	—								
% Extrap									
Cl/F (L/hr)	122.8 ± 61.7 (50.2) [120.3]	62.5 ± 39.6 (63.4) [53.5]	0.5	—	—	—	—	—	—
$Cl/F^{wt\ normalized}$ (L/hr x kg^{-1})	1.6 ± 1.0 (62.7) [1.3]	0.9 ± 0.6 (62.5) [0.8]	0.6	—	—	—	—	—	—
V/F (L)	2354.6 ± 1262.3 (53.6) [1794.8]	1001.3 ± 432.7 (43.2) [886.8]	0.4	—	—	—	—	—	—
$V/F^{wt\ normalized}$ (L/kg)	30.0 ± 19.1 (63.5) [22.5]	15.0 ± 10.4 (69.0) [11.2]	0.4	—	—	—	—	—	—
$t_{1/2}$ (hours)	13.8 ± 4.6 (33.3) [13.1]	14.7 ± 9.8 (66.5) [10.3]		13.7 ± 4.6 (33.4) [12.9]	29.3 ± 10.0 (33.9) [25.5]		12.7 ± 4.9 (38.7) [11.9]	19.5 ± 6.1 (31.3) [32.1]	1.5

Table 66 Statistical Analysis of Exposure to Duloxetine and Selected Metabolites in Patients with ESRD on Hemodialysis and Healthy Controls (Study HMBJ)

Metrics	Summary Statistics		Geometric Means		GM Ratio (90% CI)	p Value
	Healthy Volunteers	ESRD	Healthy Volunteers	ESRD		
	Duloxetine					
Cmax (ng/ml)	34.4 ± 18.3 (53.3) [33.9]	73.4 ± 37.8 (51.5) [69.9]	30.59	65.88	**2.15 (1.50, 3.10)**	**0.0015**
AUCt (ng/ml x hr^{-1})	653 (92)	1448 (81)	535.77	1163.86	**2.17 (1.35, 3.50)**	**0.0105**
AUC_∞ (ng/ml x hr^{-1})	672.2 ± 615.9 (91.6) [469.5]	1482.6 ± 1203.3 (81.2) [1121.3]	554.08	1198.54	**2.16 (1.35, 3.46)**	**0.0100**
Cl/F (L/hr)	122.8 ± 61.7 (50.2) [120.3]	62.5 ± 39.6 (63.4) [53.5]	108.29	50.06	**0.46 (0.29, 0.74)**	**0.0100**
V/F (L)	2354.6 ± 1262.3 (53.6) [1794.8]	1001.3 ± 432.7 (43.2) [886.8]	2080.26	930.81	**0.45 (0.32, 0.62)**	**0.0004**
$t_{1/2}$ (hours)	13.8 ± 4.6 (33.3) [13.1]	14.7 ± 9.8 (66.5) [10.3]	13.32	12.89	0.97 (0.71, 1.31)	0.8517
	4-Hydroxy Duloxetine Glucuronide					
Cmax (ng/ml)	304.7 ± 189.1 (62.1) [253.8]	656.3 ± 347.9 (53.0) [552.1]	234.79	584.8	**2.49 (1.69, 3.68)**	**0.0006**
AUCt (ng/ml x hr^{-1})	5220 (71)	40057 (61)	3887.21	35168.32	**9.05 (6.09, 13.45)**	**0.0001**
AUC_∞ (ng/ml x hr^{-1})	5267.8 ± 3732.1 (70.8) [4099.0]	37756.3 ± 22519.4 (59.6) [29273.8]	3935.61	36685.67	**9.32 (6.26, 13.88)**	**0.0001**
	5-Hydroxy,6-Methoxy-Duloxetine Sulfate					
Cmax (ng/ml)	227.2 ± 118.7 (52.2) [202.3]	484.5 ± 232.4 (48.0) [997.3]	183.58	423.27	**2.31 (1.51, 3.52))**	**0.0026**
AUCt[a] (ng/ml x hr^{-1})	2986 (43)	21117 (43)	2567.23	19086.74	**7.43 (5.30, 10.44)**	**0.0001**
AUC_∞ (ng/ml x hr^{-1})	3025.2 ± 1269.5 (42.0) [2772.9]	21307.8 ± 9142.4 (42.9) [39469.7]	2614.99	19294.70	**7.38 (5.28, 10.30)**	**0.001**

Figure 32 Duloxetine Plasma Concentration Time Profiles in Patients with ESRD on Hemodialysis and Healthy Controls after a Single 60 mg Dose (Study HMBJ)

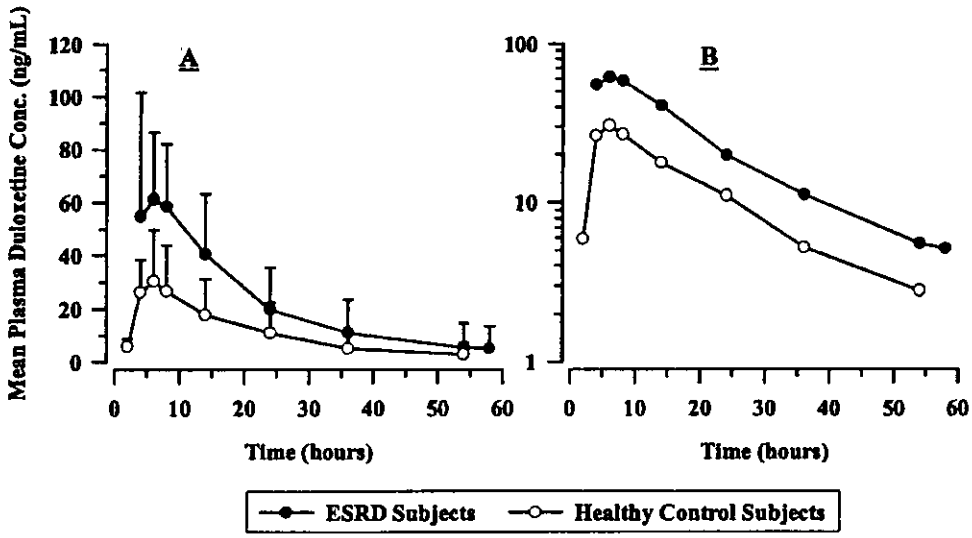

Figure HMBJ.11.1. Mean plasma concentration-time curves of duloxetine following a single 60-mg dose to ESRD subjects and healthy controls. Panel A: Linear scale with ± SD; Panel B: Semilogarithmic scale.

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Figure 33 Duloxetine, 4-Hydroxy-Duloxetine Glucuronide, and 5-Hydroxy, 6-Methoxy-Duloxetine Sulfate Plasma Concentration Time Profiles in Patients with ESRD on Hemodialysis and Healthy Controls after a Single 60 mg Dose (Study HMBJ)

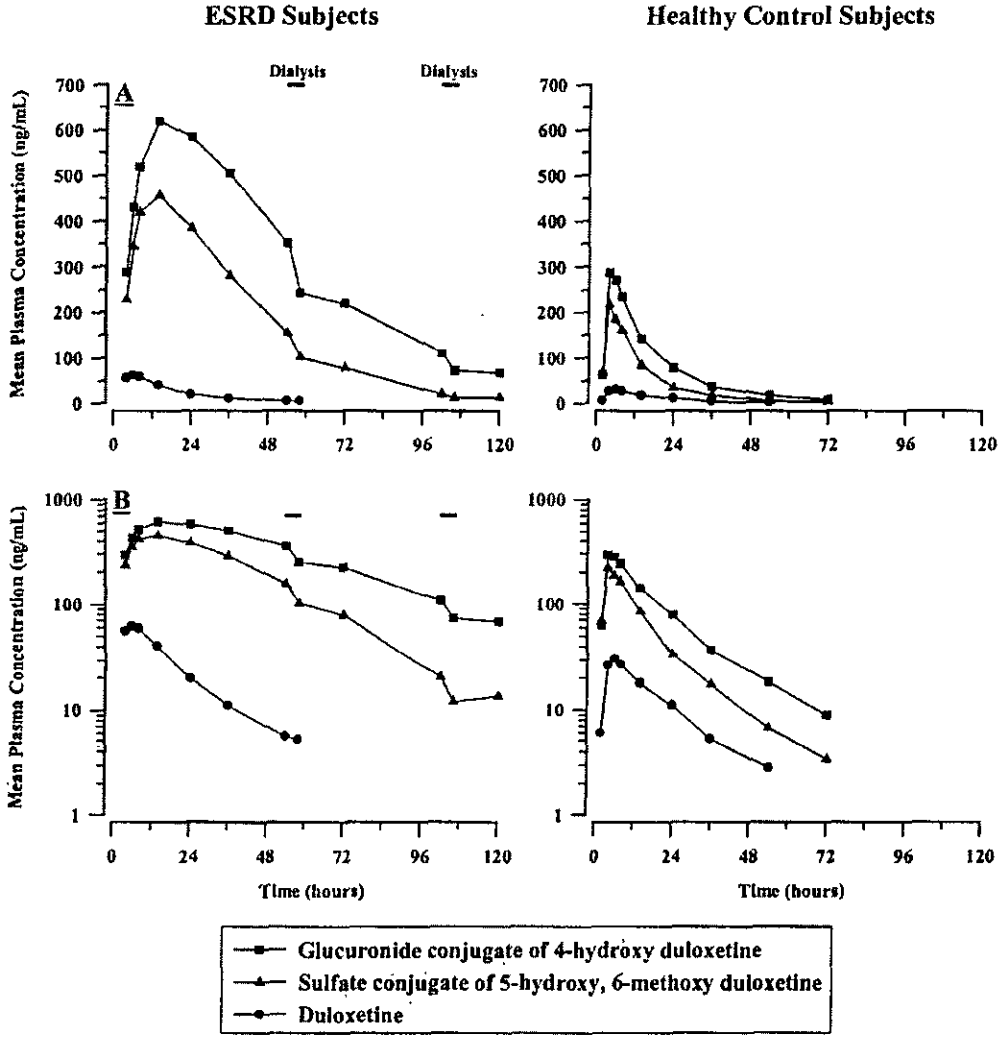


Figure HMBJ.11.2. Mean plasma concentration-time curves of the glucuronide conjugate of 4-hydroxy duloxetine and the sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine (as compared with the parent) in ESRD subjects and healthy controls receiving a single 60 mg dose of duloxetine. Panel A: Linear scale; Panel B: Semilogarithmic scale.

8.9.8.4 Adverse Events in ESRD

Adverse events as reported by the sponsor follow: *"As presented in Table HMBJ.12.1, 22 of 24 subjects reported a total of 22 adverse events occurring on or after the first dose of the study drug. One ESRD subject developed a clotted hemodialysis access (classified as coagulation disorder) which required a surgical revision. The investigator did not believe this event was related to duloxetine."* (See Table 67).

Table 67 Table HMBJ.12.1. Adverse Events Occurring On or After First Dose (Study HMBJ)

Event Class Term	ESRD Subjects (n=12)		Healthy Subjects (n=12)	
	Total Subjects with Events	Total Occurrences	Total Subjects with Events	Total Occurrences
Abdominal Pain	1	1	1	1
Coagulation Disorder	1	1		
Diarrhea	4	4	1	1
Dizziness	1	1	1	1
Nausea	4	4	1	1
Rash	1	1		
Somnolence	1	1	1	1
Surgical Procedure	1	1		
Vomiting	3	3		

"Table HMBJ.12.2 presents adverse events that were judged to be possibly or probably related to duloxetine. Nausea, diarrhea, and vomiting were somewhat more frequent in the ESRD subjects than in healthy subjects. Although nausea and vomiting are not uncommon in this population, especially during the few hours following the hemodialysis session, the fact that these symptoms were not present in these subjects prior to duloxetine administration suggested that they could be drug-related.

Vital Signs

The data indicate that modest increases in systolic pressure 6 hours after dosing may have occurred in the ESRD subjects, particularly in the supine position. These changes were not considered to be clinically significant. Only one healthy subject (3023) had a supine blood pressure > 160 mm Hg systolic or >100 mm Hg diastolic 6 or 12 hours after receiving duloxetine. This subject had a supine blood pressure of 168/92 mm Hg 6 hours after dosing and 160/102 mm Hg 12 hours after dosing. Although this subject did not have a stated history of hypertension, his pre-dose and discharge blood pressures were also above normal (148/90 and 146/92 mm Hg, respectively). Four ESRD subjects (3003, 3005, 3018, 1019) exhibited elevated supine blood pressures after receiving duloxetine. Systolic blood pressures in these four subjects at 6 or 12 hours after dosing ranged from 130 to 170 mm Hg. Diastolic blood pressures ranged from 96 to 110 mm Hg. All four ESRD subjects had a previous history of hypertension. Blood pressure returned to baseline values at discharge."

8.9.8.5 Sponsor's Assessment

Simulations were also performed to estimate what dose of duloxetine might provide an equivalent concentration vs. time profile in patients with ESRD as compared with healthy controls. The sponsor only simulated duloxetine concentrations, using the rationale that the conjugated metabolites are not

pharmacologically active. The proposed labeled dosage and the dosages used in the simulations were as follows:

Table 68 Proposed Labeled Dosages and Dosages Used Simulations with Healthy Controls and Patients with ESRD on Hemodialysis (Study HMBJ)

Subject Profile	Description	Dosage Regimen	Dose Relative to Proposed Labeled Dose
Healthy Controls	Proposed Labeled Regimen	60 mg BID	—
ESRD	Simulation A	60 mg BID	1
ESRD	Simulation B	60 mg QD	1/2
ESRD	Simulation C	30 mg BID	1/2
ESRD	Proposed Regimen as per Sponsor's Study Report and PK Summary	30 mg BID	1/2
ESRD	Proposed Regimen as per Sponsor's Proposed Labeling	30 mg QD	¼

The results of these simulations with first order absorption and elimination are shown in Figure 34. Based upon these simulations the sponsor recommended a starting dose of 30 mg BID in ESRD, (Clcr < 30 ml/min), in this study report and in the HPBIO summary. However, the proposed labeling decreases this by half to 30 mg QD without providing a rationale.

Figure 34 Sponsor's Simulations of Duloxetine Plasma Concentrations Upon Multiple Dosing in Patients with ESRD on Hemodialysis and Healthy Controls (Study HMBJ)

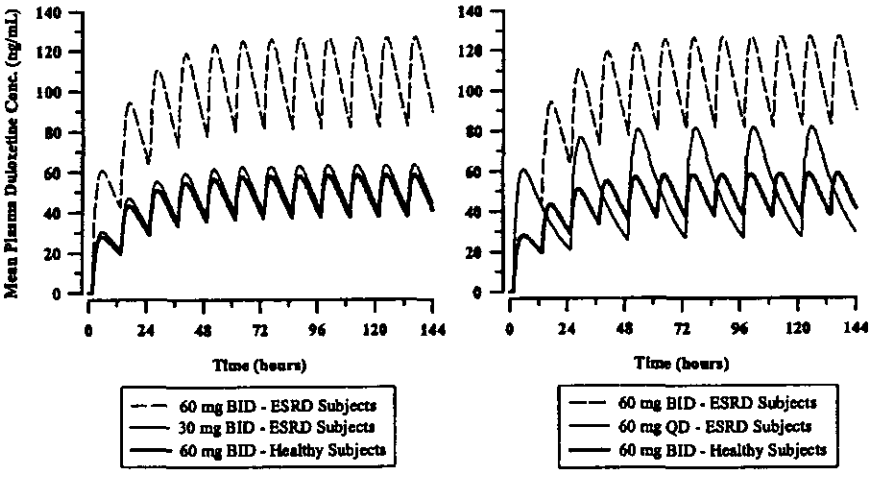


Figure HMBJ.13.1. Simulation of duloxetine plasma concentration-time curves following the BID administration of 30 mg (left) and the QD administration of 60 mg (right) to a typical ESRD subject versus the BID administration of 60 mg to a typical healthy subject.

8.9.8.6 Reviewer's Assessment

The simulations do not take into account the lag time and are likely to be inaccurate. In addition, as mentioned earlier they do not take into account the nonlinearity in duloxetine kinetics and thus provide underestimates of duloxetine exposures in healthy volunteers. This is confirmed by examining steady-state duloxetine concentrations with doses of 60 mg BID in other studies, (see § 10.5). Even adjusting for sex, primarily males, and smoking status, primarily nonsmokers, the steady-state estimates of duloxetine concentrations in normals are low, i.e. mean $Cmax_{pred}$ ~ 50 ng/ml as compare to a mean $Cmax_{obs}$ of ~ 100 ng/ml.

The higher incidence of AEs in a small number of subjects and the coagulapathy requiring surgical intervention indicates that duloxetine should not be administered to patients with ESRD without additional study. In addition, the lack of information in severe renal insufficiency, (Clcr < 30 ml/min) is also of concern.

8.10 EFFECT OF EXTRINSIC FACTORS

8.10.1 TOBACCO USE

As a CYP1A2 substrate we expect that smoking and the use of tobacco products will induce CYP1A2 and increase duloxetine clearance, resulting in a decreased exposure.

Although not formally studied, evidence consistent with this hypothesis is routinely seen when the studies where subgroups of smokers, or containing a fair number of smokers are examined and compared with similar nonsmoking subgroups in the same studies. Overall the effect of smoking is to decrease duloxetine exposures on average 50% or more. (See studies HMBN and HMAP in § 10.7 and § 10.8))

We would expect that the greatest effect of smoking would be seen in those subjects with low baseline CYP1A2 activity in the absence of smoking. In these individuals who are CYP2D6 PMs, duloxetine exposures will be decreased but since baseline concentrations are high, therapeutic plasma concentrations are more likely to be maintained. In contrast, in subjects who are CYP2D6 EMs their baseline concentrations would be lower and CYP1A2 induction might result in subtherapeutic duloxetine dosing.

Since the baseline CYP1A2 activity in the subjects studied are unknown we should assume that their baseline CYP1A2 activity represents the overall population. Thus the subpopulation identified above could have even greater decreases.

Unfortunately, it is impractical to phenotype CYP1A2 activity in the general population. The only practical way to do this would be to identify individuals who take theophylline and have rapid clearances, or possibly to identify individuals who are relatively tolerant to the effects of caffeine, although this latter suggestion is speculative.

Due to the lower expression of CYP1A2 activity in women it is possible that induction due to smoking may be more pronounced in women.

8.10.2 FOOD & DIET

8.10.2.1 Effect of Food on Absorption and Bioavailability

The effect of food on duloxetine absorption and bioavailability was formally examined in studies HMAO and SBAA. When a high caloric, high fat meal was given with duloxetine in study HMAO, there was a delay in Tlag and in Tmax for 2 different clinical trial formulations without any other differences in pharmacokinetic metrics, (see Table 69). Similar effects were also seen in study SBAA (see Table 70, and).

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 the mean change in exposures did not change in a consistent manner or by a large percentage.

In contrast administration of duloxetine either 2 hours before or after meals in studies SAAY and HMBN does not appear to have major effects on Tlag or Tmax, (see Table 118 in § 10.7 and Table 119 in § 10.8).

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.

Table 69 Comparison of Pharmacokinetic Metrics[a] from Duloxetine 10% EC Pellet Formulation and Duloxetine 5% EC Pellet Formulation Under Single Dose Fasting Conditions in the Presence and Absence of Food - (Study HMAO)

Treatment Arm	N	wt (kg)	Tlag (hrs)	Cmax (ng/ml)	Tmax (hrs)	t1/2 (hrs)	AUCt (ng/ml x kg^{-1})	AUCinf (ng/ml x kg^{-1})	CL/F (L/hr)	CL/kg (L/hr x kg^{-1})	Vb/F (L)	Vd/kg (L/kg)
20 mg 10% Capsule Fasting	7 M	71.2 ± 4.7 (6.5) 71.0	3.3 ± 1.2 (35.1) 1.5 - 5	10.7 ± 5.4 (50.7)	5.6 ± 1.0 (17.5) 5.0	9.0 ± 4.2 (46.7) 9.3	108.0 ± 76.3 (70.6) 88.1	142.0 ± 85.8 (60.4) 110.9	204.7 ± 146.3 (71.5) 180.3	2.9 ± 2.0 (70.7) 2.4	1999.0 ± 567.7 (28.4) 1759.0	28.5 ± 9.9 (34.9) 24.4
20 mg 10% Capsule Fed	7 M	70.8 ± 4.2 (6.0) 69.5	6.3 ± 2.5 (39.0) 1.5 - 9	9.0 ± 3.3 (36.0)	8.7 ± 2.4 (27.1) 7.0	10.3 ± 2.6 (25.3) 9.3	118.6 ± 69.1 (58.3) 98.8	167.6 ± 63.6 (37.9) 164.6	116.9 ± 61.8 (52.9) 121.5	1.7 ± 0.9 (55.7) 1.6	1890.3 ± 471.1 (24.9) 1942.0	26.7 ± 6.8 (25.4) 28.2
4 x 5 mg 5% Capsule Fasting	7 M	71.7 ± 4.9 (6.8) 72.3	3.1 ± 0.9 (30.8) 1.5 - 5	10.2 ± 4.3 (41.9)	4.7 ± 0.8 (16.0) 5.0	8.3 ± 3.2 (38.3) 7.3	89.2 ± 62.5 (70.1) 79.3	136.6 ± 75.6 (55.3) 117.0	190.9 ± 106.1 (55.6) 171.0	2.7 ± 1.5 (54.9) 2.4	1983.0 ± 709.5 (35.8) 1808.0	27.8 ± 9.9 (35.7) 23.1
4 x 5 mg 5% Capsule Fed	7 M	71.6 ± 4.6 (6.5) 71.5	5.6 ± 2.4 (43.9) 1.5 - 9	9.1 ± 4.0 (44.5)	8.6 ± 3.5 (40.9) 7.0	9.7 ± 1.3 (13.7) 10.1	127.9 ± 61.2 (47.9) 113.1	162.9 ± 60.1 (36.9) 148.5	136.6 ± 46.5 (34.0) 134.7	1.9 ± 0.7 (37.3) 1.9	1898.3 ± 627.0 (33.0) 1901.0	26.7 ± 9.5 (35.6) 24.7

Table 70 Duloxetine 20 mg – Food Effect SBAA

Metrics	Fed	Fasted	Fasted 2	%Change	p-Value
n F	14	14	14		
Age (years)	36.2 ± 10.7 (29.6) 18 - 50 [37]				
Weight (kg)	67.1 ± 10.2 (15.2) 53.5 - 84.8 [63.95]				
Tlag (hours)	5.0 ± 1.6 (31.9) [5]	2.9 ± 1.2 (39.9) [3]	2.3 ± 1.4 (63.2) [2]		
Tmax (hours)	10.0 ± 3.2 (31.9) [10]	6.7 ± 1.6 (23.4) [6]	5.4 ± 2.3 (42.0) [6]	3.8 hr	<0.001
Cmax (ng/ml)	24.1 ± 11.4 (47.1) [23.65]	27.5 ± 8.3 (30.3) [27.75]	26.7 ± 9.3 (34.9) [28.55	-6%	0.405
AUCt (ng/ml x hr^{-1})	384.6 ± 161.7 (42.0) [458.5]	448.1 ± 150.7 (33.6) [535.56]	457.0 ± 185.1 (40.5)		
AUCinf (ng/ml x hr^{-1})	402.3 ± 164.5 (40.9) [413.985]	464.3 ± 148.9 (32.1) [470.505]		-11%	0.060
Cl/F (L/hr)	120.38 ± 69.44 (57.69) [94.95]	97.8 ± 44.0 (45.0) [85.02]			
Cl/F weight normalized (L/hr x kg^{-1})	2.01 ± 1.51 (75.24) [1.35]	1.61 ± 0.99 (61.58) [1.35]	2.03 ± 2.11 (103.90) [1.20]		
Vss/F (L)	2519.0 ± 1649.6 (65.5) [1986.025]	1935.4 ± 1222.1 (63.1) [1629.95]	2262.7 ± 2028.2 (89.6) [1633.28]		
Vss/F weight normalized (L/kg)	42.4 ± 35.7 (84.2) [30.7]	32.3 ± 26.7 (82.6) [27.0]	38.5 ± 42.9 (111.4) [24.2]		
t1/2 (hours)	10.3 ± 2.1 (20.8) [10.2]	12.5 ± 2.9 (23.4) [12.05]	11.7 ± 2.3 (19.8) [11.4]		

8.10.2.2 Effect of Diet

8.10.2.2.1 Effect of Dietary Factors on Duloxetine Pharmacokinetics

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 who are CYP2D6 EMs might lose clinical efficacy (see § 8.10.1).

8.10.2.2.2 Effect of Dietary Factors on Duloxetine Pharmacodynamics

8.10.2.2.2.1 Tryptophan

The following information on tryptophan interactions is from the approved labeling for paroxetine.

'Tryptophan: As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are co-administered. Adverse experiences, consisting primarily of headache, nausea, sweating and dizziness, have been reported when tryptophan was administered to patients taking paroxetine hydrochloride. Consequently, concomitant use of paroxetine with tryptophan is not recommended.'

Since duloxetine also inhibits serotonin reuptake, and from the *in vivo* pharmacodynamic information it appears that duloxetine may be a selective reuptake inhibitor, (see § 8.8), a similar pharmacodynamic interaction with duloxetine should be considered a possibility.

8.10.3 DRUG INTERACTIONS

8.10.3.1 Pharmacokinetic Drug-Drug Interactions

8.10.3.1.1 P450 CYP 2D6

8.10.3.1.1.1 Desipramine and Duloxetine

Desipramine is metabolized to 2-OH-desipramine by CYP2D6 followed by glucuronidation and excretion in the urine. Tmax occurs approximately 4.5 hours after oral dosing and in CYP2D6 extensive metabolizers, the elimination half-life ranges from —— hours (average 17.1 hours). In contrast slow metabolizers have a half-life of approximately 77 hours. The usual dose is 100 – 200 mg /day up to 300 mg /day and at steady-state dosing is frequently as a single dose in the evening. Dosing may also be as 25 mg per day in divided doses in the elderly.

As duloxetine is also metabolized extensively by CYP2D6 a pharmacokinetic interaction study to evaluate the potential of duloxetine as a CYP2D6 inhibitor was undertaken. Equal numbers of healthy men and women (7M/7F) received duloxetine at the to be marketed dose 60 mg q12h (8 AM / 8 PM). Subjects also received a single oral dose of desipramine 50 mg at 8 AM under fasting conditions in the absence of duloxetine and after duloxetine had achieved steady-state. All subjects were CYP2D6 extensive metabolizers.

8.10.3.1.1.1.1 Effect of Desipramine on Duloxetine

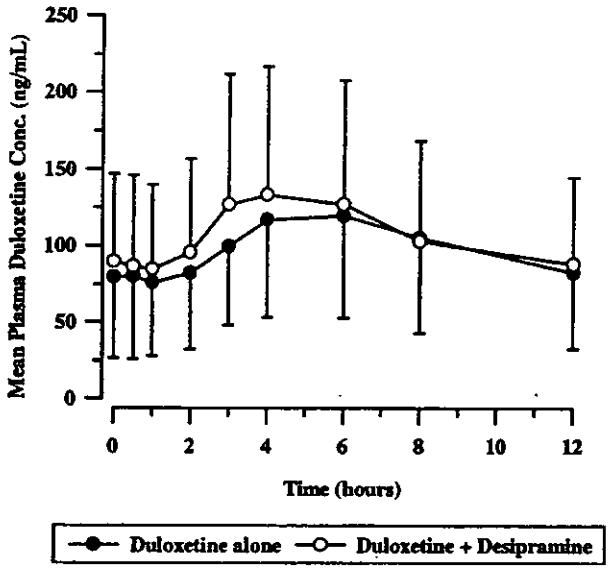
At 50 mg desipramine did not effect the pharmacokinetics of duloxetine (see Table 71 and Figure 35). However, this does not imply that a stronger inhibitor of CYP2D6 or higher doses would not inhibit duloxetine elimination.

Table 71 Steady-State Pharmacokinetic Parameters of Duloxetine in Subjects Receiving an Oral Dose of 60 mg Every 12 Hours, Alone and Concurrently with Desipramine 50 mg (Study HMAZ)

Metric	Descriptive Statistics[a]		Geometric Means		Geometric Mean Ratio [90% CI]	Significance p-Value
	Test Duloxetine + Desipramine (n=13)	Reference Duloxetine + PBO (n=13)	Test Duloxetine + Desipramine (n=13)	Reference Duloxetine + PBO (n=13)		
$Cmax_{ss}$ (ng/ml)	4.36 ± 1.15 (26.41) [4.00]	5.07 ± 1.73 (34.12) [5.00]				
$Tmax_{ss}$ (hr)	136.34 ± 87.02 (63.83) [114.40	128.48 ± 68.86 (53.59) [117.10]	111.1	110.7	1.00 (0.91, 1.09)	0.95
$Cmin_{ss}$ (ng/ml)	88.92 ± 56.22 (63.22) [74.90]	81.26 ± 49.15 (60.48) [70.95]				
Cav_{ss} (ng/ml)	107.57 ± 68.02 (63.23) [85.20]	99.62 ± 55.52 (55.73) [87.90]				
$AUC\tau^{ss}$ (ng/ml x hr^{-1})	1291.98 ± 815.56 (63.13) [1022.27]	1195.60 ± 666.21 (55.72) [1054.67]	1045.7	1020.7	1.02 (0.94, 1.11)	0.61
CLp/F (L/hr)	73.96 ± 60.17 (81.37) [58.70]	72.57 ± 46.48 (64.04) [65.03]	57.5	58.8	0.98 (0.90, 1.06)	0.63
CLp/F (L/hr x kg^{-1})	1.02 ± 0.77 (75.81) [0.75]	1.01 ± 0.59 (57.85) [0.84]				

a Mean ± SD, (CV), Range, [median]

Figure 35 Comparison of Naïve Pooled Duloxetine Concentration vs. Time Profiles (Mean ± SD) for Duloxetine 60 mg q12h in the Presence and Absence of Desipramine 50 mg



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8.10.3.1.1.1.2 Effect of Duloxetine on Desipramine

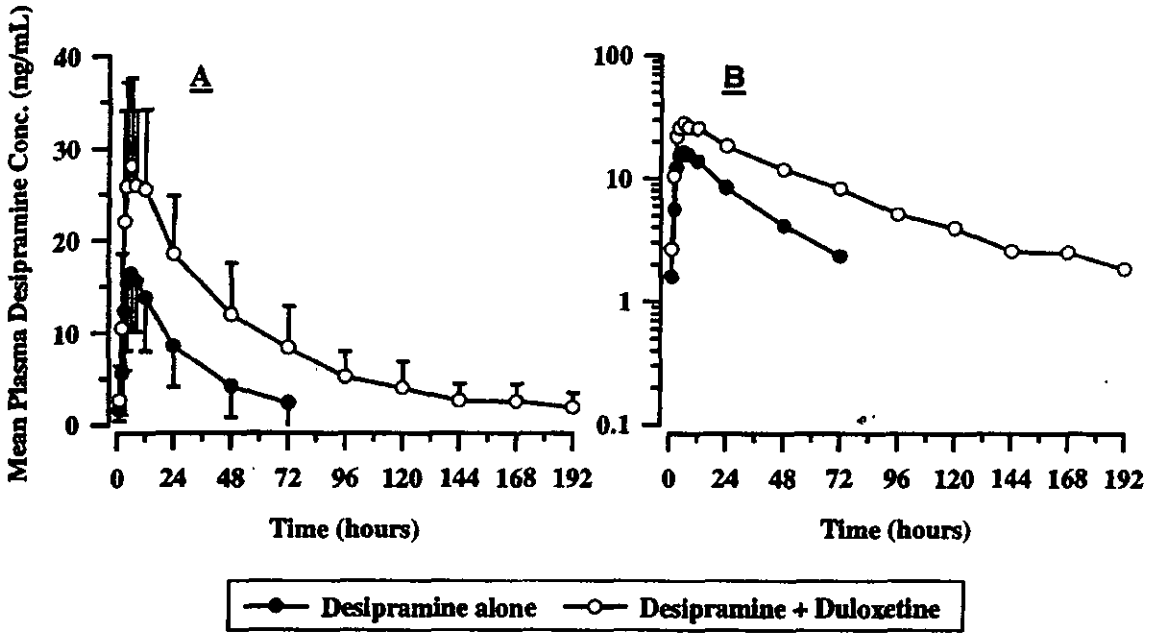
In contrast, duloxetine resulted in 3 fold average increase in desipramine exposure, with clearance/F decreasing on average by 2/3s (see Table 72 and Figure 36). Half-life nearly doubled, which is less than expected from the change in clearance, although volume of distribution/F also decreased (see Table 72). From the present study it's not possible to tell if duloxetine truly effects volume or if this is an artifactual finding due to using oral administration.

Table 72 Table HMAZ.11.3. Mean Ratios of Desipramine Pharmacokinetic Parameters with Duloxetine Relative to Desipramine Alone (Study HMAZ)

Metric	Descriptive Statistics		Geometric Means		Geometric Mean Ratio [90% CI]	Significance p-Value
	Test	Reference	Test	Reference		
	Desipramine + Duloxetine	Duloxetine + PBO	Desipramine + Duloxetine	Duloxetine + PBO		
	(n=13)	(n=13)	(n=13)	(n=13)		
Cmax (ng/mL)	29.98 ±10.31 (34) [30.70]	17.85 ± 6.72 (38) [15.90]	28.4	16.8	1.69 (1.58, 1.81)	< 0.0001
$Tmax_{ss}$ (hr)	7.9 ± 3.6 (45.2) [6.00]	5.7 ± 1.7 (29.3) [6.00]	—	—	—	—
AUC0-∞ (ng/ml x hr^{-1})	1671.7 ± 725.9 (43.4) [1577.75]	623.5±440.65 71 479.7	1522.0	522.1	2.92 (2.55, 3.34)	< 0.0001
CLp/F (L/hr)	36.3 ± 17.6 (48.6) [31.69]	109.6 ± 52.9 (48.2) [104.23]	32.9	95.8	0.34 (0.30, 0.39)	< 0.0001
Vz/F (L)	2095.2 ± 749.8 (35.8) [1991.05]	3280.5 ± 1236.6 (37.7) [3168.5]	1971.3	3089.5	0.64 (0.59, 0.69)	< 0.0001
CLp/F (L/hr x kg^{-1})	0.51 ± 0.19 (37.41) [0.48]	1.54 ± 0.65 (41.9) [1.60]	—	—	—	—
Vz/F (L/kg)	29.3 ± 8.1 (27.8) [28.9]	46.0 ± 14.2 (30.9) [44.9]	—	—	—	—
t1/2 (hr)	43.96 ±16.40 (37) [39.19]	24.57 ± -- -- [20.35]	41.6	22.4	1.86 (1.69, 2.05)	< 0.0001

a Mean ± SD, (CV), Range, [Median]

Figure 36 Comparison of Naïve Pooled Concentration vs. Time Profiles for Desipramine 50 mg administered alone and concurrently with Duloxetine 60 mg po q12h. Panel A: Linear Scale with Means and SD; Panel B: Semilogarithmic Scale



8.10.3.1.1.2 Paroxetine and Duloxetine

Paroxetine, a SSRI antidepressant, is a potent inhibitor of CYP2D6, a labeled dosage of 20 – 50 mg qAM in depression and up to 60 mg qAM in other psychiatric disorders. Paroxetine itself is metabolized by 2D6 and exhibits nonlinear kinetics, with multiple daily doses of 30 mg steady-state C_{min} values were about 14 times what would be predicted from single-dose studies with steady-state achieved after as long as 2 weeks in some individuals. However, although these are nonlinear conditions, 2D6 inhibition is not complete, consequently with maximum dosing the degree of 2D6 inhibition is expected to be even greater and the time to achieve steady-state even longer.

The effect of CYP2D6 inhibition on the pharmacokinetics of duloxetine was examined in study SBAG. In this study the fasting pharmacokinetics of duloxetine 40 mg qd administered for 5 days at 8 AM in 14 males was examined in the presence and absence of paroxetine 20 mg po daily after 5 days when also dosed at 8AM. Subjects were both genotyped for 2D6 status as well as phenotyped with dextromethorphan prior to drug administration and after paroxetine dosing. All subjects were extensive metabolizers by genotyping, and although 1 subject did phenotype as a poor metabolizer, he did demonstrate increased duloxetine exposure in the presence of paroxetine.

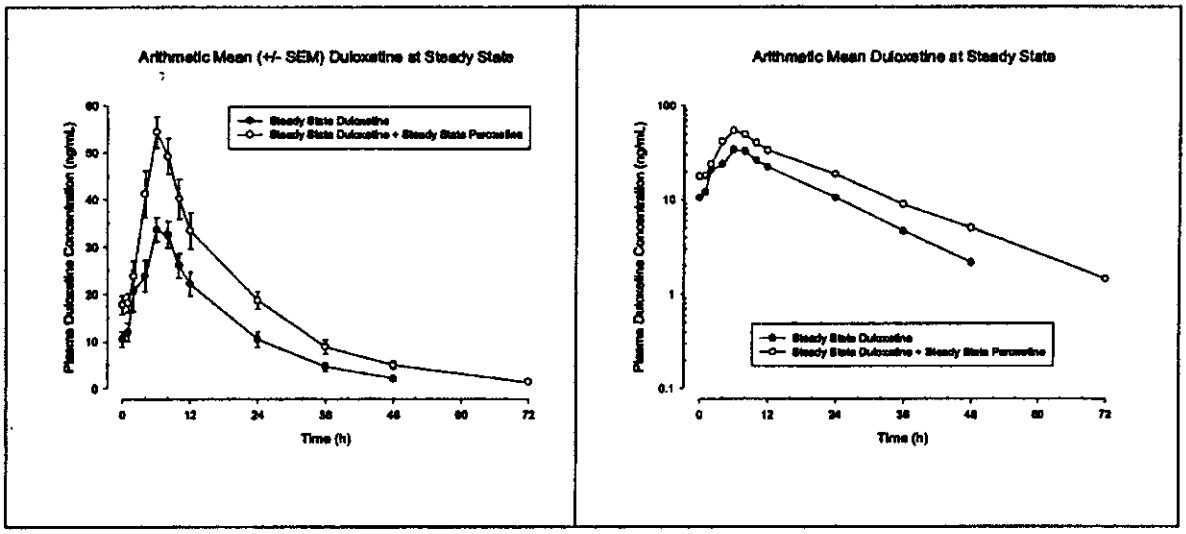
CYP2D6 inhibition did inhibit the elimination of duloxetine with a mean 1.6 fold increase in AUC, (90% confidence interval 1.27 to 1.99), (see Table 73 and Figure 37), However, it should be noted that this was a low dose of paroxetine and it was not at steady-state. Consequently, with maximal paroxetine dosing and steady-state conditions, for example when treating for OCD, the relative degree of increase in duloxetine exposure is likely to be even greater, and this would be compounded by the higher doses of duloxetine that will be used clinically.

Table 73 Effect of Paroxetine 20 mg on Steady-State Duloxetine Pharmacokinetics (Study SBAG)

Metric	Summary Statistics		LS Means			
	Test	Ref	Test	Ref	Geometric Mean Ratio 90% CI for GMR	p Value for difference in means
	Duloxetine 40 mg + Paroxetine 20 mg	Duloxetine 40 mg Alone	Paroxetine 20 mg + Duloxetine 40 mg	Duloxetine 40 mg Alone		
n			10	9		
Tmin (hrs)	5.8 ± 10.3 (179.0) [1.0]	10.9 ± 12.4 (114.3) [1.0]				
$Cmin_{ss}$	17.6 ± 6.0 (34.1) [19.5]	9.9 ± 5.6 (56.9) [7.5]				
Tmax (hrs)	6.0 ± 1.0 (16.7) [6.0]	6.2 ± 1.9 (29.8) [6.0]	6.0 4.0, 8.0	6.0 2.0, 8.0	0.0 Median of differences	0.999[a]
$Cmax_{ss}$ (ng/ml)	55.7 ± 10.0 (17.9) [56.0]	34.5 ± 8.6 (24.8) [33.9]	54.85	34.32	1.60 (1.36, 1.88)	0.001
Cav_{ss} (ng/ml)	32.5 ± 8.5 (26.2) [35.1]	20.4 ± 7.2 (35.3) [19.6]	31.45	19.76	1.59 (1.27, 1.99)	0.002
PTF (%)	126.8 ± 25.3 (20.0) [116.5]	132.9 ± 32.8 (24.7) [135.1]	123.2	130.1	0.95 (0.81, 1.11)	0.571
$t_{1/2}$ (hrs)	12.6 ± 1.8 (14.7) [11.8]	10.3 ± 2.1 (19.9) [9.3]	12.6	10.01	1.26 (1.11, 1.43)	0.005
$AUC\tau^{ss}$ (ng/ml x hr^{-1})	780.0 ± 204.0 (26.1) [843.4]	489.7 ± 173.1 (35.3) [469.3]	754.93	473.88	1.59 (1.27, 1.99)	0.002
Vz/F (L)	1865.8 ± 2585.6 (138.6) [969.2]	1281.6 ± 282.9 (22.1) [1168.1]				
Cl_{ss}/F (L/hr)	26.9 ± 35.6 (132.3) [15.3]	19.2 ± 5.0 (26.1) [19.4]	52.99	84.41	0.63 (0.50, 0.79)	0.002
$Vz/F^{wt\ normalized}$ (L/kg)	54.9 ± 15.6 (28.5) [47.4]	90.3 ± 28.8 (31.9) [85.2]				
$Cl_{ss}/F^{wt\ normalized}$ (L/hr x kg^{-1})	0.8 ± 0.2 (28.2) [0.8]	1.3 ± 0.4 (32.5) [1.3]				

a Wilcoxon Signed Rank Test

Figure 37 Mean (± SD)Steady-State Duloxetine 40 mg qAM Plasma Concentrations in the Presence and Absence of Low Dose Non-Steady State Exposure to Paroxetine (Study SBAG)



8.10.3.1.2 P450 CYP1A2

8.10.3.1.2.1 Theophylline and Duloxetine

8.10.3.1.2.1.1 Effect of Duloxetine on Theophylline

The ability of duloxetine to inhibit CYP1A2 *in vivo* was examined in study HMBF by examining the effect of duloxetine on theophylline pharmacokinetics in study HMBF.

The structural formula for theophylline is 1,3,7-methylxanthine and it is metabolized to 1,3-dimethyluric acid (1,3-DMU), 3-methylxanthine (3-MX) and 1-methylxanthine (1-MX). The demethylations are mediated primarily by cytochrome P-450 1A2, although isozymes 3A3, and 2E1 are also believed to be involved.

Study HMBF was a single-center, subject-blind, randomized, two-way balanced crossover study performed on 10 healthy non-smoking adult males. The 2 treatments included theophylline and duloxetine or placebo. Dosing was as follows with a minimum of a 12 day inter-period washout:

- Duloxetine, 60 mg, or placebo, q 12h orally for 4 days followed by a single morning dose of 60 mg, or placebo. On days 3 - 5 the AM doses were administered fasting, whereas all evening doses were administered after dinner.

- Theophylline was administered on day 5, four hours after the duloxetine (or placebo) dose, as a single 197.5 mg IV infusion for 30 min, given as 250 mg aminophylline via an IV pump.

On the morning of Day 5, sequential blood samples were obtained after the dose of theophylline for the purpose of measuring theophylline plasma concentration. From Day 5 to Day 8, sequential urine samples were collected for measuring theophylline and its CYP1A metabolites: i.e. 1,3-DMU, 3-MX, and 1-MX.

There were 2 significant protocol violations, although neither should effect the results of the study. First, subject 003 inadvertently received 3 capsules of duloxetine instead of placebo in the evening of Day 3. However, most of the duloxetine should be eliminated prior to his receiving aminophylline, and the circulating metabolites are not likely to be significantly metabolized by CYP1A2. Secondly, for subject

902, the aminophylline dose that was co-administered with duloxetine was administered over 20 minutes, instead of 30 minutes. However, the peak concentrations were only 10% higher. Results of this study indicate that there was no effect of duloxetine on the pharmacokinetics of theophylline or its metabolites, thereby indicating that duloxetine is not an inhibitor of CYP1A2 *in vivo,* (see Table 74 and Figure 38 and Table 75 and Figure 39).

Table 74 IV Theophylline (Aminophylline) Pharmacokinetic Metrics in the Presence and Absence of Duloxetine 60 mg q 12h (Study HMBF)

Metric	Summary Statistics[a]		Statistical Comparison of Theophylline Pharmacokinetic Parameters[a]			
			LS Geometric Mean		Geometric Mean Ratio (90% CI)	p-Value
	Theophylline + Placebo	Theophylline + Duloxetine	Theophylline + Placebo	Theophylline + Duloxetine		
Total Amount (mg)	197.5	197.5	—	—	—	—
Duration of Infusion (hr)	0.47 ± 0.05 (11) [0.48]	0.49 ± 0.01 (2.7) [0.49]	—	—	—	—
Infusion Rate (mg/hr)	429.5 ± 600.9 (14) [411.6]	405.0 ± 110.0 (2.7) [403.2]	—	—	—	—
Tmax (hr)	0.56 ± 0.24 (42.0) [0.48]	0.64 ± 0.25 (39.56) [0.49]	—	—	—	—
Cmax (µg/mL)	7.208 ± 1.217 (17) [6.914]	7.8245 ± 1.648168 (21.0642) [8.0805]	7.1	7.6	1.07 (0.92, 1.25)	0.4081
t½ (hr)	11.40 ±2.72 (23.9) [11.27]	11.49 ± 2.43 (21.13) [10.51]	11.1	11.3	1.02 (0.86, 1.21)	0.8498
$AUC_{0-\infty}$ (µg/ml x hr^{-1})	68.87 ± 15.67 (23) [64.64]	73.53 ± 14.85 (20) [69.31]	67.3	72.3	1.07 (1.01, 1.15)	0.0793
MRT (hr)	12.85 ± 2.65 (21) [12.97]	13.30 ± 2.59 (19) [13.23]	—	—	—	—
CL (L/hr)	3.00 ± 0.65 (22) [3.07]	2.78 ± 0.50 (18) [2.85]	2.9	2.7	0.93 (0.87, 0.99)	0.0793
CLr (L/hr)	0.707 ± 0.246 (35) [0.656]	0.653 ± 0.253 (39) [0.644]	—	—	—	—
Vss (L)	38.16 ± 11.01 (29) [33.37]	36.59 ± 8.62 (24) [34.26]	37.0	35.8	0.97 (0.85, 1.10)	0.6480

a Mean ± SD, CV(%), range, [median]

b Analyses of pharmacokinetic parameters were based on log-transformed data

Figure 38 Mean Theophylline Plasma Concentration vs. Time Profiles in the Presence and Absence of Duloxetine 60 mg q12h (Study HMBF)

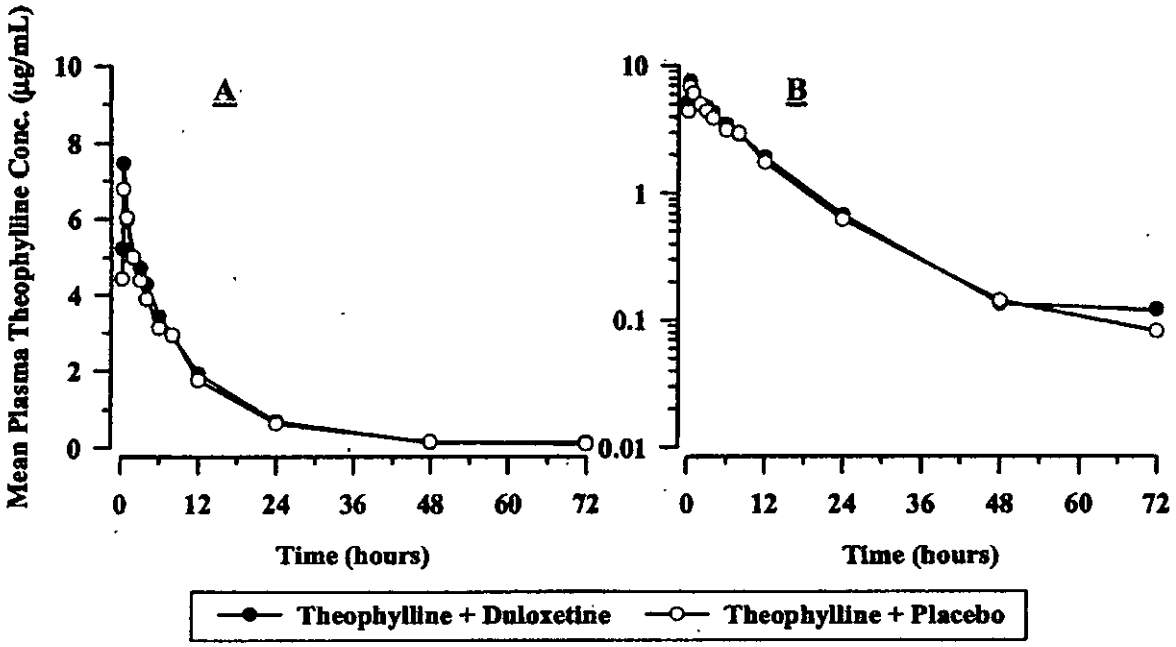


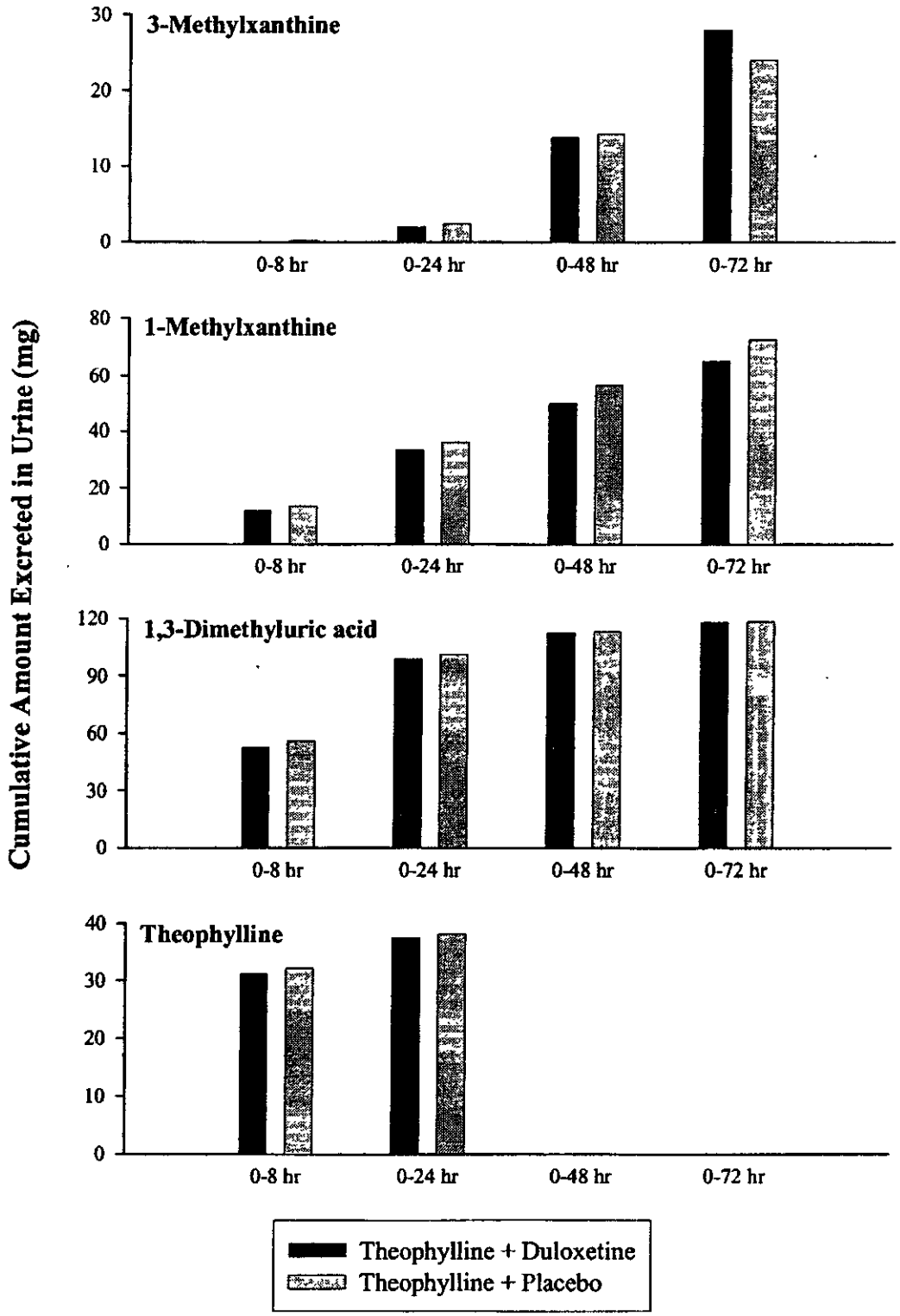
Table 75 Cumulative Amount Excreted and Formation Clearance for Theophylline Metabolites[a]

Metabolite	Treatment	N	0-8 (hrs)	0-24 (hrs)	0-48 (hrs)	0-72 (hrs)	% Excreted	CLf (L/hr)
3-Methylxanthine (µg) [3-MX]	Theophylline + Duloxetine	0 - 9	—	1955 ± 1302 (67) [1647]	13795 ± 14556 (106) [9130]	27974 ± 27876 (100) [17807]	15.4 ± 15.3 (100) [9.8]	0.43 ± 0.45 (104) [0.33]
	Theophylline + Placebo	0 - 10	1215 ± 0 (0) [1215]	2350 ± 1445 (61) [2418]	14336 ± 10445 (73) [12927]	24018 ± 17197 (72) [20410]	13.2 ± 9.4 (72) [11.2]	0.40 ± 0.30 (76) [0.28]
1-Methylxanthine (µg) [1-MX]	Theophylline + Duloxetine	10	11472 ± 3162 (28) [11010]	33201 ± 12371 (37) [29378]	49485 ± 19446 (39) [43541]	64909 ± 27676 (43) [56212]	35.7 ± 15.2 (43) [30.9]	1.04 ± 0.57 (54) [0.88]
	Theophylline + Placebo	10	13364 ± 6670 (50) [11773]	36182 ± 13478 (37) [31851]	56560 ± 28028 (50) [43721]	72335 ± 29512 (41) [64057]	39.7 ± 16.2 (41) [35.2]	1.20 ± 0.54 (45) [1.10]
1,3-Dimethyl Uric Acid (µg) [1,3-MUA]	Theophylline + Duloxetine	10	52444 ± 10483 (20) [47043]	98911 ± 15295 (15) [100828]	112584 ± 15051 (13) [116550]	117977 ± 16871 (14) [122880]	54.9 ± 7.8 (14) [57.1]	1.54 ± 0.44 (28) [1.62]

	Theophylline + Placebo	10	56380 ± 9370 (17) [58196]	101312 ± 13733 (14) [99052]	113373 ± 14828 (13) [116471]	118181 ± 15301 (13) [120605]	55.0 ± 7.1 (13) [56.1]	1.65 ± 0.45 (27) [1.57]

a Values are mean ± SD, (CV%), Range, [median].

Figure 39 Cumulative Urinary Excretion of Theophylline and its Metabolites in the Presence and



Absence of Duloxetine 60 mg q 12hr (Study HMBF)

8.10.3.1.2.1.2 Effect of CYP1A2 iinhibiton on Duloxetine

The effect of CYP1A2 inhibition on duloxetine pharmacokinetics was not examined. Inhibition by common CYP1A2 inhibitors such as fluroquinilones or cimetidine could result in excessive exposures and adverse effects, especially in CYP2D6 poor metabolizers. This is primarily of concern when starting or stopping a medication. If the offending co-medication is one that is commonly taken in combination, the interaction may be more easily managed. However in the present case these drugs are of additional concern as both fluroquinilones and cimetidine may be taken acutely and not chronically, and may be prescribed by different physicians than those prescribing duloxetine, and in the case of cimitidine is available as a non-prescription drug.

8.10.3.1.2.1.3 Effect of CYP1A2 induction on Duloxetine

The effect of CYP1A2 induction on duloxetine pharmacokinetics was not examined. Induction would be expected to decrease exposure to duloxetine and would be of most concern in an individual with both low baseline CYP1A2 and CYP2D6 activity who is on a lower dose than usual for most patients.

CYP1A2 induction, can occur secondary to polyaromatic hydrocarbons, indoles, and tryptophan and pyrolysis products. Polyaromatic hydrocarbons, certain indoles and tryptophan and pyrolysis products can be found in certain dietary constituents and are discussed in § 8.10.2.2.,

In addition, herbal products and even some drugs may contain indoles, e.g. 5-HT receptor agonists & antagonists and indomethacin

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8.10.3.1.3 P450 CYP2C11

8.10.3.1.3.1 Temazepam and Duloxetine

The pharmacokinetic interaction of temazepam and duloxetine was examined in study HMAJ.

Temazepam is eliminated almost exclusively by metabolism, primarily via O-glucuronidation (~90%). A small percent (~7%) is eliminated by O-demethylation, followed by glucuronidation. O-demethylation appears to be mediated via CYP2C11 and possibly CYP2D1. Duloxetine is metabolized to N-Desmethyl-duloxetine, possibly by CYP2C11. Normally this is a quantitatively minor pathway, and would constitute less than 20% of total body clearance (see § 8.6.2).

Study HMAJ was a 3-way crossover study in healthy males. Subjects received Restoril™ (temazepam) 30 mg qhs at 11 PM, duloxetine 20 mg qhs at 11 PM, or both drugs together at 11 PM. Drugs were dosed for 6 days, presumably until steady-state was achieved.

The 30 mg Restoril dose is the maximum labeled dose, however, there are still a number of design flaws with this study.

A 20 mg duloxetine dose is subtherapeutic, the recommended dose is 60 mg QD or 40 mg BID. Thus duloxetine concentrations are well below clinically achieved concentrations.

The Tmax's for both drugs were not achieved as closely together as they would be in practice. Both drugs were administered at 11 PM. Restoril has a very late Tmax compared to most sedatives. The Tmax is quoted as occurring at 1.4 hours and is usually dosed 1 – 2 hours before bedtime. In the present study temazepam Tmax occurred between 2 and 6 hours (1 AM – 5 AM). Dosing at 9 PM would thus be expected to produce Tmax at 11 PM to 3 AM.

In all of the bid studies with duloxetine; duloxetine was dosed at 8 PM. In the present study Tmax occurred at 3 – 13 hours, (2 AM – Noon), median 10 hours (i.e. 9 AM). Dinner was provided at 5:30 PM, and a snack at 9:30 PM. Consequently, either the food or the evening administration could have produced the exceptionally delayed Tlag, Tmax, and lower Cmax as compared to studies under fasting conditions. If duloxetine is taken at 7 PM, Tmax would be expected to occur between 10 PM and 8 AM (median 5 AM). Thus Tmax for both drugs could occur concurrently.

Lastly, drugs were only dosed for a week, if induction is to be fully addressed a longer period of dosing might be needed in order to see maximal induction.

Given all these caveats, the following observations were made:

a) No effect of temazepam on duloxetine exposure (see Table 76 and Figure 40).
b) No effect of duloxetine on temazepam exposure (see Table 78 and Figure 42).
c) Decreased exposure to desmethy-duloxetine in the presence of temazepam (Table 77 and Figure 41).

This last effect may be due to induction of elimination of desmethyl-duloxetine or competitive inhibition of 2C11, which forms the desmethyl metabolite. Whether this is due to induction of transporters eliminating desmethyl-duloxetine or inhibition and metabolic shunting can't be determined from the present study. However, upon therapeutic dosing the effect may be either greater or smaller depending upon the mechanism and without additional information we can't determine if it will be clinically significant or not. As desmethyl-duloxetine is a metabolite, there is inherent higher variability in metabolite exposures. In fact, the variability in kinetics masks any differences when naïve pooled data is compared, (see Figure 41).

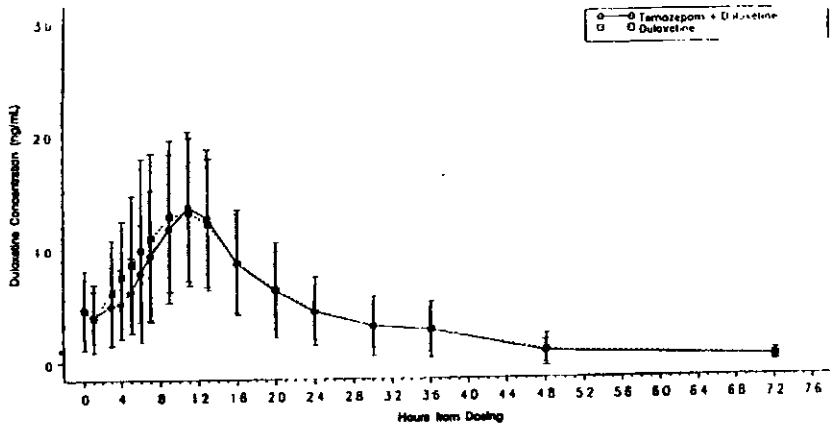
8.10.3.1.3.1.1 Effect of Temazepam on Duloxetine

Table 76 Effect of Temazepam on Duloxetine Pharmacokinetic Metrics (Study HMAJ)

Pharmacokinetic Metric	Test Duloxetine + Temazepam	Reference Duloxetine alone	Geometric Mean Ratios [90% CI]
Tlag hours	4.17 ± 1.64 (39.4) [4]	5.09 ± 1.87 (36.7) [5]	p-value = 0.396[a]
Cmax ng/ml	14.72 ± 5.96 (40.5)	14.2 ± 6.34 (44.6)	103.8 [91.5, 117.7]
Tmax hours	10 ± 3 (32)	8 ± 3 (39)	
AUCτ ng/ml x hr^{-1}	195.42 ± 90.72 (46.4)	206.48 ± 112.89 (54.7)	96.4 [87.3, 106.5]
Cav ng/ml	8.142 ± 3.78 (46.4)	8.603 ± 4.704 (54.7)	96.6 [87.5, 106.6]
Cmin ng/ml	3.32 ± 1.91 (57.6)	3.55 ± 2.98 (83.9)	104.5 [94.6, 115.5]
Fluctuation Index	1.546 ± 0.476 (30.8)	1.398 ± 0.432 (30.9)	—
Ae_{0-48}^{urine}	0.037 ± 0.027 (71.5)	.035 ± 0.025 (71.2)	—
fu (%)	0.12% ± 0.09% 0.02% - 0.34%	0.12% ± 0.08% 0.03% - 0.30%	—

a - Wilcoxon Signed Rank Test

Figure 40 Naïve Pooled Duloxetine Plasma Concentration – Time Profiles in the Presence and Absence of Temazepam (Study HMAJ)

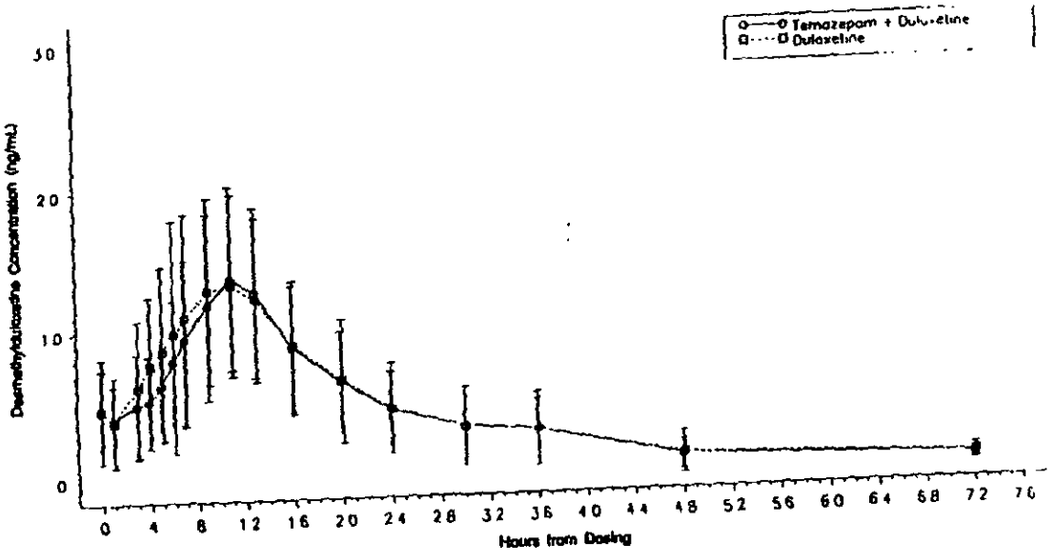


8.10.3.1.3.2 Effect of Temazepam on Desmethyl-Duloxetine

Table 77 Effect of Temazepam on Desmethyl-duloxetine Pharmacokinetic Metrics (Study HMAJ)

Pharmacokinetic Metric	Test Duloxetine + Temazepam	Reference Duloxetine alone	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)	—

Figure 41 Naïve Pooled Desmethyl-Duloxetine Plasma Concentration – Time Profiles in the Presence and Absence of Temazepam (Study HMAJ)



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