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APPLICATION NUMBER: 020974

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

/S/ 1997
FEB 16 1999

NDA20-974
Prozac® (Fluoxetine HCl)
(10 & 20mg Tablets)

Type of submission: Original NDA (new dosage form)
Submission Date: March 19. 1998

Sponsor: Lily Research Lab.

INDICATION: antidepressant agent

REVIEWER: Rae Yuan, Ph.D.

Introduction:

The currently approved marketed dosage forms of fluoxetine include capsules (Pulvules®) and an oral liquid formulation. This application seeks to gain approval for two strengths (10 and 20 mg) of a new tablet dosage form for fluoxetine. The two strengths are compositionally proportional

One open-label, randomized, single dose, two period, crossover study has been conducted to test the bioequivalence of new tablet formulations at10 & 20 mg to the marketed capsule formulations at10 & 20 mg, respectively. New dissolution method and specification have been proposed for the tablet formulation

Study Design:

Forty eight healthy male and female subjects were enrolled in the study and 45 completed the study. During screening process, each subject was phenotyped for CYP2D6 activity. Then the subjects were randomly assigned to group 1 to receive 10 mg formulations (as 2x 10 mg) or group 2 to receive 20 mg formulations Within each treatment group, the subjects were further randomized into one of the two dosing sequences for the test or reference formulation. Subjects received single oral dose fluoxetine after overnight fasting in each treatment period. Each period was separated by 5 days. Blood samples were obtained at 0, 2, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 216, 264, 336, 432, 576, and 720 hours post dosing.

Results:

1. Mean Pharmacokinetic parameters can be found in Tables 3-6 of the attachment.

2. Two subjects (#36 and #46) were identified as, and one (#32) was close to be, CYP2D6 poor metabolizers, because their dextromethorphan/dextrophan ratios (an index for CYP2D6 activity) were over or close to 0.3. The large variation found in the 20 mg dosing group (c.v. was 95% for tablet AUC and 88% for capsule AUC) was due to the three subjects, who showed exceedingly large AUC, as compared to the rest of the group. Interestingly, one subject who contributed to the large variation in 2x10 mg treatment group (#24) was a fast CYP2D6 metabolizer, yet exhibited "outlier" phamacokinetic parameters, compared to the rest of the group. However, these intrinsic pharmacological difference among individuals did not affect the assessment of bioequivalence or the interpretation of the study because each subject served as their own control in a crossover design and analysis (see the Attachment I).
3. Among 3 subjects who dropped out of the study, only one was suspected to be related to the adverse event (tachycardia 35 days after receiving 20 mg tablet dosing). There was no significant difference with regard to adverse events between the tablet treatment or capsule treatment period.
4. In spite of the large variations for Cmax and AUC (all > 30%) for all treatment group, statistic analysis demonstrated that tablet formulation was bioequivalent to the capsule formulation at both doses. The ranges of 90% confidence interval for log transformed Cmax and $AUC_{0-\infty}$ of fluoxetine at 10 mg were 93.2-105.4 and 92.3-107.7, respectively; and at 20 mg were 92.1-101.7 and 92.7-102.4, respectively. The ranges for norfluoxetine, the active metabolite of fluoxetine, at 10 mg were [redacted] and [redacted], respectively and at 20 mg were [redacted], and [redacted] respectively.

Dissolution:

APPEARS THIS WAY
ON ORIGINAL

Comments:

1. The sponsor has conducted a well-designed bio-study to test equivalence between the two immediate-release dosage forms. In spite of the large inter-individual variation within each treatment group, fluoxetine tablets at 10 & 20 mg were demonstrated to be bioequivalent to the respective reference capsules. The variation in 20 mg treatment group could be explained by polymorphism of fluoxetine metabolic enzyme activities, but that in 10 mg treatment group could not be explained.

2. Based on the individual dissolution data on both dosage strengths, the dissolution method proposed by the sponsor is acceptable, but the specification should be set at:

Apparatus: USP Dissoution Apparatus I at 100 rpm
Media: Deaerated 0.1 N HCl of 1000 ml at 37°C
Specification: Q___ , at 15 min.

Recommendation:

The sponsor has demonstrated that 10 and 20 mg tablet formulations were bioequivalent to the respective approved product, based on Cmax and AUC of both fluoxetine and norfluoxetne.

Please convey comment 1 to the medical officer and comment 2 to the sponsor.

Rae Yuan, Ph.D. /S/ - 2/16/99

Team Leader: Chandra Sahajwalla, Ph.D. /S/ 2/16/99

Date of Signature:

Office of Clinical Pharmacology and Biopharmaceutics/Division I

CC list: HFD-120; CSO; HFD-860 (Yuan, Sahajwalla, Mehta); CDR (Barbara Murphy)

6 page(s)
TRADE Secret/
Confidential
Commercial

Table #5. The Pharmacokinetic and Statistical Analyses of Fluoxetine in Group 2 Following Doses of 20 mg Fluoxetine Tablets or Capsules (Treatments C and D)[a]

Fluoxetine Pharmacokinetic Parameters	Treatment C Arithmetic Mean (SD)	Treatment D Arithmetic Mean (SD)	Mean Ratio (%) Treatment C versus Treatment D	90% Confidence Interval Treatment C versus Treatment D
Cmax (ng/mL)	8.885 (3.422)	8.991 (2.948)		
AUC(0-t) (ng*hr/mL)	390.6 (393.6)	393.8 (359.0)		
AUC(0-inf) (ng*hr/mL)	486.5 (462.7)	490.4 (435.4)		
Tmax (hr)	7.09 (1.75)	7.65 (1.30)		
Kel (1/hr)	0.0253 (0.0125)	0.0245 (0.0115)		
T1/2el (hr)	43.27 (41.94)	43.17 (39.99)		
LN(Cmax)	2.114 (0.3872)	2.145 (0.3280)	96.8	92.1 - 101.7
LN[AUC(0-t)]	5.638 (0.7656)	5.675 (0.7550)	96.4	90.9 - 102.2
LN[AUC(0-inf)]	5.895 (0.7152)	5.921 (0.7096)	97.4	92.7 - 102.4

[a] Study B1Y-LC-HCIS
Treatment C: 1 x 20 mg fluoxetine tablets by Eli Lilly and Company, fasted.
Treatment D: 1 x 20 mg marketed fluoxetine capsules by Eli Lilly and Company, fasted.

Table #6. The Pharmacokinetic and Statistical Analyses of Norfluoxetine in Group 2 Following Doses of 20 mg Fluoxetine Tablets or Capsules (Treatments C and D)[a]

Norfluoxetine Pharmacokinetic Parameters	Treatment C Arithmetic Mean (SD)	Treatment D Arithmetic Mean (SD)	Mean Ratio (%) Treatment C versus Treatment D	90% Confidence Interval Treatment C versus Treatment D
Cmax (ng/mL)	7.229 (2.914)	7.065 (2.610)		
AUC(0-t) (ng*hr/mL)	1591 (590.3)	1596 (576.7)		
AUC(0-inf) (ng*hr/mL)	1915 (614.1)	1848 (601.5)		
Tmax (hr)	61.0 (46.5)	58.6 (35.7)		
Kel (1/hr)	0.0055 (0.0024)	0.0060 (0.0019)		
T1/2el (hr)	145.6 (57.67)	128.1 (69.83)		
LN(Cmax)	1.896 (0.4266)	1.884 (0.3981)	101.2	98.1 - 104.4
LN[AUC(0-t)]	7.299 (0.4041)	7.306 (0.3927)	99.4	95.6 - 103.3
LN[AUC(0-inf)]	7.501(0.3559)	7.467 (0.3494)	101.7	98.1 - 105.3

[a] Study B1Y-LC-HCIS
Treatment C: 1 x 20 mg fluoxetine tablets by Eli Lilly and Company, fasted.
Treatment D: 1 x 20 mg marketed fluoxetine capsules by Eli Lilly and Company, fasted.

Table 8CI8.4.3. Plasma Fluoxetine Pharmacokinetic Parameters Following 2 x 10 mg Fluoxetine Tablets (Treatment A)

Subject Number	Treatment Sequence	Study Period	Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	T 1/2el hr	Kel 1/hr	Log-Parameters LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1	AB	1									
2	AB	1									
3	AB	1									
4	AB	1									
5	AB	1									
6 *	A	1									
7	AB	1									
8	AB	1									
9	AB	1									
10	AB	1									
11	AB	1									
12	AB	1									
13	BA	2									
14	BA	2									
16	BA	2									
17	BA	2									
18	BA	2									
19	BA	2									
20	BA	2									
21	BA	2									
22	BA	2									
23	BA	2									
24	BA	2									
Mean			9.711	7.41	328.5	378.2	26.47	0.0289	2.167	5.626	5.797
S.D.			5.190	1.18	238.7	250.0	8.542	0.0095	0.4531	0.5675	0.5059
C.V.(%)			53.45	14.8	72.66	66.12	32.27	33.06	20.91	10.09	8.728
S.E.M.			1.107	0.234	50.89	53.31	1.821	0.0020	0.0966	0.1210	0.1079
N			22.00	22.0	22.00	22.00	22.00	22.00	22.00	22.00	22.00
Minimum											
Maximum											

* = Subject did not complete the study and was excluded from summary statistics.
. = Sample value missing or not reportable.

Table HCIS.4.4. Plasma Fluoxetine Pharmacokinetic Parameters Following 2 x 10 mg Marketed Fluoxetine Capsules (Treatment B)

Subject Number		Treatment Sequence	Study Period	Parameters Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	T 1/2el hr	Kel 1/hr	Log-Parameters LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1		AB	2									
2		AB	2									
3		AB	2									
4		AB	2									
5		AB	2									
7		AB	2									
8		AB	2									
9		AB	2									
10		AB	2									
11		AB	2									
12		AB	2									
13		BA	1									
14		BA	1									
15	*	B	1									
16		BA	1									
17		BA	1									
18		BA	1									
19		BA	1									
20		BA	1									
21		BA	1									
22		BA	1									
23		BA	1									
24		BA	1									
Mean				9.753	7.73	326.9	383.4	28.62	0.0266	2.176	5.604	5.800
S.D.				4.731	1.70	243.3	260.8	9.544	0.0080	0.4547	0.5965	0.5275
C.V.(%)				48.50	22.0	74.44	68.03	33.34	30.35	20.89	10.61	9.096
S.E.M.				1.009	0.362	51.88	55.61	2.035	0.0017	0.0969	0.1267	0.1125
N				22.00	22.0	22.00	22.00	22.00	22.00	22.00	22.00	22.00
Minimum												
Maximum												

* = Subject did not complete the study and was excluded from summary statistics.
. = Sample value missing or not reportable.

Table HCI8.4.12. Plasma Norfluoxetine Pharmacokinetic Parameters Following 2 x 10 mg Fluoxetine Tablets (Treatment A)

Subject Number		Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	T 1/2el hr	Kel 1/hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1		AB	1									
2		AB	1									
3		AB	1									
4		AB	1									
5		AB	1									
6	*	A	1									
7		AB	1									
8		AB	1									
9		AB	1									
10		AB	1									
11		AB	1									
12		AB	1									
13		BA	2									
14		BA	2									
16		BA	2									
17		BA	2									
18		BA	2									
19		BA	2									
20		BA	2									
21		BA	2									
22		BA	2									
23		BA	2									
24		BA	2									
Mean				8.493	50.5	1807	2039	115.2	0.0066	2.089	7.411	7.569
S.D.				2.791	38.7	810.5	830.6	37.43	0.0022	0.3259	0.4285	0.3800
C.V.(%)				32.86	76.7	44.86	40.76	32.49	33.14	15.60	5.781	5.034
S.E.M.				0.5951	8.25	172.8	177.1	7.979	0.0004	0.0696	0.0913	0.0810
N				22.00	22.0	22.00	22.00	22.00	22.00	22.00	22.00	22.00
Minimum												
Maximum												

* = Subject did not complete the study and was excluded from summary statistics.
. = Sample value missing or not reportable.

Table HCIS.4.13. Plasma Norfluoxetine Pharmacokinetic Parameters Following 2 x 10 mg Marketed Fluoxetine Capsules (Treatment B)

Subject Number		Treatment Sequence	Study Period	Parameters Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	T 1/2el hr	Kel 1/hr	Log-Parameters LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
1		AB	2									
2		AB	2									
3		AB	2									
4		AB	2									
5		AB	2									
7		AB	2									
8		AB	2									
9		AB	2									
10		AB	2									
11		AB	2									
12		AB	2									
13		BA	1									
14		BA	1									
15	*	B	1									
16		BA	1									
17		BA	1									
18		BA	1									
19		BA	1									
20		BA	1									
21		BA	1									
22		BA	1									
23		BA	1									
24		BA	1									
Mean				9.097	59.8	1846	2080	111.7	0.0070	2.160	7.445	7.570
S.D.				2.942	39.4	797.3	862.4	42.12	0.0024	0.3165	0.3895	0.3748
C.V.(%)				32.34	65.9	43.19	41.46	37.69	35.37	14.65	5.232	4.951
S.E.M.				0.6271	8.41	170.0	183.9	8.979	0.0005	0.0674	0.0830	0.0799
N				22.00	22.0	22.00	22.00	22.00	22.00	22.00	22.00	22.00
Minimum												
Maximum												

* = Subject did not complete the study and was excluded from summary statistics.
. = Sample value missing or not reportable.

Table ECIS.4.21. Plasma Fluoxetine Pharmacokinetic Parameters Following 1 x 20 mg Fluoxetine Tablets (Treatment C)

Subject Number		Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	T 1/2el hr	Kel 1/hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
25		CD	1									
26		CD	1									
27	*	C	1									
28		CD	1									
29		CD	1									
30		CD	1									
31		CD	1									
32		CD	1									
33		CD	1									
34		CD	1									
35		CD	1									
36		CD	1									
37		DC	2									
38		DC	2									
39		DC	2									
40		DC	2									
41		DC	2									
42		DC	2									
43		DC	2									
44		DC	2									
45		DC	2									
46		DC	2									
47		DC	2									
48		DC	2									
Mean				8.885	7.09	390.6	486.5	43.27	0.0253	2.114	5.638	5.895
S.D.				3.422	1.75	393.6	462.7	41.94	0.0125	0.3872	0.7656	0.7152
C.V.(%)				38.51	24.7	100.8	95.11	96.94	49.63	18.32	13.58	12.13
S.E.M.				0.7135	0.366	82.07	98.65	8.942	0.0026	0.0807	0.1596	0.1525
N				23.00	23.0	23.00	22.00	22.00	22.00	23.00	23.00	22.00
Minimum												
Maximum												

* = Subject did not complete the study and was excluded from summary statistics.
. = Sample value missing or not reportable.

Table BCIS.4.22. Plasma Fluoxetine Pharmacokinetic Parameters Following 1 x 20 mg Marketed Fluoxetine Capsules (Treatment D)

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	T 1/2el hr	Kel 1/hr	Log-Parameters: LN(Cmax)	LN(AUC(0-t))	LN(AUC(0-inf))
25	CD	2									
26	CD	2									
28	CD	2									
29	CD	2									
30	CD	2									
31	CD	2									
32	CD	2									
33	CD	2									
34	CD	2									
35	CD	2									
36	CD	2									
37	DC	1									
38	DC	1									
39	DC	1									
40	DC	1									
41	DC	1									
42	DC	1									
43	DC	1									
44	DC	1									
45	DC	1									
46	DC	1									
47	DC	1									
48	DC	1									
Mean			0.991	7.65	393.8	490.4	43.17	0.0265	2.145	5.675	5.921
S.D.			2.948	1.30	359.9	435.4	39.99	0.0115	0.3280	0.7550	0.7096
C.V.(%)			32.79	17.0	91.16	88.79	92.62	47.03	15.29	13.30	11.99
S.E.M.			0.6147	0.271	74.85	92.83	8.525	0.0026	0.0683	0.1574	0.1513
N			23.00	23.0	23.00	22.00	22.00	22.00	23.00	23.00	22.00
Minimum											
Maximum											

* = Subject did not complete the study and was excluded from summary statistics.
. = Sample value missing or not reportable.

Table HCIS.4.24. Plasma Fluoxetine Pharmacokinetic Parameter Ratios: Treatment C versus Treatment D

Subject Number	Treatment Sequence	Parameters: Cmax	Tmax	AUC(0-t)	AUC(0-inf)	T 1/2el	Kel
25	CD						
26	CD						
27 *	C						
28	CD						
29	CD						
30	CD						
31	CD						
32	CD						
33	CD						
34	CD						
35	CD						
36	CD						
37	DC						
38	DC						
39	DC						
40	DC						
41	DC						
42	DC						
43	DC						
44	DC						
45	DC						
46	DC						
47	DC						
48	DC						
Mean		0.9792	0.944	0.9749	0.9820	1.000	1.045
S.D.		0.1432	0.243	0.1498	0.1244	0.2023	0.2489
C.V.(%)		14.63	25.8	15.37	12.67	20.22	23.82
S.E.M.		0.02986	0.0507	0.03124	0.02652	0.04312	0.05307
N		23.00	23.0	23.00	22.00	22.00	22.00
Minimum							
Maximum							

Ratio = Treatment C / Treatment D
C = 1 x 20 mg Fluoxetine Tablets
D = 1 x 20 mg Marketed Fluoxetine Capsules
* = Subject did not complete the study and was excluded from summary statistics.
. = Sample value missing or not reportable.

Table HCI8.4.30. Plasma Norfluoxetine Pharmacokinetic Parameters Following 1 x 20 mg Fluoxetine Tablets (Treatment C)

Subject Number		Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	T 1/2el hr	Kel 1/hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
25		CD	1									
26		CD	1									
27	*	C	1									
28		CD	1									
29		CD	1									
30		CD	1									
31		CD	1									
32		CD	1									
33		CD	1									
34		CD	1									
35		CD	1									
36		CD	1									
37		DC	2									
38		DC	2									
39		DC	2									
40		DC	2									
41		DC	2									
42		DC	2									
43		DC	2									
44		DC	2									
45		DC	2									
46		DC	2									
47		DC	2									
48		DC	2									
Mean				7.229	61.0	1591	1915	165.6	0.0055	1.896	7.299	7.501
S.D.				2.914	46.5	590.3	614.1	57.67	0.0024	0.4246	0.4041	0.3559
C.V.(%)				40.31	76.1	37.10	32.07	39.61	44.34	22.39	5.537	4.745
S.E.M.				0.6076	9.69	123.1	130.9	12.30	0.0005	0.0885	0.0842	0.0758
N				23.00	23.0	23.00	22.00	22.00	22.00	23.00	23.00	22.00
Minimum												
Maximum												

* = Subject did not complete the study and was excluded from summary statistics.
. = Sample value missing or not reportable.

Table HCI3.4.31. Plasma Norfluoxetine Pharmacokinetic Parameters Following 1 x 20 mg Marketed Fluoxetine Capsules (Treatment D)

Subject Number	Treatment Sequence	Study Period	Parameters: Cmax ng/mL	Tmax hr	AUC(0-t) ng*hr/mL	AUC(0-inf) ng*hr/mL	T 1/2el hr	Kel 1/hr	Log-Parameters: LN(Cmax)	LN[AUC(0-t)]	LN[AUC(0-inf)]
25	CD	2									
26	CD	2									
28	CD	2									
29	CD	2									
30	CD	2									
31	CD	2									
32	CD	2									
33	CD	2									
34	CD	2									
35	CD	2									
36	CD	2									
37	DC	1									
38	DC	1									
39	DC	1									
40	DC	1									
41	DC	1									
42	DC	1									
43	DC	1									
44	DC	1									
45	DC	1									
46	DC	1									
47	DC	1									
48	DC	1									
Mean			7.065	58.6	1596	1848	126.1	0.0060	1.884	7.306	7.467
S.D.			2.610	35.7	576.7	601.5	49.83	0.0019	0.3981	0.3927	0.3494
C.V.(%)			36.94	61.0	36.13	32.54	38.89	32.55	21.12	5.375	4.679
S.E.M.			0.5442	7.45	120.3	125.4	10.39	0.0004	0.0830	0.0818	0.0728
N			23.00	23.0	23.00	23.00	23.00	23.00	23.00	23.00	23.00
Minimum											
Maximum											

* = Subject did not complete the study and was excluded from summary statistics.
. = Sample value missing or not reportable.

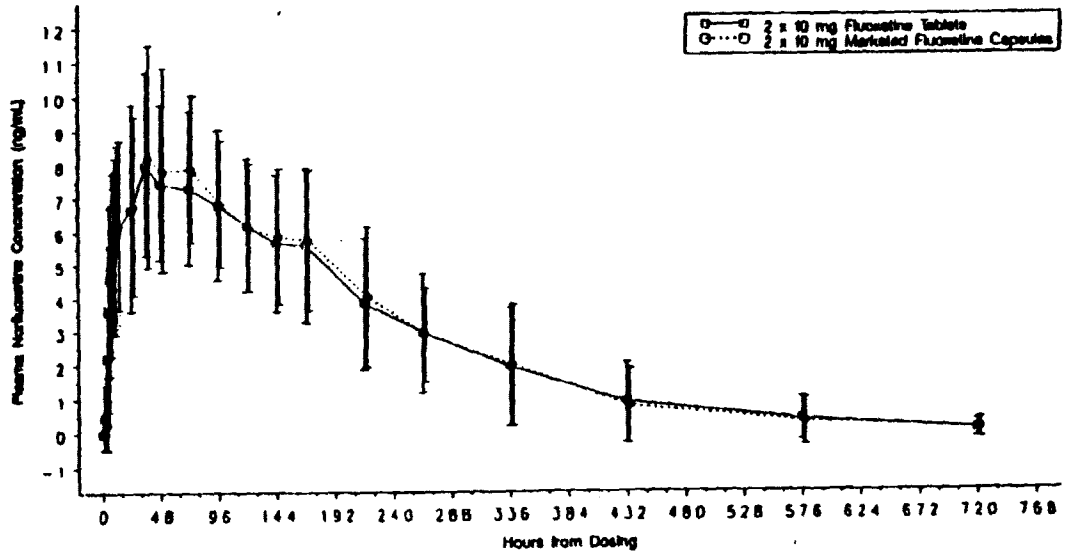
Table HCI#.4.31. Plasma Norfluoxetine Pharmacokinetic Parameter Ratios: Treatment C versus Treatment D

Subject Number	Treatment Sequence	Parameters Cmax	Tmax	AUC(0-t)	AUC(0-inf)	T 1/2el	Kel
25	CD						
26	CD						
27 *	C						
28	CD						
29	CD						
30	CD						
31	CD						
32	CD						
33	CD						
34	CD						
35	CD						
36	CD						
37	DC						
38	DC						
39	DC						
40	DC						
41	DC						
42	DC						
43	DC						
44	DC						
45	DC						
46	DC						
47	DC						
48	DC						
Mean		1.015	1.57	0.9984	1.021	1.135	0.9376
S.D.		0.08747	1.51	0.1061	0.09631	0.3375	0.2146
C.V.(%)		8.616	96.2	10.62	9.433	29.72	22.89
S.E.M.		0.01824	0.315	0.02212	0.02053	0.07195	0.04576
N		23.00	23.0	23.00	22.00	22.00	22.00
Minimum							
Maximum							

Ratio = Treatment C / Treatment D
C = 1 x 20 mg Fluoxetine Tablets
D = 1 x 20 mg Marketed Fluoxetine Capsules
* = Subject did not complete the study and was excluded from summary statistics.
. = Sample value missing or not reportable.

Lilly Research Laboratories
Protocol No. B1Y-LC-HCIS
Harris Laboratories Project 16760

Figure HCIS.4.27. Mean (S.D.) Plasma Norfluoxetine Concentrations (Linear Scale)



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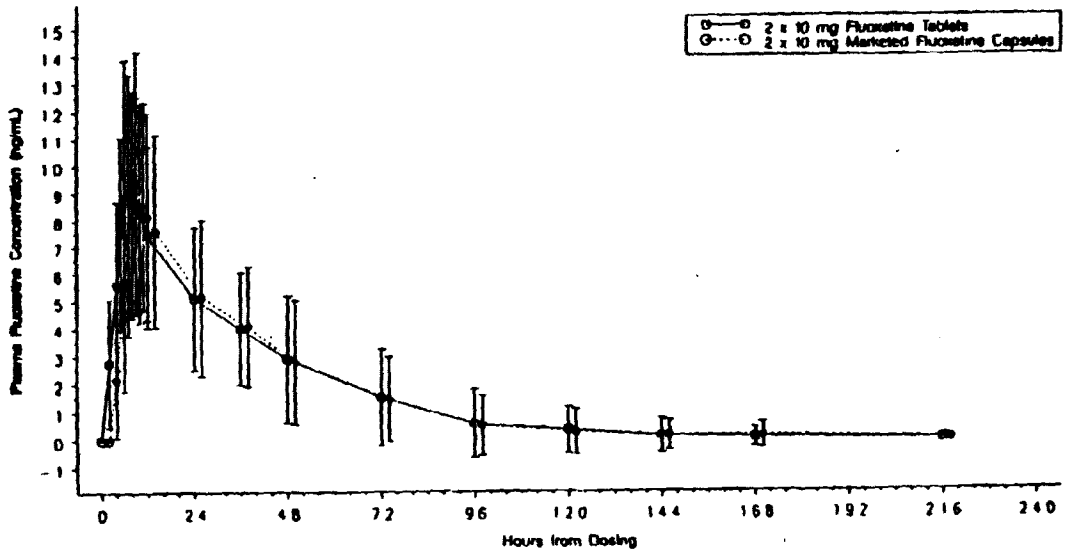
Harris Laboratories Project 18760

Figure HCIS.4.1. Mean (S.D.) Plasma Fluoxetine Concentrations (Linear Scale)



Treatment B is shifted to the right for ease of reading