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CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

NDA: 20-990  
DRUG: Sertraline HCl (Zoloft®)  
FORMULATION(S): 100 mg oral solution  
APPLICANT: Pfizer Pharmaceuticals  
FINAL REVIEW: 12/30/98

REVIEWER: Vanitha J. Sekar, Ph.D.  
TEAM LEADER: Chandra Sahajwalla, Ph.D.  
SUBMISSION DATE: April 15, 1998  
DRAFT REVIEW: 11/3/98

BACKGROUND

Sertraline hydrochloride (Zoloft®) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It is chemically unrelated to other SSRI's, tricyclic, tetracyclic, or other available antidepressant agents. Sertraline is supplied for oral administration as tablets containing 25 mg, 50 mg and 100 mg sertraline. It is indicated for the treatment of depression, obsessive compulsive disorder (OCD) and panic disorder. The recommended dose in adults for depression and OCD is 50 mg once daily. The recommended initial dose for panic disorder is 25 mg once daily for one week, followed by 50 mg once daily. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5-HT). The  $t_{1/2}$  of sertraline following once-daily dosing over the dose range of 50 mg – 200 mg per day for 14 days, is about 26 hours. The pharmacokinetics are dose-proportional over the dose range of 50-200 mg sertraline. Sertraline undergoes extensive first pass metabolism.; the primary metabolic pathway is N-demethylation. The primary metabolite, N-desmethylsertraline has a  $t_{1/2}$  of [redacted] and has been shown to be less active than sertraline. In a study with radiolabeled sertraline, about [redacted] of the administered radioactivity was recovered in the urine over 9 days; unchanged sertraline was not detected in the urine. Over the same time period [redacted] of the radioactivity was recovered in the feces, including [redacted] unchanged sertraline. Sertraline is highly bound to serum proteins (98%) in the range of [redacted]

SYNOPSIS

This NDA contains CMC and bioequivalence data to support an oral solution formulation of sertraline. Studies submitted to the Human Pharmacokinetics and Bioavailability section include: 1) a pilot bioequivalence (BE) study (050-027) comparing the currently approved 100 mg sertraline tablet to 100 mg of the oral concentrate, 2) a pivotal BE study (050-028) comparing the currently approved 100 mg sertraline tablet to 100 mg of the oral concentrate, and 3) a relative bioavailability study (with a food-effect component) comparing a 100 mg sertraline capsule formulation (not marketed) to 100 mg of the oral concentrate.

The oral solution of sertraline contains glycerin and ethyl alcohol as the vehicle system, menthol as the flavoring agent and a small quantity of butylated hydroxytoluene as an antioxidant. In a telecon held between the applicant and the Division of Neuropharm Drug Products, it was agreed that BE studies using the oral concentrate instead of the solution would be acceptable to demonstrate bioequivalence.

Study 050-027 was a pilot BE study ; the objective of this study was to compare the pharmacokinetics of a single 100 mg oral dose of sertraline administered as a tablet and as an oral solution diluted from a 20 mg/ml concentrate. It was a randomized, open-label, two period, crossover study in 12 healthy males. Bioequivalence of the test and reference formulations was assessed using 90% confidence intervals (CI) on the differences in mean LnAUC and Ln  $C_{max}$ . The data from this study failed to demonstrate that the 100 mg sertraline tablet is bioequivalent to the 100 mg sertraline oral solution (20 mg/ml).

Study 050-028 was a pivotal BE study for the oral sertraline solution. The study aimed to compare the pharmacokinetics of a single 100 mg oral dose of sertraline administered as a tablet and as an oral solution diluted from a 20 mg/ml concentrate. It was a randomized, open-label, two

period, crossover study in 20 healthy males (n=8) and females (n=12). Bioequivalence of the test and reference formulations was assessed using 90% confidence intervals (CI) on the differences in mean LnAUC and LnC<sub>max</sub>. The data from this study demonstrated that the 100 mg sertraline tablet is bioequivalent to the 100 mg sertraline oral solution (20 mg/ml) when all of subjects (n=20) were included in the analysis. However, when Subjects 13, 14, 17 and 18 were excluded from the analysis (recommendations from DSI), the oral solution was bioequivalent to the tablet with respect to AUC, but not with respect to C<sub>max</sub> (90% CI for C<sub>max</sub>: 114.9%, 126.4%)

Study 050-029 was designed to assess the relative bioavailability of the liquid concentrate and a capsule formulation (not marketed in the USA). It was a 3-way crossover study in 18 subjects designed to compare the pharmacokinetics of the liquid concentrate under fed and fasted conditions with those of the capsule under fasted conditions. Results failed to demonstrate the bioequivalence of the concentrate to the capsule. Statistical analysis indicated that the pharmacokinetics following a single 100 mg dose of sertraline oral solution are similar under fed and fasted conditions, suggesting that food does not affect the pharmacokinetics of sertraline oral solution. However, when 8 subjects (6, 9, 14, 16, 17, 18, 22, 23) were excluded from the analysis (recommendations from DSI), statistical analysis indicated that AUC for the oral solution in the fed state was slightly increased compared to the AUC in the fasted state. The slightly increased AUC observed for oral solution in the fed state compared to that in the fasted state is probably not clinically significant.

The applicant is planning to reevaluate the bioavailability of the oral solution relative to the capsule formulation in a 4 period, 2 treatment study under fasting conditions. The applicant plans to use a repeated measure design (solution→capsule→capsule→solution or capsule→solution→solution→capsule) to allow for the assessment of intra subject variability.

#### CONCLUSIONS AND RECOMMENDATIONS

The pivotal BE study failed to demonstrate bioequivalence between the oral sertraline solution and the marketed sertraline tablet. Statistical analysis indicated that the oral solution did not pass the bioequivalence criteria for C<sub>max</sub>. The clinical significance of the slightly increased C<sub>max</sub> observed following the oral solution compared to that following the tablet will be determined by the medical officer.

#### LABEL

A copy of the annotated package insert is attached.

APPROVED FOR  
ON ORIGINAL

#### COMMENTS TO APPLICANT:

1. Based on recommendations from the Division of Scientific Investigations, subjects 13, 14, 17 and 18 were excluded from the analysis (for Study 050-028). Analysis of the data showed that the oral solution failed bioequivalence criteria for C<sub>max</sub> (90% CI for C<sub>max</sub>: 114.9%, 126.4%). Therefore, we request that the sentence, "Zoloft Oral Concentrate has been determined to be bioequivalent to the tablet" be removed from the proposed label. Please add the following sentence in its place: "In a study comparing the pharmacokinetics of a 100 mg sertraline tablet to 100 mg of the oral solution in 16 healthy adults, the solution to tablet ratios for AUC and C<sub>max</sub> were 114.8% (90% CI=109.4, 120.6) and 120.6% (90% CI=114.9, 126.6), respectively.

**Study Title:** Study # 050-027: A Phase I, Study to Compare the Pharmacokinetics of a Single 100 mg Oral Dose of Sertraline Administered as a Tablet or as a Solution to Healthy, Male Volunteers.

**Study Objective:** The objective of this study was to compare the pharmacokinetics of a single 100 mg oral dose of sertraline administered as a tablet and as an oral solution diluted from a 20 mg/ml concentrate.

**Formulations:** Sertraline 100 mg tablets (Lot# ED-B-382-Z90), 100 mg solution (Lot# ED-O-358-Y93; diluted from a 20 mg/ml concentrate)

**Study Population:** This study was conducted in 12 healthy adult males between the ages of 18-28 years. Of these, ten subjects were Caucasian and two were Latin American.

**Study Design:** This study utilized a single-center, randomized, open-label, two period, crossover design. Each subject received a single 100 mg dose of each of the 2 treatments:

**Treatment A: Sertraline 100 mg (1x100 mg tablet): Reference or,**

**Treatment B: Sertraline 100 mg (diluted from a 20 mg/ml oral concentrate): Test**

There was a 14-day washout period between each dose administration. Subjects were randomly assigned to one of two sequences:

Group	No. of subjects	Period 1	Period 2
A	6	A	B
B	6	B	A

Subjects were fasted for a period of 8 hours prior to each dose administration and 4 hours post-dose; they maintained their normal diets throughout the study.

**Plasma Sample Collection for Sertraline Concentrations:** Blood samples for sertraline were drawn from each subject at the following times: 0 hr and at 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours following drug administration.

**Pharmacokinetic and Statistical Analysis:** Pharmacokinetic parameters were estimated by noncompartmental methods. The 100 mg solution (Trt. B) was the test formulation and the 100 mg tablet (Trt. A) was the reference formulation. Log-transformed AUC and C<sub>max</sub>, and untransformed T<sub>max</sub> and K<sub>el</sub> were analyzed using an analysis of variance (ANOVA) model for a

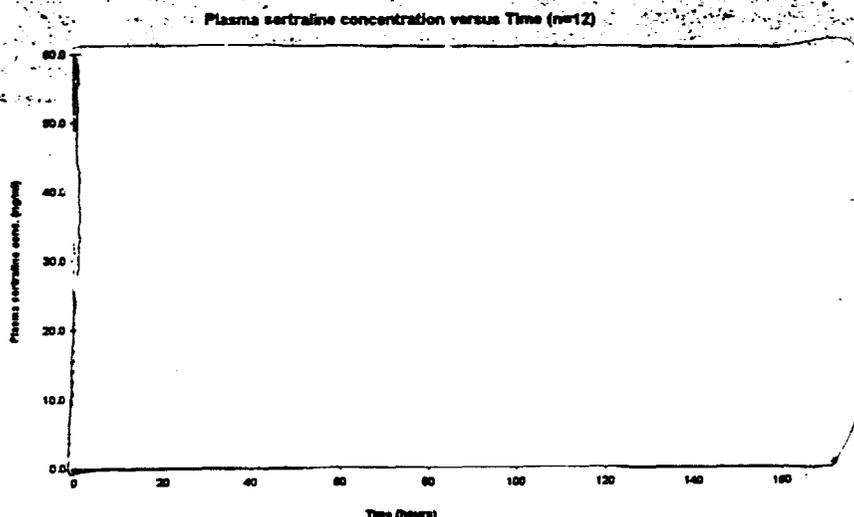
two period crossover at a significance level of 0.05 containing sequence, subject within sequence, period and treatment effect. Bioequivalence of the test and reference formulations was assessed using 90% confidence intervals (CI) on the differences in mean LnAUC and Ln  $C_{max}$ .

Mean pharmacokinetic parameters (n=12) and mean plasma concentration-time profile (n=12) for sertraline following administration of the 100 mg tablet and the solution are shown below.

Mean (SD) Pharmacokinetic Parameters (n=12)

PK Parameter	Oral Solution (100 mg)	Tablet (100 mg)	Ratio	90% Confidence Limits
AUC (ng.h/ml) <sup>a</sup>	938 (322)	829 (352)	113.1%	(99.5%, 128.7%): Fail
C <sub>max</sub> (ng/ml) <sup>a</sup>	37.0 (11.0)	28.9 (8.2)	128.1%	(110.2%, 149.0%): Fail
T <sub>max</sub> (h) <sup>b</sup>	7.5 (1.7)	7.0 (1.3)	0.5 (difference)	(96%, 118%)
K <sub>el</sub> (1/h) <sup>b</sup>	0.0348 (0.0089)	0.0346 (0.0089)	0.0002 (difference)	(91.3%, 110.5%)

<sup>a</sup> geometric mean      <sup>b</sup> arithmetic mean



The statistical analysis indicated that there was no significant sequence or period effect for AUC<sub>0-∞</sub>, C<sub>max</sub>, T<sub>max</sub> or K<sub>el</sub>. There was a statistically significant treatment effect for treatment for C<sub>max</sub> (p=0.014). There were no significant treatment effects for T<sub>max</sub> and K<sub>el</sub>. The 90% CI for differences in the log transformed AUC<sub>0-∞</sub> and C<sub>max</sub> between test and reference were outside of the (0.8-1.25) goal post.

Following the inspections by the Division of Scientific Investigations, a Form 483 was issued at the analytical site. Based on the findings of the Division of Scientific Investigations, the following recommendations were made for this study:

- 1) Data from Subject 5, Period 2 be excluded from the analysis for bioequivalence determinations,
- 2) Data from Subject 9, Period 1 and 2 be excluded from the analysis for bioequivalence determinations,
- 3) Data from Subject 1, Period 1 and 2 be excluded from the analysis for bioequivalence determinations,
- 4) Data from Subject 2, Period 1 be excluded from the analysis for bioequivalence determinations.

The data from Subjects 1, 2, 5 and 9 from both periods 1 and 2 were excluded (so that data are balanced) and the analysis was performed by this reviewer using SAS. Log-transformed AUC and C<sub>max</sub>, and untransformed T<sub>max</sub> and K<sub>el</sub> were analyzed using an ANOVA model for a two period

crossover at a significance level of 0.05 containing sequence, subject within sequence, period and treatment effect. Bioequivalence of the test and reference formulations was assessed using 90% confidence intervals (CI) on the differences in mean LnAUC and Ln C<sub>max</sub>. Statistical analysis using 8 subjects yielded significant differences between treatments for AUC<sub>0-</sub> (p=0.042), C<sub>max</sub> (p=0.028) and T<sub>max</sub> (p=0.0007). The 90% CI for differences in the log transformed AUC<sub>0-</sub> and C<sub>max</sub> between test and reference were outside of the [ ] goal post. Mean pharmacokinetic parameters (n=8) and mean plasma concentration-time profile (n=8) are shown below.

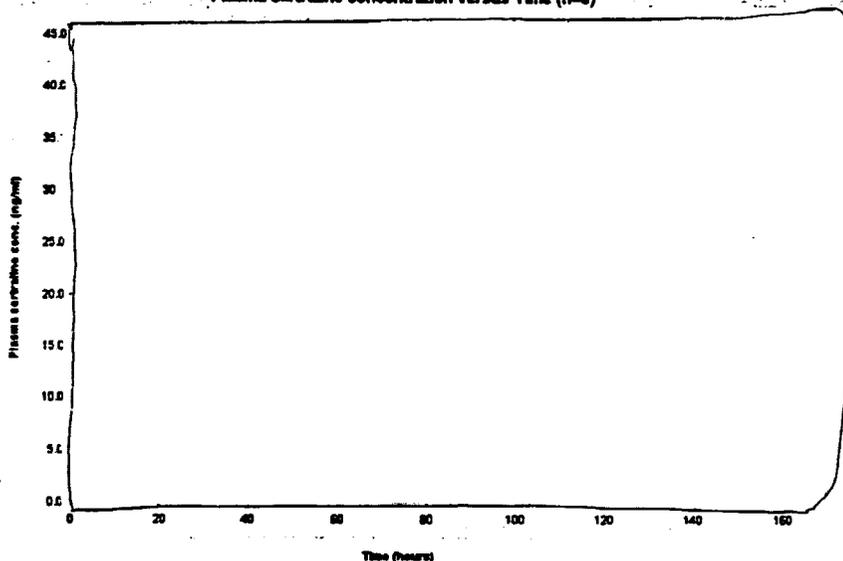
Mean (SD) Pharmacokinetic Parameters (n=8)

PK Parameter	Oral Solution (100 mg)	Tablet (100 mg)	Ratio	90% Confidence Limits
AUC (ng.h/ml) <sup>a</sup>	982 (357)	820(377)	119.7%	(109.2%, 139.6%): Fail
C <sub>max</sub> (ng/ml) <sup>a</sup>	36 (6)	28 (8)	128.9%	(106.4%, 134.9%): Fail
T <sub>max</sub> (h) <sup>b</sup>	8 (2)	7 (1)	1.0 (difference)	(115.4%, 126.5%)
Kel (1/h) <sup>c</sup>	0.0349 (0.0102)	0.0358 (0.0070)	-0.0009 (difference)	(84.1%, 111.7%)

<sup>a</sup>geometric mean

<sup>b</sup>arithmetic mean

Plasma sertraline concentration versus Time (n=8)



**Adverse Events:** The majority of the adverse events reported in this study involved the gastrointestinal (nausea, diarrhea, vomiting), and nervous systems (dizziness, headache, nervousness). No subject discontinued the study due to a side effect and no serious adverse events were reported.

**Conclusion:** The data from this study failed to demonstrate that the 100 mg sertraline tablet is bioequivalent to the 100 mg sertraline oral solution (20 mg/ml).

Individual Plasma Sertraline Concentrations: Trt A, Reference (100 mg tablet)

Subject	Period	Plasma Sertraline Concentration (ng/ml) at time															
		0	1	2	4	6	8	12	16	24	36	48	72	96	120	144	
1	2																
2	2																
3	1																
4	1																
5	2																
6	1																
7	2																
8	1																
9	2																
10	1																
11	1																
12	2																
Mean		0.0	0.5	6.0	18.4	28.0	28.5	21.8	18.6	13.6	9.1	5.8	3.1	1.3	0.5	0.1	
SD		0	0.8	4.7	8.7	7.4	8.1	7.0	7.2	5.3	4.1	3.3	1.8	1.2	0.6	0.3	
%COV			155.7	78.1	47.3	26.4	28.4	31.9	38.7	38.8	45.1	57.3	59.3	92.6	147.8	346.4	

Individual Plasma Sertraline Concentrations: Trt B; Test, 100 mg oral solution

Subject	Period	Plasma Sertraline Concentration (ng/ml) at time															
		0	1	2	4	6	8	12	16	24	36	48	72	96	120	144	
1	1																
2	1																
3	2																
4	2																
5	1																
6	2																
7	1																
8	2																
9	1																
10	2																
11	2																
12	1																
Mean		0.0	3.3	15.7	28.2	36.1	33.8	24.5	20.1	14.2	9.7	6.0	2.9	1.5	0.6	0.2	
SD		0	1.8	8.1	6.6	14.4	6.8	6.8	6.2	4.7	4.1	2.8	2.0	1.4	0.8	0.4	
%COV			54.9	51.9	23.4	40.1	20.1	27.9	30.9	33.0	42.6	45.8	66.7	96.1	149.2	233.8	

Individual Pharmacokinetic Parameters

Subject	AUC (ng.h/ml)		Cmax (ng/ml)		Tmax (hr)		Kel (1/hr)		T1/2 (hr)	
	solution	tablet	solution	tablet	solution	tablet	solution	tablet	solution	tablet
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean	989	896	39	30	8	7	0	0	21	21
SD	338	344	14	8	2	1	0	0	5	5
%COV	34	38	36	26	23	19	25	20	25	22

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**Study Title:** Study # 050-028: A Phase I, Study to Compare the Pharmacokinetics of a Single 100 mg Oral Dose of Sertraline Administered as a Tablet or a Solution to Healthy Male/Females.

**Study Objective:** The objective of this study was to compare the pharmacokinetics of a single 100 mg oral dose of sertraline administered as a tablet and as an oral solution diluted from a 20 mg/ml concentrate.

**Formulations:** Sertraline 100 mg tablets (Lot# ED-B-382-Z90), 100 mg solution (Lot# ED-O-113-494; diluted from a 20 mg/ml concentrate)

**Study Population:** This study was conducted in 20 healthy adult males (n=8) and females (n=12) between the ages of 19-38 years. Of these, 13 subjects were Caucasian and 1 Black, 1 Latin American and 1 was Hispanic.

**Study Design:** This study utilized a single-center, randomized, open-label, two period, crossover design. Each subject received a single 100 mg dose of each of the 2 treatments:

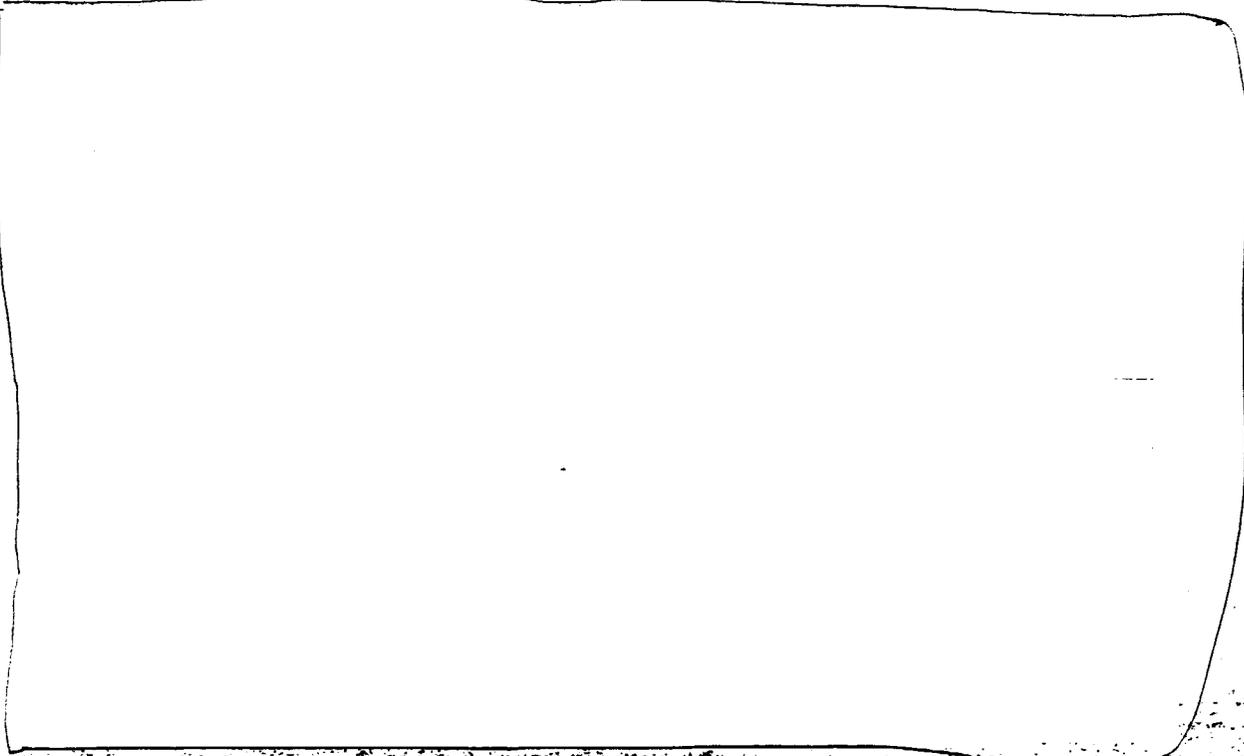
**Treatment A:** Sertraline 100 mg (1x100 mg tablet): Reference or,

**Treatment B:** Sertraline 100 mg (diluted from a 20 mg/ml oral concentrate): Test

There was a 14-day washout period between each dose administration. Subjects were randomly assigned to one of two sequences:

Group	No. of subjects	Period 1	Period 2
A	6	A	B
B	6	B	A

Subjects were fasted for a period of 8 hours prior to each dose administration and 4 hours post-dose; they maintained their normal diets throughout the study.



**Pharmacokinetic and Statistical Analysis:** Pharmacokinetic parameters were estimated by noncompartmental methods. The 100 mg solution (Trt. B) was the test formulation and the 100 mg tablet (Trt. A) was the reference formulation. Log-transformed AUC and  $C_{max}$ , and untransformed  $T_{max}$  and  $K_{el}$  were analyzed using an analysis of variance (ANOVA) model for a

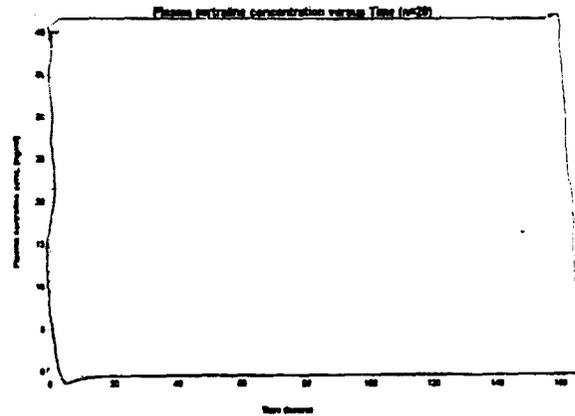
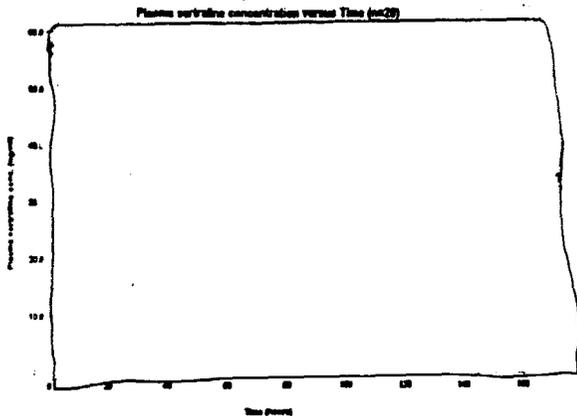
two period crossover at a significance level of 0.05 containing sequence, subject within sequence, period and treatment effect. Bioequivalence of the test and reference formulations was assessed using 90% confidence intervals (CI) on the differences in mean LnAUC and Ln C<sub>max</sub>.

Mean pharmacokinetic parameters (n=20) and mean plasma concentration-time profile (n=20) for sertraline following administration of the 100 mg tablet and the solution are shown below.

Mean (SD) Pharmacokinetic Parameters (n=20)

PK Parameter	Oral Solution (100 mg)			Tablet (100 mg)			Ratio (n=20)	90% Confidence Limits (n=20)
	Males (n=8)	Females (n=12)	Pooled (n=20)	Males (n=8)	Females (n=12)	Pooled (n=20)		
AUC (ng.h/ml) <sup>a</sup>	802 (249)	841 (345)	825 (304)	705 (161)	765 (284)	740 (241)	111.4%	(105.8%, 117.3%)
C <sub>max</sub> (ng/ml) <sup>a</sup>	30 (6)	39 (13)	35 (12)	25 (4)	33 (11)	30 (10)	118.4%	(113.4%, 123.6%)
T <sub>max</sub> (h) <sup>b</sup>	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)	6 (1)	1.0 (difference)	(79.2, 100.1)
K <sub>el</sub> (1/h) <sup>b</sup>	0.0312 (0.0038)	0.0352 (0.0097)	0.0336 (0.008)	0.0350 (0.0097)	0.0318 (0.0076)	0.0325 (0.0073)	0.0011 (difference)	(92.3, 114.4)

<sup>a</sup>geometric mean      <sup>b</sup>arithmetic mean



Although no formal statistical analysis was performed to assess gender effects, plasma concentrations of sertraline following administration of both, the solution as well as the tablet, appeared to be higher in females compared to males. The statistical analysis on LnAUC indicated that there was a significant sequence (p=0.001) and period effect (p=0.04). For LnC<sub>max</sub>, there was a statistically significant sequence effect (p=0.02). The analysis also yielded significant differences between treatments for AUC<sub>0-∞</sub> (p=0.0018), and C<sub>max</sub> (p=0.0001). The 90% CI for differences in the log transformed AUC<sub>0-∞</sub> and C<sub>max</sub> between test and reference were within the (0.8-1.25) goal post. Based on the statistical analysis for AUC and C<sub>max</sub>, the two formulations were bioequivalent.

Following the inspections by the Division of Scientific Investigations, a Form 483 was issued at the analytical site. Based on the findings of the Division of Scientific Investigations, the following recommendations were made for this study:

- 1) Data from Subject 13 and 18, Periods 1 and 2 be excluded from the analysis for bioequivalence determinations (due to unacceptable QC results),
- 2) Data from Subject 14, Period 1 be excluded from the analysis for bioequivalence determinations (due to unacceptable QC results),
- 3) Data from Subject 17, Period 2 be excluded from the analysis for bioequivalence determinations (due to unacceptable QC results),
- 4) The conclusions drawn from study 057-028 should take into consideration that the accuracy of the reported sertraline concentrations could not be confirmed since the firm failed to

document preparation of standards and QC's and to verify the amount of sertraline weighed for the preparation of stock solutions.

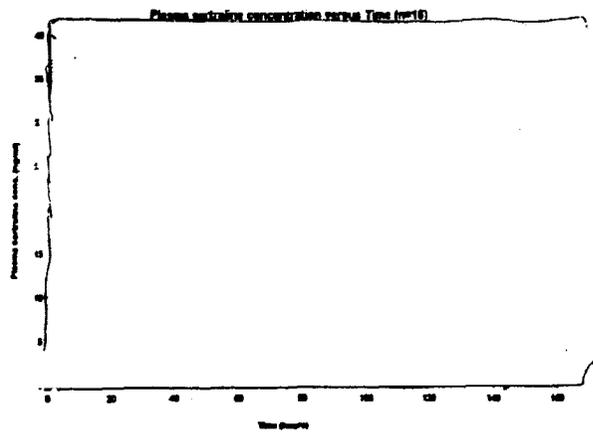
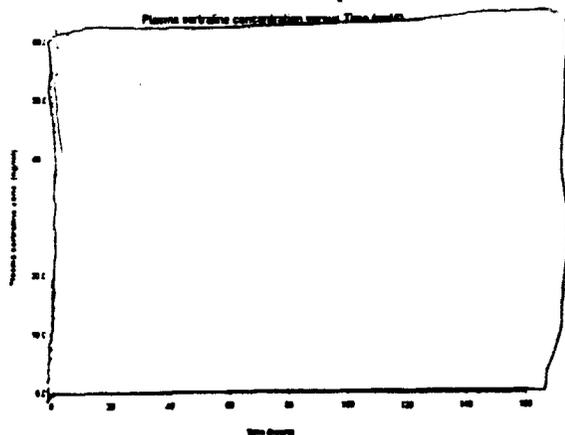
The data from Subjects 13, 14, 17 and 18 from both periods 1 and 2 were excluded (so that data are balanced) and the analysis was performed by the reviewer. Log-transformed AUC and  $C_{max}$ , and untransformed  $T_{max}$  and  $K_{el}$  were analyzed using an ANOVA model for a two period crossover at a significance level of 0.05 containing sequence, subject within sequence, period and treatment effect. Bioequivalence of the test and reference formulations was assessed using 90% confidence intervals (CI) on the differences in mean LnAUC and Ln  $C_{max}$ . Statistical analysis using 16 subjects yielded significant differences between treatments for  $AUC_{0-}$  ( $p=0.0002$ ) and  $C_{max}$  ( $p=0.0001$ ). For LnAUC, there was a significant sequence ( $p=0.0009$ ) and period effect ( $p=0.004$ ). For Ln  $C_{max}$ , there was a statistically significant period effect ( $p=0.04$ ). The 90% CI for differences in the log transformed  $C_{max}$  between test and reference was slightly outside of the (0.8-1.25) goal post for the oral solution (114.9, 126.4). Mean pharmacokinetic parameters ( $n=8$ ) and mean plasma concentration-time profile ( $n=8$ ) are shown below.

Mean (SD) Pharmacokinetic Parameters ( $n=16$ )

PK Parameter	Oral Solution (100 mg)			Tablet (100 mg)			Ratio ( $n=16$ )	90% Confidence Limits ( $n=16$ )
	Males ( $n=7$ )	Females ( $n=9$ )	Pooled ( $n=16$ )	Males ( $n=7$ )	Females ( $n=9$ )	Pooled ( $n=16$ )		
$AUC$ (ng.h/ml) <sup>a</sup>	774 (256)	855 (376)	818 (324)	673 (133)	746 (299)	713 (240)	1.148%	(109.4, 120.6)
$C_{max}$ (ng/ml) <sup>a</sup>	29 (7)	39 (15)	34 (13)	25 (4)	32 (12)	28 (10)	1.206%	(114.9, 126.4)
$T_{max}$ (h) <sup>b</sup>	5 (1)	5 (1)	5 (1)	7 (1)	5 (1)	6 (1)	1.0 (difference)	(74.0, 100.4)
$K_{el}$ (1/h) <sup>b</sup>	0.0319 (0.0034)	0.0348 (0.0088)	0.0335 (0.0070)	0.0337 (0.0077)	0.0344 (0.0052)	0.0341 (0.0061)	0.0003	(88.2, 108.2)

<sup>a</sup> geometric mean

<sup>b</sup> arithmetic mean



**Adverse Events:** The majority of the adverse events reported in this study involved the gastrointestinal (nausea, diarrhea, vomiting), and nervous systems (dizziness, headache, nervousness). No subject discontinued the study due to a side effect and no serious adverse events were reported.

**Conclusions:** The data from this study demonstrated that the 100 mg sertraline tablet is bioequivalent to the 100 mg sertraline oral solution (20 mg/ml) when all of subjects ( $n=20$ ) were included in the analysis. However, when Subjects 13, 14, 17 and 18 were excluded from the analysis (recommendations from DSI), statistical analysis indicated that the oral solution was bioequivalent to the tablet with respect to AUC, but not with respect to  $C_{max}$ . The slightly increased  $C_{max}$  observed following the oral solution compared to that following the tablet is probably not clinically significant.



**Study Title:** Study # 050-029: A Phase I, Open Label Study to Compare the Pharmacokinetics of a Single 100 mg Oral Dose of Sertraline Administered as a Capsule Under Fasting Conditions or as a Solution Under Fed and Fasted Conditions in Healthy, Male or Female Volunteers.

**Study Objective:** The objective of this study was to compare the pharmacokinetics of a single 100 mg oral dose of sertraline administered as a capsule under fasting conditions and as an oral concentrate solution under both, fed and fasting conditions.

**Formulations:** Sertraline 100 mg capsule (Lot# 402-72071), 100 mg solution (Lot# ED-O-113-494).

**Study Population:** This study was conducted in 20 healthy adult males (n=6) and females (n=14), of which 17 completed the study and 18 were included in the pharmacokinetic analysis. Subjects were between the ages of 18-44 years. Of the 20 subjects, sixteen were Caucasian and four were Hispanic.

**Study Design:** This study utilized a single-center, open label, randomized, open-label, three period, crossover design. Each subject received a single 100 mg dose of each of the 3 treatments:

**Treatment A: Sertraline 100 mg solution (Fasting)**

**Treatment B: Sertraline 100 mg solution (Fed)**

**Treatment C: Sertraline 100 mg capsule (1x100 mg capsule)**

There was a 14-day washout period between each dose administration. Subjects were randomly assigned to one of 6 sequences:

Sequence	No. of subjects	Period 1	Period 2	Period 3
A	3	C	A	B
B	3	C	B	A
C	3	A	C	B
D	3	B	C	A
E	3	A	B	C
F	3	B	A	C

The 100 mg capsule was to be administered under fasting conditions. The 100 mg oral solution was to be administered under both, fed and fasting conditions. For the fasted condition, subjects were to be fasted for 8 hours prior to the morning of sertraline dosing; for the fed condition, subjects were to be fasted for 8 hours prior to ingesting a standard breakfast which was eaten just prior to dosing. The standard breakfast was to be completely consumed over 20 minutes and was to consist of 2 eggs fried in butter, 2 strips of bacon, 6 oz. of hash brown potatoes, 2 pieces of toast with 2 pats of butter, and 8 oz. of whole milk. The sertraline oral solution was to be administered immediately after consumption of the breakfast.

**Plasma Sample Collection for Sertraline Concentrations:** Blood samples for sertraline were drawn from each subject at the following times: 0 hr and at 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, and 120 hours following drug administration.

**Pharmacokinetic and Statistical Analysis:** Pharmacokinetic parameters were estimated by noncompartmental methods. Log-transformed AUC and C<sub>max</sub>, and untransformed T<sub>max</sub> and K<sub>el</sub> were analyzed using an analysis of variance (ANOVA) model for a 3 period crossover at a significance level of 0.05 containing sequence, subject within sequence, period and treatment effect. Bioequivalence of the test and reference formulations was assessed using 90% confidence intervals (CI) on the differences in mean LnAUC and LnC<sub>max</sub>.

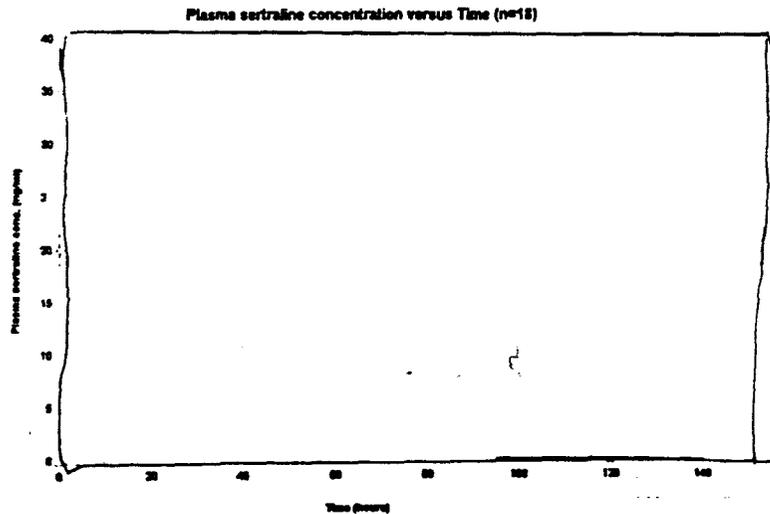
Mean pharmacokinetic parameters (n=18) and mean plasma concentration-time profile (n=18) for sertraline following administration of the 100 mg capsule and the solution (fed and fasted) are shown below.

Mean (SD) Pharmacokinetic Parameters (n=18)

PK Parameter	A: Solution (fasting)	B: Solution (Fed)	C: Capsule (fasting)	Ratios	90% Confidence Limits
AUC (ng.h/ml) <sup>a</sup>	803.3 (322)	837.3 (381)	694.4 (288)	A/C = 115.7% B/A = 104.2%	(104.9%, 127.6%): FAIL (94.5%, 114.9%): PASS
C <sub>max</sub> (ng/ml) <sup>a</sup>	31.8 (9.2)	32.5 (11.2)	27.0 (8.6)	A/C = 118.1% B/A = 101.9%	(108.8%, 128.1%): FAIL (93.9%, 110.6%): PASS
T <sub>max</sub> (h) <sup>b</sup>	5.9 (1.0)	7.0 (1.7)	6.8 (1.2)	A-C = -0.9 B-A = 1.1	(75.6%, 98.1%) (106%, 132.1%)
K <sub>el</sub> (1/h) <sup>b</sup>	0.0336 (0.0090)	0.0350 (0.0095)	0.0362 (0.0164)	A-C = -0.0026 B-A = 0.0014	(77.1%, 108.4%) (87.3%, 121%)

<sup>a</sup> geometric mean

<sup>b</sup> arithmetic mean



Although no formal statistical analysis was performed to assess gender effects, plasma concentrations of sertraline following administration of both, the solution as well as the capsule, appeared to be higher in females compared to males. The variability was also higher in females compared to males. Mean (SD) pharmacokinetic parameters for males and females are shown below:

PK Parameter	Oral Solution (100 mg; fed)		Oral Solution (100 mg; fasted)		Capsule (100 mg)	
	Males (n=6)	Females (n=12)	Males (n=6)	Females (n=12)	Males (n=6)	Females (n=12)
AUC (ng.h/ml) <sup>a</sup>	671 (110)	935 (720)	637 (140)	902 (477)	603 (228)	746 (459)
C <sub>max</sub> (ng/ml) <sup>a</sup>	26 (4)	36 (19)	26 (9)	35 (10)	21 (8)	30 (8)
T <sub>max</sub> (h) <sup>a</sup>	7 (2)	7 (2)	6 (1)	6 (1)	7 (1)	7 (1)
K <sub>el</sub> (1/h) <sup>b</sup>	0.0373 (0.0065)	0.0338 (0.0112)	0.0388 (0.0088)	0.0310 (0.0087)	0.0337 (0.0076)	0.0374 (0.0202)

The statistical analysis indicated that there a statistically significant treatment effect for LnAUC (p=0.0071) and C<sub>max</sub> (p=0.0008). The 90% CI for differences of the ratios of the means for both AUC and C<sub>max</sub> were outside of the (0.8-1.25) goal post when the capsule was compared to the oral solution under fasted conditions. This study failed to demonstrate bioequivalence of the 100 mg capsule to the 100 mg solution. The 90% CI for differences in the log transformed AUC<sub>0-∞</sub> and C<sub>max</sub> were within the (0.8-1.25) goal post when the oral solution was compared in fed and fasted state. Food does not appear to affect the pharmacokinetics of sertraline oral solution following a single dose of 100 mg.

Following the inspections by the Division of Scientific Investigations of the clinical and analytical sites (Pharmaco LSR, Austin, TX), a Form 483 was issued at both sites. Based on the findings of the Division of Scientific Investigations, the following recommendations were made for this study: 1) Nine subjects out of 20 (subjects 6, 9, 11, 14, 16, 17, 18, 22, 23) who did not meet the inclusion/exclusion criteria were enrolled into the study without sponsor approval. DSI recommends that the impact of this finding should be evaluated by the OCPB reviewer.

The data from Subjects 6, 9, 11, 14, 16, 17, 18, 22, and 23 were excluded and the analysis was performed by this reviewer using SAS. Log-transformed AUC and C<sub>max</sub>, and untransformed Tmax and Kel were analyzed using an ANOVA model for a 3 period crossover at a significance level of 0.05 containing sequence, subject within sequence, period and treatment effect. Bioequivalence was assessed using 90% confidence intervals (CI) on the differences in mean LnAUC and Ln C<sub>max</sub>. Statistical analysis using 10 subjects yielded significant differences between treatments LnC<sub>max</sub> (p=0.02). The 90% CI for differences of the ratios of the means for both AUC and C<sub>max</sub> were outside of the (0.8-1.25) goal post when the capsule was compared to the oral solution under fasted conditions. Bioequivalence of the 100 mg capsule to the 100 mg solution was not demonstrated in this smaller subset of subjects. The 90% CI for differences in the log transformed AUC (91.3%, 126.3%) was slightly outside the (0.8-1.25) goal post when the oral solution was compared in fed and fasted state. Mean pharmacokinetic parameters (n=10) and mean plasma concentration-time profile (n=10) are shown below.

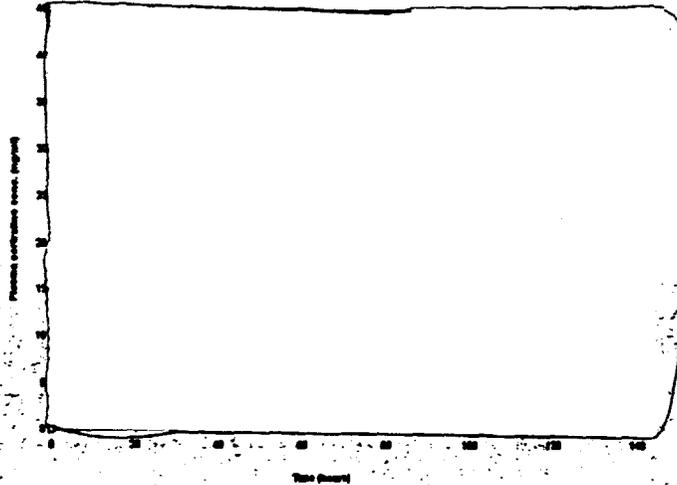
Mean (SD) Pharmacokinetic Parameters (n=10)

PK Parameter	A: Solution (fasting)	B: Solution (Fed)	C: Capsule (fasting)	Ratios	90% Confidence Limits
AUC (ng.h/ml) <sup>a</sup>	899 (524)	969 (767)	755 (515)	A/C = 119.1% B/A = 107.7%	(100.4%, 138.8%): FAIL (91.3%, 126.3%): FAIL
C <sub>max</sub> (ng/ml) <sup>a</sup>	35 (12)	37 (20)	29 (10)	A/C = 122.8% B/A = 106.4%	(105.2%, 136.8%): FAIL (91.8%, 119.4%): PASS
T <sub>max</sub> (h) <sup>a</sup>	6 (1)	6 (1)	7 (1)	A-C = -1.129 B-A = 0.685	(72.3%, 94.5%) (82.4%, 104.6%)
K <sub>el</sub> (1/h) <sup>b</sup>	0.0339 (0.0105)	0.0336 (0.0089)	0.0392 (0.0218)	A-C = -0.0056 B-A = 0.0002	(60.9%, 111.0%) (70.3%, 128.6%)

<sup>a</sup> geometric mean.

<sup>b</sup> arithmetic mean

Plasma sertraline concentration versus Time (hr)



**Adverse Events:** The majority of the adverse events reported in this study involved the gastrointestinal (nausea, diarrhea), and nervous systems (somnolence, dizziness, anorexia). No serious adverse events were reported. Two subjects discontinued from the study on the first day of dosing due to side effects, both after receiving sertraline solution under fed state. One subject discontinued due to a vasovagal episode (unrelated to study drug) and the other subject discontinued due to vomiting (related to study drug). One subject who completed all three study periods did not return for his last visit and was lost to follow-up.

**Conclusions:** The data from this study demonstrated that the 100 mg sertraline capsule is not bioequivalent to the 100 mg sertraline oral solution. Statistical analysis indicated that the pharmacokinetics following a single 100 mg dose of sertraline oral solution are similar under fed and fasted conditions, suggesting that food does affect the pharmacokinetics of sertraline oral solution. However, when 8 subjects (6, 9, 14, 16, 17, 18, 22, 23) were excluded from the analysis (recommendations from DSI), statistical analysis indicated that AUC for the oral solution in the fed state was slightly increased compared to the AUC in the fasted state. The slightly increased AUC observed for oral solution in the fed state compared to the fasted state is probably not clinically significant.

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Individual Pharmacokinetic Parameters

Subject	Gender	Weight (kg)	Sequence	AUC (ng.h/ml)			C <sub>max</sub> (ng/ml)			T <sub>max</sub> (hr)			K <sub>el</sub> (1/hr)			
				solution (fed)	solution (fasted)	capsule (fasted)	solution (fed)	solution (fasted)	capsule (fasted)	solution (fed)	solution (fasted)	capsule (fasted)	solution (fed)	solution (fasted)	capsule (fasted)	
2 F		52.3	C													
4 F		55.5	D													
5 F		56.8	A													
6 F		70.8														
7 F		57.8	B													
9 F		63.6	E													
10 F		64.6	F													
12 F		51.1	A													
14 F		70.9	B													
15 F		66.4	F													
17 F		68.1	C													
23 F		68.1	D													
1 M		74.3	E													
8 M		77.3	C													
13 M		64.1	E													
16 M		62.7	D													
18 M		69.1	A													
22 M		67.9	F													
Mean				837	803	895	32	32	27	7	6	7	0.0260	0.0336	0.0362	
SD				613	424	400	16	11	9	2	1	1	0.0098	0.0093	0.0169	
%COV				73	53	58	51	33	34	24	18	18	28	28	28	47

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/S/ 12/30/98

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