

NONPRESCRIPTION DRUGS  
ADVISORY COMMITTEE AND  
ARTHRITIS ADVISORY  
COMMITTEE

JULY 20, 1999

NDA 21070 FLEXERIL OTC  
SWITCH

PHARMACOKINETICS REVIEW  
(CLINICAL PHARMACOLOGY/  
BIOPHARMACEUTICS REVIEW)

## CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

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**NDA:** 21-070 **SUBMISSION DATE:** 12/18/98  
**PRODUCT:** Flexeril 5 mg Tablets (cyclobenzaprine HCl) 01/18/99, 5/10/99, 06/09/99  
**SPONSOR:** Merck & Co.  
Sumneytown Pike, P.O. Box 4, BLA-33  
West Point, PA 19486  
**TYPE OF SUBMISSION:** Original Submission **REVIEWER:** Sue-Chih Lee, Ph.D.

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### SYNOPSIS

Flexeril MR 5 mg Tablets are intended to be an OTC product for the treatment of acute painful muscle spasm or strain of the back or neck. The higher strength (10 mg) tablet was approved for use by the Agency in 1977 as a prescription-only product (NDA 17-821) for similar indications. To support this NDA, the sponsor conducted four new pharmacokinetic studies (single- and multiple-dose pharmacokinetics and dose proportionality; PK in hepatic impairment patients; PK in elderly subjects and a bioavailability/bioequivalence study). In addition, more than 20 literature articles and study reports were provided, of which the studies related to cyclobenzaprine metabolism and drug-drug interactions are considered most relevant. Food effect study will be conducted as Phase IV. It should be noted that clinical efficacy and safety studies were conducted without regard to the timing of meals.

### NOTE TO THE ADVISORY COMMITTEE

The sponsor has not fully responded to our most recent comments, the new information when submitted will be evaluated and may affect some sections of this review.

### COMMENTS

1. Re: Study 010 (Elderly subjects)
  - a. There are errors in the data (Tables 3, 4, 5 & 6; Volume 1.8, pp. 464-467), most likely due to errors in data for healthy subjects. The sponsor should revise and submit the corrected analysis. The comparison both including and excluding the 2 elderly subjects who fell ill during the study should be provided.
  - b. Two elderly patients who fell ill had unusually high plasma cyclobenzaprine concentrations. The sponsor claimed that the high concentrations found in these 2 subjects were due to binding of cyclobenzaprine to  $\alpha_1$ -acid glycoprotein. Data on plasma  $\alpha_1$ -acid glycoprotein levels for several elderly subjects were provided to support this speculation. However, it is unclear that the sponsor has data to show that cyclobenzaprine does bind to  $\alpha_1$ -acid glycoprotein.
  - c. Mean plasma concentrations in healthy elderly subjects were in the same range as those previously observed in young subjects receiving the prescription dose of 10 mg every 8

hours. This would mean that a reduced dose may be more appropriate for the elderly patients.

d. The mean body weight of elderly subjects in this study is higher than that of healthy subjects in Study 005. If the body weight were the same, the difference in plasma concentrations between elderly and young subjects may be even greater.

2. Re: Study 007 (Hepatic impairment patients)

- a. Subjects were matched for age but not smoking. Since CYP1A2 may be involved in the metabolism of cyclobenzaprine, smoking may be a confounding factor.
- b. Because only one patient in this study had moderate hepatic impairment, this is basically a study in mild hepatic impairment patients. Based on the current analysis, it would be more appropriate to reduce dose in this patient group. There is little or no PK information in patients with moderate or severe hepatic impairment.

3. Re: Effect of gender

Studies 005 and 011 suggested there were gender differences in cyclobenzaprine AUC and C<sub>max</sub> that could not be accounted for by body weight differences. Based on across-study analysis of three multiple dose studies (#005, 010 and 007), the sponsor concludes that the magnitude of any difference in cyclobenzaprine pharmacokinetics between males and females is small relative to intersubject variability. However, the variability may be partly attributed to body weight differences. The sponsor should reanalyze the data of studies 005 and 011 using both gender and weight as covariates, and provide a scatter plot (along with a data table) for studies 005, 010 and 007 using body weight normalized parameters. This will provide a better picture to see if female subjects with low body weight will have significantly higher plasma cyclobenzaprine concentrations.

4. Re: Metabolism of cyclobenzaprine

- a. The sponsor conducted in vitro studies and concluded that N-demethylation of cyclobenzaprine is mediated primarily via CYP3A4 and 1A2, with CYP2D6 playing only a minor role. Therefore, genetic polymorphism should not be a concern for this drug. These studies were carried out at a cyclobenzaprine concentration of 100  $\mu$ M (or 31.2  $\mu$ g/mL; near the K<sub>m</sub> value for N-demethylation), which is more than 2000-fold of the peak plasma concentrations of cyclobenzaprine at steady state. (Mean steady state C<sub>max</sub> after 5 mg tid dosing was  $\leq$ 15 ng/mL.) Therefore, the conclusion may not be applicable at clinically relevant concentrations. Other studies such as in vivo drug interaction studies with specific inhibitors of CYP isozymes may be needed to provide conclusive evidence of the importance of specific isozymes.
- b. From the literature provided, it is unclear whether the major metabolic pathway is through N-demethylation. It is noted that the recovery of total (urine + feces) radioactivity in a mass balance study was low (~64% of dose) and a major urinary metabolite was not identified. Thus, the information submitted does not provide a clear picture of metabolite profiles of cyclobenzaprine.

5. Re: Drug-drug interaction
  - a. The sponsor conducted in vitro studies and concluded that cyclobenzaprine has a low potential to inhibit metabolism of other drugs because of the high  $K_i$  values observed. However, the study report as provided in the NDA submission is too brief to afford a thorough review. The sponsor has been requested to provide a detailed study report.
  - b. Since it is unclear which isozyme actually plays a major role in the metabolism of cyclobenzaprine at the clinically relevant concentrations, it is not possible to predict drug-drug interaction potentials.
6. Re: Dissolution

Based on the dissolution profiles provided of three batches, the dissolution specification should be tightened. This issue will be discussed with the Chemist before it is conveyed to the sponsor.
7. The sponsor contended that while plasma levels increased in the first four days before steady state was reached, somnolence generally occurred in the first few days after treatment began, was mild, and resolved despite continued treatment. This statement should be evaluated by the Medical Officer.

#### RECOMMENDATION

From the standpoint of clinical pharmacology and biopharmaceutics, the submission is acceptable provided that the above issues are addressed satisfactorily. Please convey Comment #7 to the Medical Officer. Comments #1-6 should be communicated to the sponsor.

Sue-Chih Lee, Ph.D.  
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Dennis Bashaw, Pharm.D. \_\_\_\_\_

CC:  
NDA 21-070  
HFD-550 (Div.File)  
HFD-550 (CSO/Schmidt)  
HFD-880 (Bashaw)  
HFD-880 (Lazor)  
HFD-880 (Lee)  
HFD-870 (attn: CDR. Barbara Murphy)  
HFD-344 (Viswanathan)

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## **I. BACKGROUND**

Cyclobenzaprine hydrochloride is structurally related to several tricyclic antidepressants. It is a centrally acting muscle relaxant that relieves skeletal muscle spasm of local origin without interfering with muscle function. It has been hypothesized that cyclobenzaprine provides relief by interrupting a self-reinforcing pathway of muscle spasm and local pain. The main side effect of the prescription strength is sedation. Cyclobenzaprine hydrochloride is freely soluble in water with a pKa of 8.47. It is highly (93%) plasma protein bound over a concentration range of 0.1 to 1.0 µg/mL. Previous studies indicate that cyclobenzaprine is subject to enterohepatic circulation.

## **II. FORMULATION**

The formulation of Flexeril MR tablets is given below. The proposed dosage regimen is one tablet every 6-8 hours but not to exceed 3 tablets every 24 hours and for no more than 10 days.

Ingredient	Mg/Tablet
Tablet Core	
Cyclobenzaprine Hydrochloride USP	5.0
Lactose Monohydrate NF	112.0
Pregelatinized Starch NF	25.0
Yellow Ferric Oxide NF	0.15
Starch NF, Corn	7.0
Magnesium Stearate NF	1.0
Tablet Coat	
Titanium Dioxide USP	0.43
Hydroxypropyl Cellulose USP (w/0.3% silica)	1.20
Hydroxypropyl Methylcellulose USP	1.20
Hydroxypropyl Cellulose NF	1.20
Yellow D&C #10 Aluminum Lake HT	0.012
Yellow FD&C #6 Aluminum Lake	0.048
Carnauba Wax NF	0.037 to 0.068
<b>Total Tablet Weight (mg)</b>	<b>153</b>

### III. ANALYTICAL METHODS

HPLC-MS-MS method was used for the assay of cyclobenzaprine in plasma and urine.

*Plasma samples – assay of cyclobenzaprine:* After addition of 100  $\mu$ L of internal standard (trimipramine) solution and 100  $\mu$ L of methanol to plasma (1 mL), the mixture was basified with carbonate buffer (0.2M pH 9.8, 1 mL), and cyclobenzaprine was extracted with 7 mL of hexane. The organic layer was removed and evaporated to dryness. The residue was reconstituted in 400  $\mu$ L of a mixture (50:50, v/v) of acetonitrile:water containing 0.1% formic acid. After centrifugation, the aliquot was injected into the HPLC-MS-MS system. C-18 analytical column with a C-18 guard column was used for the analysis. The mobile phase was a mixture of acetonitrile:water (90:10, v/v) containing 0.1% formic acid and 10 mM ammonium acetate delivered at a flow rate of 1 mL/min. Peak area ratios obtained from multiple-reaction monitoring of analyte ( $m/z$  276  $\rightarrow$ 215)/( $m/z$  295  $\rightarrow$ 208) were utilized for the determination of concentrations.

*Urine samples – assay of cyclobenzaprine and its glucuronide conjugate:* Urine samples (1 mL) were spiked with 100  $\mu$ L methanol, and incubated with  $\beta$ -glucuronidase (in 0.1 M pH 6.5 phosphate buffer). The mixture was incubated at 37°C for 24 hours, and the internal standard solution (100  $\mu$ L) was added, followed by 10 N sodium hydroxide (100  $\mu$ L) and hexane (5 mL). The organic layer was removed by centrifugation and evaporated to dryness. The residue was reconstituted in 1 mL of a mixture (50:50, v/v) of acetonitrile:water containing 0.1% formic acid and an aliquot was injected into the HPLC-MS-MS system. The validation results are acceptable.

Precision (%CV):	Plasma	Urine	
	1.8-5.9	2.1-7.1	(Intraday)
	7.2-7.9	3.2-8.0	(Interday)

Accuracy (%):	92.0-104.1	92.0-103.4	(Intraday)
	96.0-98.0	92.0-97.0	(Interday)
Limit of quantification:	0.1 ng/mL	10 ng/mL	
Linearity:	0.1-50 ng/mL	10-1000 ng/mL	
Specificity:	confirmed by assaying blank human plasma samples		
Stability (Storage at -20°C for more than 18 months):	Acceptable		

#### **IV. OVERALL SUMMARY OF BIO/PK/PD CHARACTERISTICS**

##### **Absorption and Bioavailability**

After a single dose administration of the 5 mg tablets in healthy young subjects, peak plasma cyclobenzaprine concentration ( $4.3 \pm 1.6$  ng/mL) was reached 4 to 5 hours postdose. The absolute bioavailability of cyclobenzaprine hydrochloride 5-mg tablets was 0.55. The clinical trial formulation and the market image were bioequivalent. Both AUC and C<sub>max</sub> were approximately dose proportional over the dose range of 2.5 to 10 mg. Multiple dose pharmacokinetics can generally be predicted from single dose pharmacokinetics.

Food effect study will be conducted as Phase IV. It should be noted that clinical efficacy and safety studies were conducted without regard to the timing of meals.

##### **Distribution**

Cyclobenzaprine is highly (~93%) plasma protein bound over a concentration range of 0.1 to 1.0 µg/mL. (There is no information on binding to specific plasma proteins.)

##### **Metabolism**

At least 50% of an orally administered dose is metabolized. Several urinary metabolites of cyclobenzaprine have been identified (see Excretion).

Based on in vitro studies, the sponsor concluded that the *N*-demethylation reaction of cyclobenzaprine was mediated primarily via cytochrome P-450s 3A4 and 1A2, while cytochrome P-450 2D6 played a minor role. As a result, the sponsor concluded that genetic polymorphism was not a concern for this drug. However, these studies were conducted at a high concentration of cyclobenzaprine (100 µM) which was more than 2000-fold of the peak plasma cyclobenzaprine concentration at steady state. Thus, the studies are not considered definitive regarding which isozyme actually plays a major role in the metabolism of cyclobenzaprine at the clinically relevant concentrations. In addition, the information as submitted by the sponsor did not indicate that *N*-demethylation is the predominant metabolic pathway (see Excretion).

## **Elimination of cyclobenzaprine**

Cyclobenzaprine is primarily eliminated through metabolism and is subject to enterohepatic circulation. Very little unchanged drug (~1% of dose) was recovered in the urine. One study estimated that at least 8% (actual percentage unknown) of the dose was recovered in the feces as the parent compound, however, it is unclear how much was attributed to biliary secretion or unabsorbed drug. In healthy young volunteers, plasma clearance of cyclobenzaprine was found to be 689 ( $\pm$ 216) mL/min and the effective half-life of cyclobenzaprine was approximately 18 hours.

## **Excretion of cyclobenzaprine and its metabolites**

A radiolabeled study (using the 10 mg tablets) suggests that 120 hours after oral administration, 50.8% of dose was recovered in urine and 13.5% in feces. (Similar recovery was observed after IV administration: 48.8% of dose in urine and 20.6% in feces).

**Urine:** The primary metabolites in urine were cyclobenzaprine glucuronide (11-22% of urinary radioactivity, UR) and 9,10-dihydroxynortriptyline (6-7% of UR). Other metabolites were cyclobenzaprine N-oxide (2-3% of UR), N-demethylated cyclobenzaprine (3% of UR) and 3-OH cyclobenzaprine (3-6% of UR). A major metabolite (7-14% of UR) was unidentified.

**Feces:** The major compound (60% of fecal radioactivity) excreted in feces was the parent compound. No information on metabolites was given.

It is noted that the recovery of total (urine + feces) radioactivity was low in this study (~64% of dose) and a major urinary metabolite was not identified. Because of this, the study does not provide a clear picture of metabolic profiles of cyclobenzaprine.

## **Special populations**

### **a. Elderly**

Steady-state plasma concentrations of cyclobenzaprine were 70-80% higher in the elderly due to longer effective half-life (33 hrs in elderly vs. 18 hrs in young volunteers). As a result, steady-state concentrations in elderly subjects receiving 5 mg every 8 hours were in the same range as those previously observed in young subjects receiving the prescription dose of 10 mg every 8 hours.

### **b. Hepatic impairment patients**

The sponsor conducted a multiple dose study comparing 16 mild-to-moderate hepatic impairment patients (11 males & 5 females) to 8 age-matched healthy subjects (5 males & 3 females). Only one patient had moderate hepatic impairment based on the Child-Pugh classification and, therefore, this is basically a study in mild hepatic impairment patients.

The effect of hepatic impairment was different in males compared to females. Cyclobenzaprine plasma concentrations after multiple dosing were significantly higher for males with hepatic impairment compared with male controls (Geometric mean ratio: 2.18 for AUC and 2.24 for C<sub>max</sub>). No such differences were observed in females (GMR: 0.92 for AUC and 1.01 for C<sub>max</sub>). However, healthy females in this study had much higher drug concentrations at steady state than previously observed in healthy young females. Steady-state plasma concentrations in both healthy and hepatically impaired females were comparable to hepatically impaired males. Plasma concentrations for hepatically impaired subjects receiving 5 mg every 8 hours are in the same range as healthy young subjects receiving the prescription dose of 10 mg every 8 hours. These patients of either gender showed about 8-fold accumulation of cyclobenzaprine in plasma over the course of the study. Mean effective half-life, calculated by fitting a monoexponential to trough plasma concentrations, was 46.2 hours (range: 22.4-188 hours) in hepatically impaired subjects and 23.1 hours (range: 10.7-51.2 hours) in control subjects. Many of the patients with hepatic insufficiency had not reached 90% of steady state by the end of the study, while all of the healthy subjects had. As a result, plasma concentrations and the degree of accumulation at steady state would be expected to be greater than was measured on Day 8 in this study for patients with mild hepatic insufficiency.

There is little or no information on cyclobenzaprine pharmacokinetics in moderate or severe hepatic impairment patients.

#### c. Gender

The effect of gender on cyclobenzaprine pharmacokinetics was not formally studied. A cross-study comparison of the effect of gender and age on AUC(0-8 hr) in healthy subjects is shown in the figure below. This graph suggests that the magnitude of any difference in pharmacokinetics between males and females is small relative to intersubject variability. However, it is noted that the sponsor did not attempt to examine the effect of body weight on cyclobenzaprine pharmacokinetics, which may contribute to the large intersubject variabilities observed. It is considered important to separate the effect of gender from the effect of body weight. This will provide a better picture to see if female subjects with low body weight will have significantly higher plasma cyclobenzaprine concentrations.

### **Drug-Drug Interaction**

In vitro studies:

- a. As stated above, in vitro studies appear to indicate that cyclobenzaprine has little potential for inhibition of cytochrome P-450-mediated reactions at clinically relevant concentrations in view of the relatively high *K<sub>i</sub>* values obtained for human liver microsomes. However, the study report as submitted in the NDA was too brief to allow a thorough evaluation of the data and the sponsor was requested to submit a detailed report.
- b. It is unclear what cytochrome P450 isozyme is the primary enzyme for the metabolism of cyclobenzaprine. Thus, it is not possible to predict which drug may potentially inhibit cyclobenzaprine metabolism.

**In vivo studies:**

The current Flexeril Rx label states that no significant effect on plasma levels of Flexeril or aspirin was noted when single or multiple doses of the two drugs were administered concomitantly. Conflicting results were found in drug interaction with diflunisal and no information regarding coadministration of Flexeril and diflunisal is included in the current Flexeril Rx label. The sponsor did not conduct any other in vivo drug-drug interaction studies.

**Report of adverse event:**

Reported in an article<sup>1</sup> was a case of QT prolongation associated with concomitant cyclobenzaprine and fluoxetine administration (among several other medications) followed by torsade de pointes potentiated by droperidol. The author considered that combination of fluoxetine and cyclobenzaprine resulted in significant QT prolongation in this patient due to inhibition of cyclobenzaprine metabolism by fluoxetine. (This QT prolongation progressed to torsade de pointes following the administration of droperidol, an agent known to prolong the QT interval.) However, no pharmacokinetic data was available to confirm the interaction. Because of this confounding third agent, the significance of this finding is unknown.

<sup>1</sup>Ann Pharmacother 1998; 32(7-8):761-5: Torsade de pointes resulting from the addition of droperidol to an existing cytochrome P450 drug interaction

## **V. SUMMARY OF INDIVIDUAL STUDIES**

### **SINGLE DOSE/MULTIPLE DOSE PHARMACOKINETICS AND DOSE PROPORTIONALITY**

**Study 005:** An open-label, randomized, three-period crossover study in healthy volunteers to investigate single- and multiple-dose pharmacokinetics and dose proportionality of cyclobenzaprine HCl tablets

*Study design:* This study was designed to investigate the pharmacokinetics and dose proportionality of cyclobenzaprine after oral single and multiple doses of 2.5, 5, and 10 mg in 18 healthy subjects. In each study period, a single oral dose was administered on Day 1, followed by multiple doses given every 8 hours from Days 8 through 14 and a final dose on the morning of Day 15. The subjects fasted overnight prior to the morning doses on Days 1 and 8 through 15, and otherwise consumed a normal diet. Blood samples were taken for drug assay at specified intervals for 168 hours following the first dose and for 8 hours following the final dose, as well as prior to each morning dose on Days 8 through 14. Urinary excretion of total (free and conjugated) cyclobenzaprine was measured for 8 hours after the first and final doses of each study period.

*Results:*

Mean plasma concentration profiles after a single oral dose of cyclobenzaprine are shown for each dose level in Figure 1. Mean plasma concentrations over an 8-hour dosing interval after the first and last dose are shown in Figure 2. A summary of mean pharmacokinetic parameters is

given in Table 1. Following multiple dosing, steady state was attained within approximately 4 days after administration of cyclobenzaprine every 8 hours. For each dose level, C<sub>max</sub> at steady state increased to 3- to 3.5-fold when compared to that after single dose. Mean T<sub>max</sub> was approximately 4 hours postdose after either single dose or multiple doses. Effective half-life at each dose level, calculated by fitting a monoexponential function to trough plasma concentrations, was about 18 hours, which is consistent with the degree of accumulation observed after dosing every 8 hours.

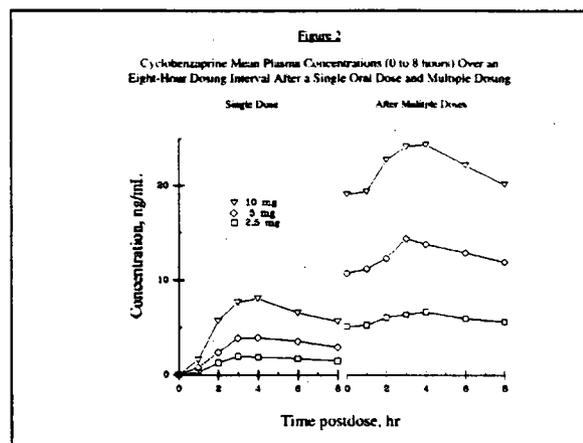
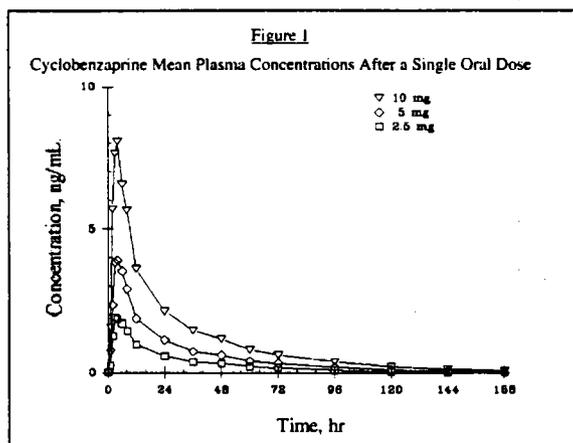


Table 1: Arithmetic Mean PK Parameters After Single Doses (Day 1) and After Dosing Every 8 Hours for 7 Days (Day 15)

Parameter (n=18)	2.5-mg Dose		5-mg Dose		10-mg Dose	
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
C <sub>max</sub> , ng/mL (SD)	2.1 (0.7)	7.1 (3.4)	4.3 (1.6)	14.9 (6.5)	8.5 (4.0)	25.9 (11.2)
T <sub>max</sub> , hr (SD)	3.9 (1.3)	3.8 (1.4)	3.9 (1.3)	4.0 (1.4)	3.8 (1.2)	3.9 (1.8)
AUC (0-8), ng <sup>a</sup> hr/mL (SD)	11.1 (4.2)	47.4 (22.6)	23.0 (8.6)	101.4 (44.8)	45.9 (21.3)	176.5 (78.4)
AUC (0-∞), ng <sup>a</sup> hr/mL (SD)	44.2 (19.9)	-	89.5 (45.8)	-	178.2 (78.8)	-
Accumulation Ratio <sup>b</sup> (Range)	-	4.0 (2.4-6.5)	-	4.3 (2.6-7.0)	-	3.9 (1.7-7.7)
Effective Half-Life, hr <sup>b</sup> (Range)	-	18.4 (9.7-47.3)	-	18.4 (9.3-41.3)	-	18.0 (8.3-36.5)
Amount Recovered in Urine <sup>d</sup> , μg (SD)	53.2 (24.9)	146.1 (94.3)	123.7 (119.7)	320.7 (238.4)	194.5 (91.8)	482.3 (316.6)
Cl <sub>r</sub> , L/hr (SD)	5.2 (3.2)	4.1 (3.7)	6.6 (6.5)	3.4 (2.4)	5.3 (3.7)	3.5 (2.9)

a Ratio of Day 8/Day 1 AUC (0-8 hr); Geometric Mean.

b Based on monoexponential fit of trough plasma concentrations to obtain accumulation rate constant.

c Harmonic mean.

d Free and conjugated cyclobenzaprine

### Dose Proportionality:

The sponsor assessed dose proportionality by determining the geometric mean ratio (and 90% CI) of dose-adjusted geometric mean AUC and Cmax between doses. After single dose (Day 1), the ratios ranged from 0.94 to 0.99 for AUC<sub>0-∞</sub>, and from 0.95 to 1.01 for Cmax (see Table 2). At steady state (Day 15), the ratios ranged from 0.91 to 1.10 for AUC<sub>0-8h</sub> and 0.92 to 1.10 for Cmax. Based on these data, the sponsor concluded that dose proportionality was established.

Table 2: Dose-Normalized PK Parameters After Single Dose And At Steady State

Dose Normalized* Geometric Mean			Geometric Mean Ratio (90% CI)		
Dose	AUC	Cmax	Comparison	AUC	Cmax
Single Dose					
2.5 mg	15.59	0.76	2.5 mg vs. 5 mg	0.99 (0.87-1.13)	0.95 (0.83-1.10)
5 mg	15.74	0.80	2.5 mg vs. 10 mg	0.94 (0.83-1.08)	0.96 (0.84-1.11)
10 mg	16.55	0.79	5 mg vs. 10 mg	0.95 (0.83-1.09)	1.01 (0.88-1.16)
Steady State					
2.5 mg	16.53	2.47	2.5 mg vs. 5 mg	0.91 (0.83-0.99)	0.92 (0.84-1.01)
5 mg	18.15	2.69	2.5 mg vs. 10 mg	1.00 (0.92-1.09)	1.01 (0.92-1.12)
10 mg	16.50	2.44	5 mg vs. 10 mg	1.10 (1.01-1.20)	1.10 (1.00-1.22)

\*Normalized to 1 mg dose

Since the above calculations were based on pairwise comparisons of log-transformed values, this reviewer examined the arithmetic mean data as given in Table 1. Based on dose-normalized values, dose proportionality was apparent for both AUC and Cmax after single dose. At steady state, both AUC and Cmax were approximately dose proportional.

### Linearity within dose:

The dose-adjusted geometric mean ratios for the single-dose AUC<sub>(0-∞)</sub> versus the last dose AUC<sub>(0-8 hr)</sub> were computed for each dose level to determine linearity within dose and the results are given in Table 3. (If linear pharmacokinetics hold, the ratio should be unity.) The geometric mean ratio for the 5-mg dose was significantly different from unity (p=0.006). However, the clinical significance of this observation is minimal in view of the following: (a) dose proportionality across doses as established above, (b) the absence of such deviation from linearity for the other doses above and below the 5-mg dose (10-mg, 2.5-mg dose), and (c) the small mean deviations from linearity that were observed (~13%).

Table 3: Ratio of Dose-Adjusted Geometric Mean AUC<sub>0-∞</sub> (First Dose/Last Dose)

Dose	Dose-Adjusted Geometric Mean (ng-hr/mL-mg)		Geometric Mean Ratio (90% Confidence Interval)
	First Dose	Last Dose	
2.5 mg	15.59	16.53	0.95 (0.857, 1.037)
5 mg	15.74	18.15	0.87 (0.788, 0.954)
10 mg	16.55	16.50	1.00 (0.912, 1.103)

**Accumulation:**

The dose-adjusted geometric mean ratios for AUC(0-8 hr) of the last dose versus the first dose were 4.03, 4.26, and 3.85 for the 2.5-, 5-, and 10-mg doses, respectively (Table 1). Therefore, there is approximately fourfold accumulation from single dose to steady state.

**Variability:**

The intrasubject variability in AUC was small (5-7% after single dose and at steady state) but greater in Cmax (86.4% after single dose; 16.0% after multiple doses). (Reviewer's note: These estimates were obtained assuming perfect dose proportionality.)

**Renal clearance:**

The renal clearance of the unchanged drug and the glucuronide metabolite was analyzed (Table 1). The geometric means were 4.15, 4.28 and 3.98 L/hr after single dose and 2.81, 2.43 and 2.34 L/hr at steady state for the 2.5, 5 and 10 mg-doses, respectively. There was no significant differences between the three treatment groups but there was a significant difference between the two periods. Renal clearance was lower at steady state than after the first dose. The sponsor did not explain why, however, this occurred across all three dose groups.

**Gender Analysis:**

A by-gender analysis was performed on pharmacokinetic parameters (AUC, Cmax, Tmax, renal clearance and accumulation rate constant) (Tables 4A & 4B). After single dose, there were no statistically significant differences between genders for any parameters tested but the geometric mean AUC was 34% higher in females than in males. At steady state, AUC, Cmax and accumulation rate constant were marginally significant, with females having greater accumulation and (~45%) higher plasma cyclobenzaprine concentrations (dose-normalized AUC<sub>0-8h</sub>: 20.2 vs. 13.8 ng.h/mL; Cmax: 3.0 vs. 2.1 ng/mL).

Table 4A: Dose-Normalized Geometric Mean Parameters (AUC, Cmax & Renal Clearance) In Males and Females

Parameter	Geometric Means					
	First Dose			Last Dose		
	Male	Female	p-value	Male	Female	p-value
AUC <sub>(0-8 hr)</sub> ng-hr/mL	3.80	4.59	0.29	13.75	20.22	0.08
AUC <sub>(0-∞)</sub> ng-hr/mL	13.56	18.16	0.19	--	--	
Cmax ng/mL	0.72	0.84	0.40	2.06	2.98	0.09
Renal clearance	5.13	3.48	0.32	2.76	2.18	0.40

Table 4B: Arithmetic Mean Parameter (Accumulation Rate Constant and Tmax) Values Between Genders

Parameter	Arithmetic Means					
	First Dose			Last Dose		
	Male	Female	p-value	Male	Female	p-value
Accumulation Rate Constant	--	--		0.05	0.035	0.08
T <sub>max</sub>	3.75	4.012	0.51	3.71	4.07	0.44

**Adverse events:**

There were no serious adverse events. One subject (Subject 008) exhibited an abnormal ECG at the post-study physical (off drug) that was considered to be possibly related to study drug.

**Conclusion:**

- Plasma concentration increases proportionally to dose and cyclobenzaprine pharmacokinetics are linear over the dose range of 2.5 to 10 mg.
- The effective half-life was approximately 18 hours, independent of the dose. Steady state was reached in approximately 4 days.
- There was an approximately 4-fold accumulation of cyclobenzaprine in plasma when dosed every 8 hours.
- In healthy young volunteers, females tended to have higher cyclobenzaprine plasma concentrations than males (~45% higher at steady state). (The sponsor indicated that gender analysis was performed in other safety and efficacy studies to further investigate its clinical significance.)

**Comment:**

In this study, female subjects had an approximately 20% lower body weight which may partially explain the higher (45% at steady state) plasma cyclobenzaprine concentrations observed in female subjects. The sponsor should reanalyze the data using gender and weight as covariates.

**BIOAVAILABILITY/BIOEQUIVALENCE**

**Study 011: An Open-Label, Three-Period Crossover Study to Determine the Bioequivalence/Bioavailability of FLEXERIL Tablets 5 mg (Planetary Process) and FLEXERIL Tablets 5 mg (High-Shear Process)**

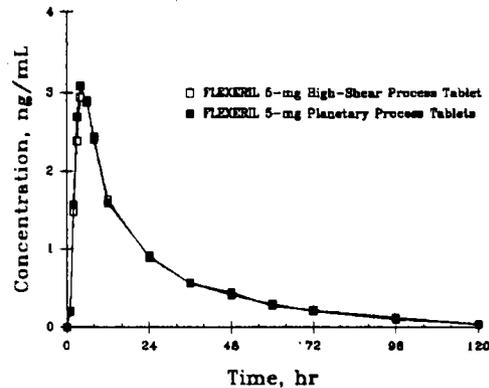
*Study Design*

This study determined the absolute oral bioavailability and bioequivalence of two tablet formulations manufactured using two different mixing processes (planetary process for clinical trial tablets and high-shear process for the proposed market image). It was a three-period, single-dose, crossover study under fasted conditions with 7-day washout between doses. In addition to the two tablet formulations, subjects also received a bioavailability reference dose of 1.25 mg cyclobenzaprine hydrochloride administered intravenously (as a bolus of 0.25 mL of 5 mg/mL cyclobenzaprine hydrochloride solution). Twenty-four subjects participated and 21 completed the study. Blood samples were collected for up to 168 hours postdose. (Subjects 007 and 011 discontinued due to personal reasons and Subject 012 was discontinued because of a positive drug screen. These subjects were not replaced.)

*Results*

As shown in Figure 1, plasma concentration profiles for the 2 tablet formulations were similar.

Figure 1. Plasma Concentrations After an Oral Dose of 5 mg Flexeril Tablet



**Bioequivalence:**

The dose normalized pharmacokinetic parameters for the two tablet formulations are provided in Table 1. The geometric mean ratios (and 90% CI) of high-shear process tablets (i.e., market image) vs. planetary process tablets were 1.00 (0.92, 1.08) for AUC<sub>0-∞</sub> and 1.00 (0.92, 1.10) for C<sub>max</sub>, indicating the two tablet formulations were bioequivalent. Mean T<sub>max</sub> was similar for both tablets (~ 4.7 hrs).

Table 1: Summary of PK Parameters for Flexeril High Sheer Tablets vs. Planetary Tablets

Ratio Analyses	Least Squares Geometric Means		Geometric Mean Ratio	90% C.I.	p-Values	
	HS	PL			Treatment	Period
Variables						
AUC <sub>(0-∞)</sub>	62.41	62.72	1.00	(0.92, 1.08)	0.922	0.850
C <sub>max</sub>	3.14	3.13	1.00	(0.92, 1.10)	0.960	0.158
Difference Analyses	Least Squares Means		Difference	90% C.I.	ANOVA p-Values HS versus PL	
	HS	PL			Treatment	Period
Variable						
T <sub>max</sub>	4.68	4.75	-0.07	(-0.53, 0.38)	0.789	0.642

NOTE: There is no significant carryover effect for AUC (p-value = 0.442). Carryover effect could not be tested for C<sub>max</sub> and T<sub>max</sub>.  
HS=High-shear tablets, PL=Planetary tablets.

**Absolute bioavailability:**

For the IV dose, the arithmetic mean AUC was 29.2±8.4 ng.h/mL. Mean systemic bioavailabilities (90% CI) of the high-shear process tablets and the planetary process tablets were both 0.55 (0.51, 0.60). (In 2 previous studies, the bioavailability of cyclobenzaprine hydrochloride 10-mg tablets was estimated to be 0.52 and 0.33. These earlier results were from a smaller number of patients.)

**Plasma clearance:**

In most subjects, plasma concentrations after I.V. administration increased initially, peaking as much as 4 hours postdose, and then declined slowly. This unusual plasma concentration profile

after I.V. administration has previously been observed for cyclobenzaprine in man as well as for total radioactivity in plasma after administration of radiolabeled cyclobenzaprine hydrochloride in rat, dog, monkey, and man. It is most likely attributable to rapid and extensive uptake of cyclobenzaprine by tissue with re-distribution into the plasma compartment. Assuming this phenomenon is distributional in nature, plasma clearance and bioavailability calculations should be reliable since these parameters are independent of distribution. Mean ( $\pm$ SD) plasma clearance was determined to be 688.6 ( $\pm$ 215.6) mL/min (range: 422-1091 mL/min).

*Conclusion:*

- The clinical trial formulation and the market image were bioequivalent.
- The absolute bioavailabilities for the two formulations were the same (0.55).

*Reviewer's comments:*

1. Both C<sub>max</sub> and AUC after a single dose were ~30% lower in this study than in Study 005. It is noted that this study had a higher male/female ratio and thus had a (~20%) greater mean body weight. Therefore, body weight could explain the most part of the differences observed between the 2 studies.
2. In this study, (young) females had a 8% lower mean body weight and ~30% higher mean AUC than (young) males. It appears that there is a gender difference in AUC unexplained by body weight, which is consistent with the results seen in Study 005.

#### PHARMACOKINETICS IN DIFFERENT SUBPOPULATIONS

##### Effect of Age (Elderly vs. Young Subjects)

**Study 010:** An Open-Label, Multiple-Dose Study to Investigate the Pharmacokinetics of MK-0130 in Elderly ( $\geq$ 65 Years) Subjects

*Study Design:* The pharmacokinetics of cyclobenzaprine in elderly subjects were investigated in a multiple-dose study in 12 elderly subjects (mean age: 71.3 years; range: 65 to 79 years; 6 males, 6 females). Each subject received oral doses of 5-mg cyclobenzaprine hydrochloride tablets t.i.d. for 7 days and a final dose on the eighth day. Cyclobenzaprine plasma concentration profiles were obtained after the first and last doses which were administered under fasted conditions. The results from this study were compared to those in healthy young subjects (mean age: 28.7 yrs; range: 22-40 yrs; 8 M & 10 F) receiving the same dosing regimen in a separate study (Protocol #005). The ANOVA model used included variables representing population, gender and gender-by-population interaction.

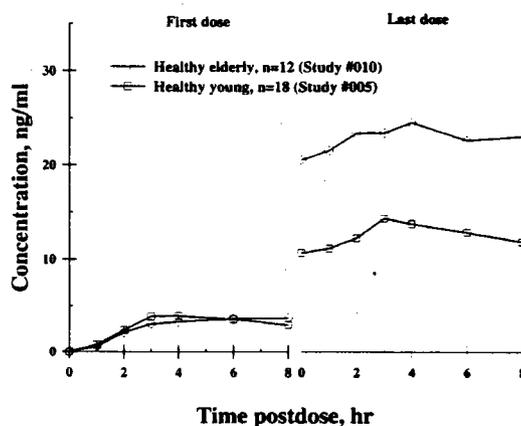
*Results:*

Unusual increases in trough plasma concentration were observed in 2 subjects who became ill with flu-like symptoms during the study. These increases corresponded with increases that were observed in plasma  $\alpha_1$ -acid glycoprotein concentrations (which occur as part of an acute-phase reaction to illness). The sponsor contends that this observation is unlikely to have clinical

significance since the increase in total plasma concentration reflects an increase in drug bound to plasma protein. These 2 subjects were excluded from the primary statistical analysis. (The results from the analysis with all subjects are provided in the Appendix.)

Mean plasma concentration profiles after the first and last doses in elderly and young subjects are shown in the figure below.

Figure 1: Mean Plasma Concentration of Cyclobenzaprine After the First and Last Doses



#### A. Day 1 Data

The statistical test did not detect any significant differences between population or genders and there was no significant population-by-gender interaction. The  $AUC_{0-8h}$  on Day 1 was similar in healthy elderly and young subjects (Table 1A). The geometric mean ratio was close to 1. Within male subjects, the elderly had a 24% higher  $AUC_{0-8h}$  than the young. Within females subjects, the elderly had a 21% lower  $AUC_{0-8h}$ . Within elderly group, mean  $AUC_{0-8h}$  was ~20% higher in males than in females but the reverse was true in young subjects. Similar results were observed for  $C_{max}$  (Table 1B).  $T_{max}$  was longer in the elderly group (5.5 vs. 3.9 hrs). (Note: A mean  $T_{max}$  of 4.8 hrs was observed in young subjects in Study 010).

Table 1A: Summary Statistics for Day 1  $AUC_{0-8h}$  (Excluding Subjects 005 & 012)

	Population Geometric Means			Geometric Mean Ratio (E/Y)*		
	Elderly	Young	Overall	GMR	90% C.I.	p-Value
Overall	20.8	21.1	21.2	0.99	(0.77,1.27)	0.936
Male	22.9	18.5	20.6	1.24	(0.87,1.78)	0.312
Female	19.0	24.1	21.4	0.79	(0.56,1.11)	0.246
GMR (M/F)	1.21	0.77	0.96			
90% C.I.	(0.81,1.80)	(0.57,1.03)	(0.75,1.23)			
NOTE: There is no significant gender effect or population-by-gender interaction.						
* E/Y = Elderly/Young						

Table 1B: Summary Statistics for Day 1 Cmax (Excluding Subjects 005 & 012)

	Population Geometric Means			Geometric Mean Ratio (E/Y)*		
	Elderly	Young	Overall	GMR	90% C.I.	p-Value
Overall	4.04	3.96	4.02	1.02	(0.81, 1.29)	0.884
Male	4.36	3.56	3.94	1.22	(0.88, 1.71)	0.308
Female	3.75	4.41	4.06	0.85	(0.62, 1.17)	0.393
GMR (M/F)	1.16	0.81	0.97			
90% C.I.	(0.80, 1.68)	(0.61, 1.06)	(0.77, 1.22)			

NOTE: There is no significant gender effect or population-by-gender interaction.  
\*E/Y = Elderly/Young

**B. Day 8 (steady state) Data**

The statistical analysis of Day 8 data indicated that there were no significant gender or population-by-gender effects. However, there was a significant population (elderly vs. young) effect, i.e., elderly had a significantly higher AUC and Cmax than young subjects. As observed on Day 1, mean Tmax was somewhat longer in the elderly group (5.0 vs. 4.0 hrs) on Day 8 as well. Comparisons of AUC(0-8 hr) and Cmax at steady state between elderly and young subjects and between male and female subjects is presented in Table 2. These comparisons are described below. Note that values in the parenthesis denotes those including the 2 elderly subjects who became ill. (Reviewer's note: There are errors in the data for healthy young subjects. The sponsor should revise and submit the corrected analysis.)

**Elderly vs. Young:**

Overall (male + female): elderly - AUC: 79% (89%) ↑ ; Cmax: 72% (84%) ↑  
 Within male subjects: elderly - AUC: 93% (110%) ↑ ; Cmax: 137% (157%) ↑  
 Within female subjects: elderly - AUC: 65% (71%) ↑ ; Cmax: 26% (31%) ↑

**Males vs. Females:**

Within elderly group: males - AUC: 41% (49%) ↑ ; Cmax: 42% (47%) ↑  
 Within young subjects: males - AUC: 32% ↓ ; Cmax: 31% ↓

Table 2: Comparison of Steady-State AUC(0-8 hr) and Cmax in Elderly\* and Young Subjects

Population	Geometric Means			
	AUC (ng•hr/mL)		Cmax (ng/mL)	
	Elderly	Young	Elderly	Young
Overall	164.5 (n=12)	92.1 (n=18)	22.9 (n=12)	13.3 (n=18)
Male	195.6 (n=6)	<del>101.2 (n=8)</del>	27.2 (n=6)	<del>11.5 (n=8)</del>
Female	138.3 (n=6)	<del>83.7 (n=10)</del>	19.2 (n=6)	<del>15.3 (n=10)</del>
Population	AUC		Cmax	
	GMR	90% CI	GMR	90% CI
Overall: Elderly/Young	1.79	1.33 - 2.40	1.72	1.30 - 2.28
Male: Elderly/Young	<del>1.93</del>	<del>1.26 - 2.96</del>	<del>2.37</del>	<del>1.58 - 3.55</del>
Female: Elderly/Young	<del>1.65</del>	<del>1.10 - 2.49</del>	<del>1.26</del>	<del>0.85 - 1.85</del>
Elderly: Male/Female	1.41	0.88 - 2.27	1.42	0.90 - 2.22
Young: Male/Female	0.68**	<del>0.85 - 1.72?</del>	0.69**	<del>0.54 - 1.05?</del>

\*Two elderly subjects (Subject 005 and 012) were excluded from the analysis. Analysis including these 2 subjects are provided in the Appendix.

\*\* Values based on this reviewer's calculations

### **C. Accumulation**

After the first dose, plasma concentration profiles up to 8 hours postdose were similar in elderly and young subjects. Therefore, differences at steady state may be attributed to changes in effective half-life of cyclobenzaprine. The accumulation ratio as determined from geometric mean ratios of AUC(0-8 hr) on Day 8 to AUC(0-8 hr) on Day 1 were 7.9 (90% CI: 7.4-8.4) for elderly subjects and 4.3 (90% CI: 4.0-4.6) for young subjects.

Mean effective half-life, calculated by fitting a monoexponential to trough plasma concentrations, was 33.4 hours (range: 20.0 - 53.4 hrs) in elderly subjects and 18.4 hours (range: 9.3 to 41.3 hours) in young subjects. These results are consistent with the differences in accumulation observed between elderly and young subjects. The basis for the differences in steady-state plasma concentrations of cyclobenzaprine between young and elderly is not known. One possible explanation for the increased accumulation in the elderly is reduced hepatic mass resulting in reduced metabolic clearance. The difference is not considered to be due to changes in renal function since these elderly subjects had normal renal functions (creatinine clearance: 67 - 101 mL/min) and subjects at the low end of this range did not show higher plasma levels of cyclobenzaprine. (Reviewer's note: Renal excretion of unchanged drug is a minor pathway in the elimination of cyclobenzaprine and, therefore, is not expected to be a factor here.)

As a result of increased accumulation, steady-state concentrations in elderly subjects receiving 5 mg every 8 hours were in the same range as those previously observed in young subjects receiving the prescription dose of 10 mg every 8 hours. The proposed nonprescription label states that subjects 65 years of age or older should ask their doctor before using cyclobenzaprine. (Reviewer's note: A lower dose such as 5 mg bid should also be considered.)

#### **Adverse events:**

No serious adverse events were observed and no one discontinued due to an adverse experience.

#### **Sponsor's conclusion:**

- Mean steady state plasma cyclobenzaprine concentrations in elderly subjects after 5 mg tid dosing were similar to those observed in healthy young subjects following 10 mg tid dosing.
- On average, elderly subjects had a 79% higher AUC and 72% higher C<sub>max</sub> than young subjects.
- Accumulation was approximately 8-fold in elderly and 4-fold in young subjects.

#### **Reviewer's comments:**

1. There are errors in the data for healthy young subjects. The sponsor should revise and submit the corrected analysis. The comparison both including and excluding the 2 elderly subjects who fell ill during the study should be provided.

2. Two elderly patients who fell ill had unusually high plasma cyclobenzaprine concentrations. The sponsor claimed that the high concentrations were due to binding of cyclobenzaprine to  $\alpha_1$ -acid glycoprotein. Data on plasma  $\alpha_1$ -acid glycoprotein levels for several elderly subjects were provided to support this speculation. However, it is unclear that the sponsor has data to show that cyclobenzaprine does bind to  $\alpha_1$ -acid glycoprotein. (Binding at elevated body temperatures may need to be considered as well.)
3. Mean plasma concentrations in healthy elderly subjects were in the same range as those previously observed in young subjects receiving the prescription dose of 10 mg every 8 hours. This would mean that a reduced dose such as 5 mg bid may be more appropriate for the elderly patients.
4. The mean body weight in this study in elderly subjects is higher than that in Study 005 for healthy young volunteers. If the body weight were the same, the difference in plasma concentrations between elderly and young subjects is believed to be even greater.

### **Effect of Hepatic Insufficiency**

**Study 007:** An Open-Label, Multiple-Dose, Parallel Study to Determine the Influence of Hepatic Insufficiency on the Pharmacokinetics MK-0130

#### *Study Design:*

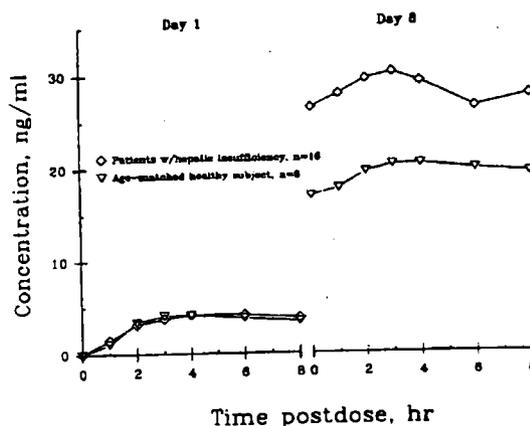
The effect of hepatic insufficiency on cyclobenzaprine pharmacokinetics was assessed in a parallel, multiple-dose study comparing 16 patients with mild-to-moderate hepatic insufficiency (11 males, 5 females) and 8 age-matched healthy subjects (5 males, 3 females). Hepatically impaired subjects in this study had a clinical diagnosis of hepatic insufficiency due to alcoholic liver disease. The severity of impairment was based on Child-Pugh classification. Serum creatinine and BUN were required to be within 150% of normal range and creatinine clearance was required to be greater than 65 mL/min/1.73 M<sup>2</sup>. Each subject received oral doses of 5-mg cyclobenzaprine hydrochloride tablets t.i.d. for 7 days and a final dose on the eighth day. Cyclobenzaprine plasma concentration profiles were obtained after the first and last doses. For the first and last doses, subjects fasted from midnight until consuming a standard lunch 4 hours postdose. Otherwise, subjects followed their normal diet and took their doses without regard to food.

#### *Results:*

##### **A. Day 1 data:**

The mean plasma concentration profile of cyclobenzaprine after the first (Day 1) and last (Day 8) doses are shown in Figure 1.

Figure 1: Mean Plasma Concentration-Time Profiles (0-8 hrs) in Hepatic Insufficiency Patients and Healthy Subjects After Single Dose and At Steady State



1) *AUC(0-8 h) on Day 1:*

Mean pharmacokinetic parameters are presented in Table 1.

Hepatic impairment patients vs. Control subjects:

- Overall (male+females): Analysis of variance indicated there was no significant population effect or population-by-gender interaction. The  $AUC_{0-8h}$  was similar between hepatically impaired patients and controls (GMR: 1.06; 90% CI: 0.80-1.40).
- By-gender analysis: Although there was no significant population-by-gender interaction, by gender analysis was carried out. (This was mostly driven by the fact that population-by-gender interaction was tested significant for both AUC and  $C_{max}$  at steady state.) Male patients had a 37% higher AUC than their control subjects while female patients had a 19% lower AUC than their controls.

Male vs. female subjects:

- The ANOVA of  $AUC(0-8 h)$  on Day 1 indicated a significant gender effect ( $p=0.011$ ). Male subjects had a 36% lower AUC compared to females (GMR: 0.64; 90% CI: 0.48-0.84).
- In the hepatically impaired group, male patients had a 17% lower AUC than female patients. For the control group, male subjects had a 51% lower AUC than females.

Table 1: Summary Statistics of  $AUC_{0-8h}$  (ng-hr/mL) on Day 1

	Population Geometric Means			Geometric Mean Ratio (H/C)		
	Hepatic	Control	Overall	GMR	90% C.I.	p-Value
Overall	26.3	24.9	24.5	1.06	(0.80,1.40)	0.734
Male	23.9	17.4	20.4	1.37	(0.99,1.91)	0.115
Female	28.9	35.5	32.0	0.81	(0.52,1.28)	0.441
GMR (M/F)	0.83	0.49	0.64			
90% C.I.	(0.59,1.15)	(0.31,0.77)	(0.48,0.84)			

NOTE: There is a significant gender effect ( $p=0.011$ ). Population-by-gender interaction was not significant.

## 2) C<sub>max</sub> on Day 1

The results on C<sub>max</sub> were parallel to those for AUC<sub>0-8h</sub>. The ANOVA indicated a significant gender effect (p=0.012) but no significant difference between populations or population-by-gender interaction. The results on C<sub>max</sub> were parallel to those for AUC<sub>0-8h</sub>, and were summarized in Table 2. Male patients had a 34% higher C<sub>max</sub> than control subjects while female patients had a 22% lower C<sub>max</sub> than their controls.

Table 2: Summary Statistics of C<sub>max</sub> on Day 1

	Population Geometric Means			Geometric Mean Ratio (H/C)		
	Hepatic	Control	Overall	GMR	90% C.I.	p-Value
Overall	4.66	4.56	4.42	1.02	(0.79,1.31)	0.890
Male	4.37	3.25	3.77	1.34	(1.00,1.81)	0.106
Female	4.97	6.40	5.64	0.78	(0.52,1.17)	0.294
GMR (M/F)	0.88	0.51	0.67			
90% C.I.	(0.65,1.19)	(0.34,0.76)	(0.52,0.86)			

NOTE: There is a significant gender effect (p=0.012). The population-by-gender interaction is not significant.

## B. Day 8 Results:

Analysis of variance performed on AUC(0-8 hr) and C<sub>max</sub> on Day 8 indicated a significant population (hepatic versus healthy)-by-gender interaction. This means that the effect of hepatic impairment was different in males compared to females in this study. Therefore, results are presented separately for males and females in Table 3.

### Hepatic impairment patients vs. Control subjects:

Cyclobenzaprine plasma concentrations after multiple dosing, were significantly higher for males with hepatic impairment compared with male controls (GMR: 2.18 for AUC and 2.24 for C<sub>max</sub>). No such differences were observed in females (GMR: 0.92 for AUC and 1.01 for C<sub>max</sub>). However, healthy females in this study had much higher drug concentrations at steady state than previously observed in healthy young females. Increases in steady-state plasma concentrations in both healthy and hepatically impaired females were comparable to increases in hepatically impaired males. Plasma concentrations for hepatically impaired subjects receiving 5 mg every 8 hours are in the same range as healthy young subjects receiving the prescription dose of 10 mg every 8 hours. It is noted that mean T<sub>max</sub> in hepatic impairment patients remained to be about 4 to 5 hours.

Table 3: Comparison of Steady-State AUC<sub>0-8 hr</sub> and C<sub>max</sub> in Hepatic Impairment Patients and Healthy Subjects

Population	Geometric Means			
	AUC (ng•hr/mL)		C <sub>max</sub> (ng/mL)	
	Hepatic	Control	Hepatic	Control
Male	190.6 (n=11)	87.6 (n=5)	27.4 (n=11)	12.2 (n=5)
Female	242.3 (n=5)	263.2 (n=3)	35.9 (n=5)	35.7 (n=3)

Population	AUC		Cmax	
	GMR	90% CI	GMR	90% CI
Hepatic (male)/Control (male)	2.18	1.47 - 3.22	2.24	1.54 - 3.24
Hepatic (female)/Control (female)	0.92	0.54 - 1.56	1.01	0.61 - 1.66
Hepatic (male)/Hepatic (female)	0.79	0.43 - 1.16	0.76	0.53 - 1.11
Control (male)/Control (female)	0.33	0.20 - 0.57	0.34	0.21 - 0.57

#### Accumulation:

Hepatically impaired subjects of both genders showed about 8-fold accumulation of cyclobenzaprine in plasma over the course of the study as shown by geometric mean accumulation ratios (Day 8 AUC(0-8 hr) / Day 1 AUC(0-8 hr)) of 8.0 and 8.4 for hepatically impaired males and females, respectively (Table 4). Corresponding accumulation ratios for the age-matched control group of healthy males and females were 5.0 and 7.4, respectively. In an earlier study of healthy young subjects, there was approximately 4-fold accumulation after dosing every 8 hours in both males and females. Mean effective half-life, calculated by fitting a monoexponential to trough plasma concentrations, was 46.2 hours (range: 22.4-188 hours) in hepatically impaired subjects and 23.1 hours (range: 10.7-51.2 hours) in control subjects. Based on the monoexponential fit of trough concentrations, many of the patients with hepatic insufficiency had not reached 90% of steady state by the end of the study, while all of the healthy subjects had. As a result, plasma concentrations and the degree of accumulation at steady state would be expected to be greater than was measured on Day 8 in this study for patients with hepatic insufficiency.

Table 4: Accumulation Ratios by Group

	Hepatic		Control	
	Male (n=11)	Female (n=5)	Male (n=5)	Female (n=3)
AUC Day 8: Mean	213.7	251.0	91.0	265.4
AUC Day 1: Mean	25.5	29.5	18.7	37.1
GMR (AUC 8/AUC 1)	8.0	8.4	5.0	7.4
90% C.I.	(7.5, 8.4)	(7.8, 9.0)	(4.2, 6.0)	(5.5, 10.1)
p-Value	<0.001	<0.001	<0.001	0.008

A comparison of accumulation between studies suggests that the population-by-gender interaction in the hepatic interaction study may be largely attributable to the higher accumulation observed in the healthy female control group. Age is a likely explanation for this higher accumulation. The female controls were 10 years older, on average, than the male controls (mean ages 58.7 years in females versus 48.8 years in males) and were approaching the age of the subjects in the elderly study where higher accumulation was also observed. The small size of the female control group (n=3) may also have been a factor.

#### Adverse events:

The percent of subjects having a clinical adverse experience in the control group (87.5%) is similar to that in the hepatically impaired subjects (81.3). There were no serious adverse experiences and no one discontinued due to an adverse experience. The most commonly reported adverse experiences were somnolence and headache.

*Sponsor's conclusion:*

While no definite conclusions regarding the effect of hepatic impairment can be drawn because of the confounding effects of age and gender, it appears that hepatic impairment increased steady-state plasma concentrations of cyclobenzaprine as the result of increased effective half-life, at least in males.

The sponsor stated that since the prescription dose is accepted as safe, the increased accumulation with 5 mg every 8 hours in older, hepatically impaired male subjects is not considered to be clinically significant. The (sponsor's) proposed nonprescription label states that subjects with liver disease should ask their doctor before using cyclobenzaprine.

Further, the sponsor contended that somnolence generally occurred in the first few days after treatment began, was mild, and resolved despite continued treatment. The absence of an apparent relationship between adverse experiences and plasma concentrations supports the contention that the changes in clearance are not clinically meaningful. The sponsor concluded that reductions in dose below 5 mg every 8 hours do not appear necessary for patients with mild-to-moderate hepatic impairment.

*Reviewer's Comments:*

1. Subjects were matched for age but not smoking. Since CYP1A2 may be involved in the metabolism of cyclobenzaprine, smoking may be a confounding factor.
2. This reviewer requested that the sponsor provide Child-Pugh scores for individual patients and analyze data separately for mild and moderate impairment patients as these two groups of patients may differ substantially. The sponsor responded that only one subject had moderate impairment and, hence, could not analyze data separately. In view of this, this study is basically a study in mild hepatic impairment patients and there is little information on moderate hepatic impairment. Based on the current analysis, it would be more appropriate to reduce dose in mild hepatic impairment patients and restrict use in moderate or severe hepatic impairment patients.
3. The sponsor contended that somnolence generally occurred in the first few days after treatment began, was mild, and resolved despite continued treatment. This statement should be verified by the Medical Officer.

**Effect of Gender**

The effect of gender on cyclobenzaprine pharmacokinetics was not formally studied, but was included in the statistical analysis of the three multiple-dose pharmacokinetics studies. The effect of gender on cyclobenzaprine pharmacokinetics in healthy subjects in each of these studies is summarized in this section.

In the single-/multiple-dose pharmacokinetics study, a subgroup analysis, by gender, was performed and there were no statistically significant differences between males and females for

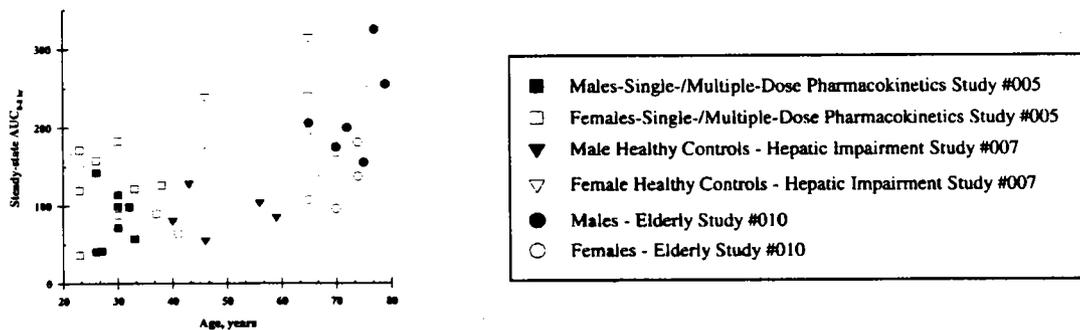
any of the pharmacokinetic parameters analyzed. However, AUC(0-8 hr) and Cmax after the last dose (as well as accumulation rate constant) were marginally significantly different between genders. These results suggest that there may have been more accumulation in females; however, this study was not powered to detect a difference. Based on this study AUC and Cmax was approximately 45% higher in females.

In the elderly, mean pharmacokinetic parameters at steady state were not significantly different in men and women, but there was an overall trend towards higher (40%↑) concentrations in men. The trend in the elderly was opposite to that observed in young subjects.

In the healthy control panel of the hepatic impairment study, steady-state plasma concentrations of cyclobenzaprine were significantly lower (65-70%↓) in males than females. However, age may contribute at least partly to these results since, on average, the females were 10 years older than the males.

A cross-study comparison of the effect of gender and age on AUC(0-8 hr) in healthy subjects using data from the above three studies is shown in Figure 1. This graph suggests that the magnitude of any difference in pharmacokinetics between males and females is small relative to intersubject variability.

Taken together, results of the three multiple-dose pharmacokinetics studies suggest that steady-state plasma concentrations of cyclobenzaprine may be different in males and females; however, the magnitude of any difference appears to be relatively small.



*Comment:*

The sponsor indicates that the above graph suggests the magnitude of any difference in pharmacokinetics between males and females is small relative to intersubject variability. However, the variability may be partly due to body weight differences. It is important to separate the effect of gender from the effect of body weight. (The sponsor should provide the graph using body weight normalized parameters as well.) This will help identify whether female subjects with low body weight may have significantly higher plasma cyclobenzaprine concentrations.

## REVIEW OF LITERATURE ARTICLES AND STUDY REPORTS

### In Vitro Metabolism

#### *Metabolism of cyclobenzaprine*

Article: R. W. Wang, L. Liu, and H. Cheng: Identification of human liver cytochrome P450 isoforms involved in the in vitro metabolism of cyclobenzaprine. *Drug Metab. Dispos.* 24, 786-791 (1996)

a. Effect of cytochrome P450 inhibitors and antibodies:

Cyclobenzaprine is structurally related to several tricyclic antidepressants that have been identified as substrates for CYP 2D6. Drugs that are metabolized predominantly via CYP 2D6 raise potential clinical concerns due to genetic polymorphism in CYP 2D6. The role of CYP 2D6 and various cytochrome P-450s in cyclobenzaprine metabolism in vitro was studied using human liver microsomes and a panel of selective cytochrome P-450 inhibitors and antibodies.

Table 1: Percent Inhibition of Cyclobenzaprine Metabolism by Various Inhibitors

CYP Isoform	1A	2C9	2D6	2E1	3A4
Inhibitor	• 7,8-benzoflavone • furafylline (0.5-1.0 $\mu$ M)	Sulfaphenazole	Quinidine	DDC	• Troleandomycin • Gestodene • Ketoconazole
%Inhibition*	20-40%	<20%	<20%	<20%	40-60%

\*Refer to inhibitor concentration of 20  $\mu$ M unless otherwise specified.

Table 2: Effect of Antibody on the Formation of Desmethylocyclobenzaprine

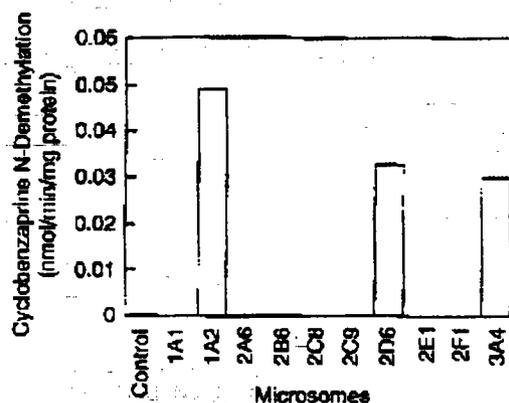
Antibody Added	Metabolite Formed (% of control)		
	HLUM517	HL20309	HL3926
Preimmune IgG	100	100	100
Anti-rat P450 1A1/2	43	13	50
Anti-human P4502C9	114	108	128
Anti-human P4502C19	90	87	106
Anti-human P4502E1	93	100	112
Anti-human P4503A4	44	24	33

The results from selective CYP inhibitors (Table 1) and antibodies (Table 2) showed that CYPs 3A4 and 1A2 are primarily responsible for cyclobenzaprine *N*-demethylation. CYP 2D6 plays only a minor role in cyclobenzaprine metabolism despite its structural similarity to other tricyclic compounds.

b. Metabolism by microsomes from cells containing recombinant human cytochrome P450:

The *N*-demethylation rates of cyclobenzaprine catalyzed by various CYP isoforms are shown in Figure 1. Only microsomes from cells expressing CYP1A2, CYP2D6 and CYP3A4 catalyzed the *N*-demethylation reaction.

Figure 1: Cyclobenzaprine N-demethylation in microsomes from cells containing human cytochrome P450



c. Correlation of Cyclobenzaprine N-demethylation with cytochrome P450 enzyme activities:

Human liver microsomes from 10 humans were used in the study. As presented in Table 3, cyclobenzaprine N-demethylation was strongly correlated with the CYP3A4-mediated testosterone 6 $\beta$ -hydroxylation ( $r=0.74$ ), CYP1A2-mediated caffeine 3-demethylation ( $r=0.75$ ), and total cytochrome P450 content ( $r=0.78$ ). Poor correlation was observed between N-demethylation of cyclobenzaprine and dextromethorphan O-demethylation (CYP2D6).

Table 3: Correlation of Cyclobenzaprine N-Demethylation and P450 Enzyme Activities in Human Liver Microsomes

P450 Enzyme Activity	Correlation Coefficient
P450 Content	0.78
Caffeine 3-demethylation (1A2)	0.75
Tolbutamide methyl-hydroxylation (2C9/10)	0.40
S-Mephenytoin 4'-hydroxylation (2C19)	0.14
Dextromethorphan O-demethylation (2D6)	0.03
Chlorzoxazone 6-hydroxylation (2E1)	0.11
Testosterone 6 $\beta$ -hydroxylation (3A4)	0.74

*Sponsor's conclusion:*

Metabolism of cyclobenzaprine is mediated primarily via CYP 1A2 and 3A4 while CYP2D6 plays only a minor role, so the genetic polymorphism of CYP2D6 should not be a concern in the clinical use of cyclobenzaprine

*Reviewer's comments:*

1. The  $k_m$  value for N-demethylation of cyclobenzaprine was determined using microsomes from three organ donors. The  $k_m$  value so determined may not represent the population (only 3 individuals: one child aged 8 yrs, and 2 adults with history of alcohol and/or drug use) although the values appeared to be close (110-139  $\mu\text{M}$ ) among the 3 subjects.
2. The above studies were carried out at a cyclobenzaprine concentration of 100  $\mu\text{M}$  (or 31.2  $\mu\text{g/mL}$ ) which was close to its  $K_m$  value for N-demethylation. However, this

concentration is more than 2000-fold of the peak plasma concentrations at steady state. (The C<sub>max</sub> after 5 mg tid dosing was only 15 ng/mL.) Because of this, the conclusion may not be applicable to the clinically relevant concentrations.

3. From the literature provided, it is unclear whether the major metabolic pathway is through N-demethylation.

### ***Inhibition of drug metabolism by cyclobenzaprine***

Article: Memo (or letter) to Chiu S-H, L. from Wang R: In vitro interaction studies with cyclobenzaprine, 29-May-1998

The potential for cyclobenzaprine to inhibit six cytochrome P-450-mediated reactions was investigated using human liver microsomes. The results indicate that the inhibition of phenacetin *O*-deethylation (CYP 1A2) and bufuralol 1'-hydroxylation (CYP 2D6) were competitive, while the inhibition of testosterone 6 $\beta$ -hydroxylation (CYP 3A4), midazolam 1'-hydroxylation (CYP 3A4/5), tolbutamide methyl-hydroxylation (CYP 2C), and chlorzoxazone 6-hydroxylation (CYP 2E1) were noncompetitive or uncompetitive.

The *K<sub>i</sub>* values for cyclobenzaprine on cytochrome P-450-mediated reactions were calculated according to the type of inhibition associated with each metabolic reaction. The *K<sub>i</sub>* values were over 150  $\mu$ M except for CYP 2D6 where the *K<sub>i</sub>* value was 43  $\mu$ M (or 13.4  $\mu$ g/mL). The values obtained are much higher than cyclobenzaprine concentrations observed in human plasma at therapeutic doses (mean peak concentration at steady state following the prescription dose of 10 mg every 8 hours was 25.9 ng/mL (0.083  $\mu$ M)). Based on this, cyclobenzaprine has very little potential for inhibition of cytochrome P-450-mediated reactions at therapeutic doses.

CYP Isoforms	Reaction	<i>K<sub>i</sub></i> , $\mu$ M
CYP3A4	Testosterone 6 $\beta$ -Hydroxylation	271
CYP3A4/5	Midazolam 1'-Hydroxylation	165
CYP1A2	Phenacetin <i>O</i> -Deethylation	370
CYP2D6	Bufuralol 1'-Hydroxylation	43
CYP2C	Tolbutamide Methyl-Hydroxylation	325
CYP2E1	Chlorzoxazone 6-Hydroxylation	300

#### ***Reviewer's comment:***

The study report as provided in the NDA submission is too brief to afford a thorough review. The sponsor has been requested to provide a detailed study report.

### **Drug-Drug Interactions**

In vitro studies:

- a. As stated above, in vitro studies appear to indicate that cyclobenzaprine has little potential for inhibition of cytochrome P-450-mediated reactions at clinically relevant concentrations in view of the relatively high *K<sub>i</sub>* values obtained for human liver microsomes. However, the

study report as submitted in the NDA was too brief to allow a thorough evaluation of the data and the sponsor was requested to submit a detailed report.

- b. It is unclear what cytochrome P450 isozyme is the primary enzyme for the metabolism of cyclobenzaprine. Thus, it is not possible to predict which drug may potentially inhibit cyclobenzaprine metabolism.

**In vivo studies:**

The current Flexeril Rx label states that no significant effect on plasma levels of Flexeril or aspirin was noted when single or multiple doses of the two drugs were administered concomitantly. Conflicting results were found in drug interaction with diflunisal and no information regarding coadministration of Flexeril and diflunisal is included in the current Flexeril Rx label. The sponsor did not conduct any other in vivo drug-drug interaction studies.

**Report of adverse event:**

Reported in an article<sup>1</sup> was a case of QT prolongation associated with concomitant cyclobenzaprine and fluoxetine administration (among several other medications) followed by torsade de pointes potentiated by droperidol. The author considered that combination of fluoxetine and cyclobenzaprine resulted in significant QT prolongation in this patient due to inhibition of cyclobenzaprine metabolism by fluoxetine. (This QT prolongation progressed to torsade de pointes following the administration of droperidol, an agent known to prolong the QT interval.) However, no pharmacokinetic data was available to confirm the interaction. Because of this confounding third agent, the significance of this finding is unknown.

<sup>1</sup>Ann Pharmacother 1998; 32(7-8):761-5: Torsade de pointes resulting from the addition of droperidol to an existing cytochrome P450 drug interaction

*Sponsor's conclusion:*

Cyclobenzaprine is subject to both oxidation and conjugation, forming numerous metabolites. Oxidation to form *N*-desmethyl cyclobenzaprine was shown to be mediated primarily by cytochrome P-450s 3A4 and 1A2 with 2D6 having a minor role. This multiplicity of metabolites and pathways indicates that cyclobenzaprine pharmacokinetics are not likely to be affected by drugs that specifically inhibit individual cytochrome P-450 enzymes. In vitro studies have also shown that cyclobenzaprine at clinically relevant concentrations has little potential to inhibit the cytochrome P-450 system and, therefore, the pharmacokinetics of other drugs.

Pharmacokinetic drug-drug interaction studies conducted to support previous applications have shown no clinically significant interaction between cyclobenzaprine and either aspirin or diflunisal. Anecdotal data from the hepatic impairment and elderly studies suggest that acetaminophen does not substantially alter cyclobenzaprine pharmacokinetics.

No reports of pharmacokinetic drug-drug interactions involving cyclobenzaprine have been identified in the literature despite extensive market experience at the prescription strength of 10 mg.

Based on these observations, cyclobenzaprine has little potential for clinically significant pharmacokinetic drug-drug interactions. No new pharmacokinetic drug-drug interaction studies were conducted in support of this application.

Several potential pharmacodynamic interactions are identified in the product circular for cyclobenzaprine hydrochloride 10-mg tablets. Cyclobenzaprine may interact with MAO inhibitors. Hyperpyretic crisis, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and MAO inhibitor drugs. Cyclobenzaprine may enhance the effects of alcohol, barbiturates, and other CNS depressants. Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds. These effects may also occur with cyclobenzaprine, which is structurally similar to tricyclic antidepressants.

It also has been reported that the risk of seizures in patients taking the analgesic tramadol is increased with concomitant administration of tricyclic antidepressants. This pharmacodynamic interaction likely reflects a reduction of the seizure threshold by the tricyclic compound. A published report indicates that seizures have been reported in 4 patients who took cyclobenzaprine and tramadol concomitantly. Based on this information, it would seem to be prudent to avoid concomitant use of cyclobenzaprine and tramadol.

*Reviewer's comments:*

1. It is noted that the recovery of total (urine + feces) radioactivity was low (~64% of dose) in a mass balance study and a major urinary metabolite was not identified. Because of this, the study does not provide a clear picture of metabolite profiles of cyclobenzaprine.
2. The sponsor concluded that the *N*-demethylation reaction of cyclobenzaprine was mediated primarily via cytochrome P-450s 3A4 and 1A2, while cytochrome P-450 2D6 played a minor role. As a result, the sponsor concluded that genetic polymorphism was not a concern for this drug. However, these studies were conducted at a high concentration of cyclobenzaprine (100  $\mu$ M) which was more than 2000-fold of the peak plasma cyclobenzaprine concentration at steady state. Thus, the studies are not considered definitive and it is unclear which isozyme actually plays a major role in the metabolism of cyclobenzaprine at the clinically relevant concentrations. In addition, the information as submitted by the sponsor did not indicate that *N*-demethylation is the predominant metabolic pathway since other metabolites such as *N*-oxide and hydroxylated compounds of cyclobenzaprine and other unidentified compounds were also excreted in the urine.

#### **IN VITRO DISSOLUTION**

The dissolution test method and specification for cyclobenzaprine hydrochloride 5-mg Tablets are described below:

Apparatus:	USP Apparatus I (baskets), 50 rpm
Medium:	900 mL of 0.1 N HCl at 37°C $\pm$ 0.5°C
Sampling time:	30 minutes
Analytical method:	UV with absorbance at 225 nm

Specification: Q= 75% at 30 minutes  
(For a dissolution profile, samples are withdrawn after 10, 15, 20, and 30 minutes.)

Dissolution test results for cyclobenzaprine hydrochloride 5-mg tablets used in the clinical studies are provided.

*Reviewer's comment:*

Based on the dissolution profiles of three batches, the dissolution specification should be tightened at least to Q=80% at 20 minutes.

# APPENDIX I

## Individual Data

**Clinical Pharmacology / Biopharmaceutics Study Summary Sheet**

NDA/IND#	21-070	Suppl. Amend		Submission date	12/18/1998	Volume	1.7
Study Type	PK			Study #	005		
Study Title	An Open-Label, randomized, Three-Period Crossover Study in Healthy Volunteers to Investigate Single- and Multiple Dose Pharmacokinetics and Dose Proportionality of Cyclobenzaprine HCl Tablets						

Clinical Investigator	Guy Florino, MD	Analytical investigator	
Site	L.A.B., Inc.	Site	Merck Research Laboratories
	700 Grand Ave		PO Box 4
	Ridgefield, NJ 07657		West Point, PA 19486

Single dose	X	Multiple dose	X	Washout period	14 days
Cross-over	X	Parallel		Other Design	

Subject breakdown									
Normal	X	Patients		Young	X	Elderly		Renal	Hepatic

	Subject type	Normal, young			Group		N=	M=	F=				
Weight (kg)	Mean	59.8	Range	53	88	Group	N=	M=	F=				
Age	Mean	28.7	Range	22	40	Group	Xover	N=	18	M=	8	F=	10

Treatment group	Dose	Dosage Form	Strength	Lot#	Lot size
1	SD/MD	FCT	2.5 mg	0130FCT003 D001	30,000
2	SD/MD	FCT	5 mg	0130FCT003 B001	30,000
3	SD/MD	FCT	10 mg	C0130FCT003A010	4.8 million

Sampling Times	
Plasma	Day 1: Predose, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144, and 168 hrs; Days 8-14: prior to dose 2, 5, 8, 11, 14, 17, and 20; Day 15: predose, 1, 2, 3, 4, 6, and 8 hrs.
Urine	1.5-hr timed collection prior to dose and 0-8 hrs postdose after the first and final doses.
Feces	NA

Assay method	HPLC-tandem mass spectrometric detection
Assay Sensitivity	0.10 and 10 ng of cyclobenzaprine per mL of plasma and urine, respectively
Assay Accuracy	Plasma: 92.0-104.1% over the concentration range 0.10-50.00 ng/mL Urine: 92.0-103.4% over the concentration range 10.00-1000.0 ng/mL

Labeling claims from study	Not applicable
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Cyclobenzaprine Oral Pharmacokinetics Study  
 D.M. #1044, M.A. #005-00 *single/multiple dose PK*

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Table I

## Demographics of Study Subjects

Subject	Sex	Age	Race	Weight (kg)	Height (cm)
1	M	32	Caucasian	71.0	170
2	M	29	Hispanic	76.5	174
3	M	29	Hispanic	66.0	170
4	F	29	Caucasian	60.0	158
5	M	29	Caucasian	82.0	167
6	F	22	Caucasian	62.0	170
7	F	37	Caucasian	57.0	168
8	F	40	Caucasian	79.0	166
9	M	31	Caucasian	88.0	187
10	M	25	Caucasian	76.0	176
11	F	25	Hispanic	63.5	153
12	F	36	Caucasian	62.0	158
13	F	32	Caucasian	68.0	161
14	F	29	Caucasian	53.0	160
15	M	26	Black	80.0	179
16	M	25	Hispanic	61.0	165
17	F	22	Hispanic	51.0	162
18	F	22	Black	61.0	172
		<i>28.9 ±</i>		<i>67.6 ±</i>	

body wt.

8 M: 75.1 ±

(1.22 x)

10 F: 61.7 ±

(0.82 x)

Cyclobenzaprine Oral Pharmacokinetics Study  
D.M. #1044, M.A. #005-00

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Table 10  
Peak Plasma Concentration,  $C_{max}$ , and Time to Peak Concentration,  $T_{max}$ , After a Single Dose (Day 1) and at Steady State (Day 15)

Subject	$C_{max}$ , ng/mL						$T_{max}$ , hr					
	2.5-mg Dose		5-mg Dose		10-mg Dose		2.5-mg Dose		5-mg Dose		10-mg Dose	
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
1	1.45	4.21	3.93	8.65	4.97	17.45	3	3	3	4	6	4
2	2.30	6.87	3.13	18.08	8.95	22.27	4	4	6	3	3	4
3	2.06	3.96	2.75	10.23	7.15	20.25	3	4	6	6	3	3
4	3.09	13.68	6.16	26.09	12.07	40.86	3	4	3	8	4	4
5	1.80	4.49	3.44	14.59	7.00	20.53	3	4	4	3	3	3
6	0.93	2.66	2.27	5.67	4.79	14.80	6	3	4	4	4	8
7	1.53	9.69	4.37	18.85	7.89	46.10	6	8	4	3	6	4
8	1.64	4.67	2.92	9.26	7.26	19.97	4	3	4	4	3	6
9	1.50	6.27	3.90	15.94	6.86	21.00	3	2	4	3	3	3
10	1.22	2.54	2.21	5.87	3.67	12.75	3	3	6	3	4	3
11	2.67	11.31	6.39	22.88	7.05	43.32	4	4	6	3	4	3
12	1.78	6.83	4.03	13.32	5.59	15.93	3	4	1	4	4	4
13	3.00	8.26	6.39	18.30	8.47	21.54	3	2	3	3	4	4
14	1.84	6.20	2.75	11.64	3.94	22.78	4	4	4	6	6	2
15	1.51	3.42	3.48	6.99	11.43	15.55	6	6	4	4	3	3
16	3.08	9.37	7.34	20.06	13.64	39.41	2	4	3	3	2	2
17	3.24	11.00	5.78	25.75	14.46	29.60	4	3	3	4	3	4
18	2.32	12.14	5.94	16.56	18.69	42.97	6	3	3	4	4	2
Mean	2.1	7.1	4.3	14.9	8.5	25.9	3.9	3.8	3.9	4.0	3.8	3.9
S.D.	0.7	3.4	1.6	6.4	4.0	11.3	1.3	1.4	1.3	1.4	1.2	1.8

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Cyclobenzaprine Oral Pharmacokinetics Study  
D.M. #1044, M.A. #005-00

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Table II

Plasma Area Under the Concentration-Time Curve (ng-hr/mL) of Cyclobenzaprine

Subject	2.5-mg Dose			5-mg Dose			10-mg Dose		
	AUC <sub>0-1</sub>		AUC <sub>0-2</sub>	AUC <sub>0-1</sub>		AUC <sub>0-2</sub>	AUC <sub>0-1</sub>		AUC <sub>0-2</sub>
	Day 1	Day 15	Day 1	Day 1	Day 15	Day 1	Day 1	Day 15	Day 1
1	7.5	30.0	24.2	20.7	57.3	70.2	26.1	118.2	116.4
2	11.4	51.9	44.4	16.3	114.0	75.5	41.9	145.3	199.4
3	11.0	27.5	40.4	15.1	71.6	42.3	39.3	128.3	111.2
4	16.3	92.7	67.2	✓34.2	✓182.9	131.9	63.1	267.0	238.4
5	9.0	31.3	25.6	19.3	99.1	68.3	38.0	140.8	134.2
6	4.2	16.7	11.8	✓10.9	✓36.1	38.1	26.3	97.8	77.8
7	9.4	60.8	43.5	✓22.6	✓126.6	90.8	43.1	293.0	202.0
8	8.6	31.7	37.4	✓15.5	✓64.0	43.7	39.7	147.1	161.2
9	8.1	42.3	40.9	23.1	98.5	111.5	43.1	146.7	190.1
10	6.5	15.5	18.2	11.3	41.1	33.7	20.8	80.0	60.1
11	16.0	78.2	88.0	37.1	✓158.2	206.8	43.6	318.5	230.8
12	9.2	44.7	31.8	26.2	✓89.7	67.7	30.9	117.1	130.7
13	15.1	52.6	53.2	31.7	✓122.1	125.3	41.1	145.5	158.2
14	10.3	41.3	41.2	15.3	✓87.7	64.6	21.4	164.0	116.9
15	7.8	23.6	32.5	16.1	41.8	63.4	54.7	92.1	178.2
16	17.2	64.7	58.9	32.6	142.5	100.1	73.4	250.1	223.8
17	19.1	73.1	66.6	33.2	✓171.6	154.8	80.6	211.6	297.8
18	13.9	73.7	69.7	32.1	✓119.9	122.7	100.0	314.3	380.1
Mean	11.1	47.4	44.2	23.0	101.4	89.5	46.0	176.5	178.2
S.D.	4.2	22.6	19.9	8.6	44.8	45.8	21.3	78.4	78.8

148.8

F: 115.9

M: 83.3

CV: 72%

F<sub>M</sub>: 1.39

Cyclobenzaprine Oral Pharmacokinetics Study  
D.M. #1044, M.A. #005-00

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Table 15

Urinary Excretion of Total Cyclobenzaprine (Free + Conjugates) Over Eight Hours  
After a Single Dose (Day 1) and at Steady State (Day 15)

Subject	Amount Excreted ( $\mu$ g) in Urine					
	2.5-mg Dose		5-mg Dose		10-mg Dose	
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
1	75.4	241.8	144.0	799.2	112.2	469.4
2	59.2	125.8	116.4	118.6	105.9	115.8
3	50.6	26.6	93.4	102.7	181.9	454.8
4	31.7	95.6	84.5	292.8	88.2	171.7
5	57.2	39.4	551.3	390.8	205.2	416.1
6	22.1	244.0	148.6	154.3	196.8	647.0
7	51.0	287.9	52.9	685.5	179.4	253.4
8	102.4	112.9	67.9	438.3	271.4	1185.7
9	51.0	384.5	208.2	637.5	262.1	546.9
10	24.8	124.0	106.2	157.9	331.8	894.8
11	55.3	41.5	108.8	302.5	169.7	938.8
12	103.1	199.8	205.5	126.9	223.4	404.2
13	32.8	119.2	35.7	665.4	379.3	129.2
14	52.0	108.9	109.3	783.2	182.3	574.1
15	27.4	111.2	100.5	91.0	129.1	437.2
16	40.6	74.6	18.6	380.5	143.5	805.2
17	68.5	185.2	43.3	331.1	316.8	148.5
18	BLQ	106.4	31.1	13.7	21.5	89.2
Mean	53.2	146.1	123.7	320.7	194.5	482.3
S.D.	24.0	94.3	119.7	238.4	91.8	316.6

BLQ = Below limit of quantification

Notebook/Page: 13101/225-236

**Clinical Pharmacology / Biopharmaceutics Study Summary Sheet**

NDA/IND#	21-070	Suppl. Amend	Submission date	12/18/1998	Volume	1.7
Study Type	PK		Study #	011		
Study Title	An open, three-period crossover study to determine the bioequivalence/bioavailability of FLEXERIL tablets 5 mg (planetary process) and FLEXERIL tablets 5 mg (high-shear process)					

Clinical investigator	James Kisicki, MD	Analytical investigator	
Site	Harris Laboratories	Site	Merck Research Laboratories
	624 Peach St.		PO Box 4
	Lincoln, NE 68502		West Point, PA 19486

Single dose	X	Multiple dose		Washout period	7 days
Cross-over	X	Parallel		Other Design	

Subject breakdown									
Normal	X	Patients		Young	X	Elderly		Renal	Hepatic

	Subject type	Normal Young				Group	N=	M=	F=
Weight (lb)	Mean	177.5	Range	116	229	Group	N= 24	M= 16	F= 8
Age	Mean	25.5	Range	19	39	Group	N=	M=	F=

Treatment group	Dose	Dosage Form	Strength	Lot#	Lot size
A	High shear	FCT	5 mg	0130FCT007 B003	3.2 million
B	Planetary	FCT	5 mg	0130FCT003 B002	150,000
C	IV	Injection	1.25 mg	0130HSS002 A001	100 mL

Sampling Times	
Plasma	Predose, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168 hrs postdose for all treatments and additionally, 5, 15, 30, 45, and 90 min postdose for the IV dose
Urine	NA
Feces	NA

Assay method	HPLC with tandem mass spectrometric detection
Assay Sensitivity	0.10 ng of cyclobenzaprine per mL of plasma
Assay Accuracy	Ranged from 94.7 to 106.0% over the standard curve from 0.10 ng/mL to 50.00 ng/mL

Labeling claims from study	NA
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Study Demographics

Subject	Gender	Age	Hi (in.)	Wt. (lb.)	Race
1	M	27	72	162	Caucasian
2	M	25	76	194	Caucasian
3	M	33	68	197	Caucasian
4	F	23	63	✓157	Caucasian
5	M	27	72	197	Hispanic
6	M	23	68	175	Caucasian
8	M	20	66	196	Caucasian
9	M	23	72	150	Caucasian
10	F	29	66	✓167	Caucasian
13	M	23	71	218	Black
14	M	28	72	183	Caucasian
15	F	20	70	✓207	Caucasian
16	M	23	76	169	Caucasian
17	F	22	63	✓116	Caucasian
18	M	22	73	229	Caucasian
19	F	28	67	✓193	Black
20	M	23	70	143	Caucasian
21	M	23	72	167	Hispanic
22	F	22	70	✓181	Caucasian
23	M	39	70	175	Caucasian
24	F	38	64	✓151	Hispanic
Mean	16 M	25.8	69.6	177.5 (80.7 Kg)	
S.D.	7 F	5.3	3.7	26.7	

F = 26%      F = 16.74 (76.1 kg) 17% (18% ✓)  
M = 25.9%      M = 18.5 (83.0 kg)  
15%

Summary of Characteristics for Subjects Completing All Three Periods

		Total
Sample Size		21
Age (yrs)	Mean (SD)	25.8 ± 5.3
Race	Caucasian	16 (76.2%)
	Hispanic	3 (14.3%)
	Black	2 (9.5%)
Sex	Female	7 (33.3%)
	Male	14 (67.7%)

**Cyclobenzaprine Pharmacokinetic Parameters After Oral Administration of  
FLEXERIL 5-mg High-Shear Process Tablets and FLEXERIL 5-mg Planetary Process Tablets**

Subject	AUC <sub>0-∞</sub> , ng-hr/mL		AUC Ratio	C <sub>max</sub> , ng/mL		C <sub>max</sub> Ratio	T <sub>max</sub> , hr	
	HS	PL		HS	PL		HS	PL
1	57.6	50.1	1.15	3.60	2.84	1.27	4	4
2	44.7	50.0	0.89	2.42	3.02	0.80	4	4
3	53.6	52.0	1.03	3.30	3.56	0.93	6	3
4	√86.7	116.8	0.74	4.05	5.40	0.75	4	4
5	76.7	72.6	1.06	3.32	2.89	1.15	6	8
6	59.3	51.6	1.15	3.26	3.06	1.06	4	4
8	52.6	48.4	1.09	2.63	2.22	1.19	4	4
9	84.1	76.8	1.10	3.06	3.05	1.00	6	4
10	√57.6	76.8	0.75	3.57	4.20	0.85	4	6
13	110.6	116.0	0.95	4.90	4.54	1.08	6	6
14	37.7	32.9	1.14	2.32	2.29	1.01	4	4
15	√82.7	83.2	0.99	3.17	3.15	1.01	6	6
16	35.4	47.5	0.74	2.13	2.76	0.77	6	6
17	√97.3	77.9	1.25	5.07	3.76	1.35	4	6
18	86.3	69.7	1.24	3.55	3.32	1.07	3	4
19	√95.4	105.8	0.90	3.08	3.81	0.81	4	4
20	22.4	36.3	0.62	1.54	3.25	0.47	3	3
21	72.0	56.6	1.27	2.85	2.29	1.25	6	6
22	√35.6	40.6	0.88	2.02	1.92	1.05	6	6
23	61.9	62.6	0.99	2.52	2.62	0.96	5	4
24	√78.4	60.2	1.30	4.96	3.27	1.52	4	4
Mean	66.1	65.9	1.00 <sup>a</sup>	3.21	3.20	1.00 <sup>a</sup>	4.7	4.8
S.D.	23.6	24.2	(0.92, 1.08) <sup>b</sup>	0.96	0.82	(0.92, 1.10) <sup>b</sup>	1.1	1.3

<sup>a</sup> - Geometric mean

<sup>b</sup> - 90% confidence interval

Geometric mean and 90% confidence interval limits calculated using analysis of variance by Department of Biostatistics and Research Data Systems

HS - High-shear process tablet  
PL - Planetary process tablet

Study 011

AUC	HS	PL
F:	76.2 ±	80.2 ±
M:	61.0 ±	58.8 ±
(F: 25% ↑)		(F: 36% ↑)

Study 011

Area Under the Plasma Concentration-Time Curve ( $AUC_{0-\infty}$ ) and Plasma Clearance ( $Cl_r$ ) Following Intravenous Bolus Administration of 1.25 mg Cyclobenzaprine Hydrochloride

Subject	$AUC_{0-\infty}$ ng-hr/mL	$Cl_r$ mL/min
1	16.9	1091
2	22.9	806
3	18.1	1019
4	33.1	556
5	34.7	532
6	27.5	672
8	30.0	614
9	39.4	468
10	36.4	507
13	43.4	425
14	17.5	1053
15	43.7	422
16	19.5	946
17	34.9	528
18	29.8	618
19	37.8	488
20	18.6	991
21	29.5	625
22	23.9	772
23	29.0	635
24	26.6	693
Mean	29.2	688.6
S.D.	8.4	215.6

Bioavailability of Cyclobenzaprine After Oral Administration of FLEXERIL 5-mg High-Shear Process Tablets and FLEXERIL 5-mg Planetary Process Tablets

Subject	Bioavailability	
	High-Shear	Planetary
1	0.85	0.74
2	0.49	0.55
3	0.74	0.72
4	0.65	0.88
5	0.55	0.52
6	0.54	0.47
8	0.44	0.40
9	0.53	0.49
10	0.40	0.53
13	0.64	0.67
14	0.54	0.47
15	0.47	0.48
16	0.45	0.61
17	0.70	0.56
18	0.72	0.58
19	0.63	0.70
20	0.30	0.49
21	0.61	0.48
22	0.37	0.43
23	0.53	0.54
24	0.74	0.57
Geo. Mean*	0.55	0.55
90% C. I.*	(0.51, 0.60)	(0.51, 0.60)

\* Geometric mean and 90% confidence interval limits calculated using analysis of variance by Department of Biostatistics and Research Data Systems

## Clinical Pharmacology / Biopharmaceutics Study Summary Sheet

NDA/iND#	21-070	Suppl. Amend		Submission date	12/18/1998	Volume	1.7
Study Type	PK			Study #	010		
Study Title	An open-label, multiple-dose study to investigate the pharmacokinetics of MK-0130 in elderly (≥65 years) subjects						

Clinical Investigator	Kenneth C. Lasseter, MD	Analytical investigator	
Site	Clinical Pharmacology Associates	Site	Merck Research Laboratories
	2060 North West 22 <sup>nd</sup> Ave.		PO Box 4
	Miami, FL 33142		West Point, PA 19486

Single dose		Multiple dose	X	Washout period	
Cross-over		Parallel	X	Other Design	X-historical controls were used from Study 005

Subject breakdown									
Normal	X	Patients		Young		Elderly	X	Renal	
								Hepatic	

	Subject type	Elderly				Group	N=	M=	F=
Weight (lb)	Mean	162.5	Range	132	207	Group	N= 12	M= 6	F= 6
Age	Mean	71.3	Range	65	79	Group	N=	M=	F=

Treatment group	Dose	Dosage Form	Strength	Lot#	Lot size
Elderly	tid	FCT	5 mg	0130FCT003 B002	150,000

Sampling Times	
Plasma	With respect to the morning dose: predose, 1, 2, 3, 4, 6, and 8 hours postdose on Days 1 and 8; predose on Days 2 to 7
Urine	NA
Feces	NA

Assay method	HPLC with tandem mass spectrometric detection
Assay Sensitivity	0.10 ng of cyclobenzaprine per mL of plasma
Assay Accuracy	Ranged from 96.8 to 112.0% over the standard curve from 0.10 ng/mL to 50.00 ng/mL

Labeling claims from study	Consult your doctor before taking this product if you are ≥65 years old.
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## Study 010: Elderly vs. Young

### Study Demographics

Subject	Gender	Age	Ht (in.)	Wt (lb.)	Race
1	F	65	65	178	Hispanic
2	F	70	66	154	Caucasian
3	F	65	66	168	Caucasian
4	F	74	65	142	Caucasian
5	F	70	69	133	Caucasian
6	F	74	65	139	Caucasian
7	M	65	68	132	Black
8	M	70	71	207	Caucasian
9	M	79	67	181	Caucasian
10	M	72	67	166	Hispanic
11	M	75	64	181	Hispanic
12	M	77	68	169	Hispanic
Mean		71.3	66.8	162.5	
S.D.		4.7	2.0	23.0	

### Young subjects, n=18 (Study #005)

Mean	10 F	29.9	66.0	148.7	5 Hispanic 11
S.D.	8 M	5.2	3.3	23.3	Caucasian
Min.		23	60.2	112.2	2 Black
Max		41	73.6	193.6	

### Summary of Subject Characteristics

Sample Size	Mean (SD)	Elderly	Young	Total
		12	18	30
Age (Years)		71.3 ± 4.7	28.7 ± 5.2	46.5
Race	Caucasian	7 (58.3%)	11 (61.1%)	18 (60%)
	Hispanic	4 (33.3%)	5 (27.8%)	9 (30%)
	Black	1 (8.3%)	2 (11.1%)	3 (10%)
Sex	Female	6 (50%)	10 (55.6%)	16 (53.3%)
	Male	6 (50%)	8 (44.4%)	14 (46.7%)

Study 010

Summary of AUC<sub>(0-∞)</sub> Day 1  
All Treated Subjects

	Population Geometric Means			Geometric Mean Ratio (E/Y)		
	Elderly	Young	Overall	GMR	90% C.I.	P-value
Overall	20.1	21.1	20.9	0.95	(0.76,1.20)	0.727
Male	22.1	18.5	20.2	1.20	(0.86,1.67)	0.353
Female	18.3	24.1	21.0	0.76	(0.55,1.04)	0.146
GMR (M/F)	1.21	0.77	0.96			
90% C.I.	(0.85,1.72)	(0.57,1.02)	(0.77,1.21)			

Summary of C<sub>max</sub> Day 1  
All Treated Subjects

	Population Geometric Means			Geometric Mean Ratio (E/Y)		
	Elderly	Young	Overall	GMR	90% C.I.	P-value
Overall	3.85	3.96	3.95	0.97	(0.79,1.21)	0.832
Male	4.12	3.56	3.83	1.16	(0.85,1.58)	0.428
Female	3.61	4.41	3.99	0.82	(0.61,1.10)	0.260
GMR (M/F)	1.14	0.81	0.96			
90% C.I.	(0.82,1.59)	(0.62,1.06)	(0.77,1.19)			

Summary of AUC<sub>(0-∞)</sub> Day 8  
All Treated Subjects

	Population Geometric Means			Geometric Mean Ratio (E/Y)		
	Elderly	Young	Overall	GMR	90% C.I.	P-value
Overall	174.4	92.1	118.1	1.89	(1.44,2.49)	<0.001
Male	212.8	101.2	146.8	2.10	(1.41,3.13)	0.004
Female	142.9	83.7	109.4	1.71	(1.17,2.49)	0.024
GMR (M/F)	1.49	1.21	1.34			
90% C.I.	(0.97,2.28)	(0.85,1.71)	(1.02,1.77)			

Summary of C<sub>max</sub> Day 8  
All Treated Subjects

	Population Geometric Means			Geometric Mean Ratio (E/Y)		
	Elderly	Young	Overall	GMR	90% C.I.	P-value
Overall	24.4	13.3	17.1	1.84	(1.41,2.39)	<0.001
Male	29.6	11.5	18.4	2.57	(1.76,3.76)	<0.001
Female	20.1	15.3	17.6	1.31	(0.91,1.89)	0.211
GMR (M/F)	1.47	0.75	1.05			
90% C.I.	(0.98,2.20)	(0.54,1.05)	(0.81,1.37)			

Study 010

Area Under the Plasma Concentration-Time Curve of Cyclobenzaprime Over the First and Last Dosing Interval and the Corresponding Accumulation Ratio (R)

Subject	AUC <sub>0-24h</sub> ng·h/ml		R
	First Dose	Last Dose	
1	15.7	196.3	12.5
2	12.1	96.1	5.3
3	15.6	107.7	6.9
4	24.0	137.4	5.7
5	15.2	168.0	(11.1) <sup>a</sup>
6	23.0	181.3	7.9
7	16.2	205.9	12.7
8	30.4	175.1	5.8
9	40.8	255.3	6.3
10	21.8	199.7	9.2
11	14.4	155.6	10.8
12	18.7	325.0	(17.4) <sup>a</sup>
Mean	21.2	183.6	7.9 <sup>a</sup>
S.D.	7.8	62.3	(5.3-12.7) <sup>a</sup>

Young subjects, n=18 (Study #005)

Mean	23.0	101.4	4.4 <sup>a</sup>
S.D.	8.6	44.8	—
Range	(10.9-37.1)	(36.1-182.9)	(2.6-9.8)

<sup>a</sup> Excluded; did not reach steady state due to illness  
<sup>a</sup>Geo. Mean <sup>a</sup>Range

Peak Plasma Concentration and Time to Peak Plasma Concentration of Cyclobenzaprime After the First and Last Dose

Subject	C <sub>max</sub> ng/ml		T <sub>max</sub> h	
	First Dose	Last Dose	First Dose	Last Dose
1	4.1	27.1	6	4
2	3.1	13.3	6	6
3	3.3	15.0	8	6
4	4.0	19.8	6	2
5	3.0	25.3	4	4
6	4.4	24.6	3	2
7	3.0	27.7	4	2
8	4.6	25.1	6	4
9	6.7	36.3	3	8
10	5.3	28.4	8	8
11	3.2	20.9	8	8
12	3.1	44.6	4	4
Mean	4.0	25.7	5.3	4.8
S.D.	1.1	8.6	1.9	2.3

Young subjects, n=18 (Study #005)

Mean	4.3	14.9	3.9	4.0
S.D.	1.6	6.5	1.3	1.4
Range	(2.2-7.3)	(5.7-26.1)	(1-6)	(2-8)

Effective Half-Life, Predicted Steady-State Trough Concentration C<sub>min</sub>(SS) and Percent of Steady State (%SS) Achieved Based on Monoexponential Fit of Cyclobenzaprime Trough Concentrations

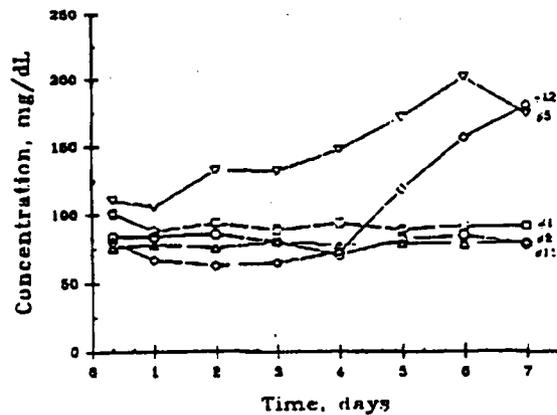
Subject	t <sub>1/2</sub> h	C <sub>min</sub> (SS), ng/ml	%SS
1	51.3	24.2	91
2	24.0	9.7	99
3	30.2	11.3	98
4	20.0	13.1	100
5 <sup>a</sup>	31.6	11.3	—
6	43.5	19.2	94
7	53.4	28.3	90
8	34.5	18.9	97
9	36.8	21.4	96
10	24.3	20.9	99
11	43.3	20.6	94
12 <sup>a</sup>	46.1	17.5	—
Mean	33.4 <sup>a</sup>	18.9	96
Range	(20-53.4)	(9.7-31.4)	(90-100)

Young subjects, n=18 (Study #005)

Mean	18.4	10.8	99
Range	(4-41.3)	(3.7-18.7)	(95-100)

<sup>a</sup> Only trough concentrations prior to onset of illness were fit  
<sup>a</sup> Harmonic Mean

Plasma Concentration of α-1-Acid Glycoprotein in Selected Subjects Receiving Cyclobenzaprime (Subjects 5 and 12 reported illness)



**Clinical Pharmacology / Biopharmaceutics Study Summary Sheet**

NDA/IND#	21-070	Suppl./ Amend		Submission date	12/18/1998	Volume	1.7
Study Type	PK			Study #	007		
Study Title	An Open-Label, multiple-dose, parallel study to determine the influence of hepatic insufficiency on the pharmacokinetics of MK-0130						

Clinical investigator	Kenneth C. Lasseter, MD	Analytical investigator	
Site	Clinical Pharmacology Associates	Site	Merck Research Laboratories
	2060 Northwest 22 <sup>nd</sup> Ave.		PO Box 4
	Miami, FL 33142		West Point, PA 19486

Single dose		Multiple dose	X	Washout period	
Cross-over		Parallel	X	Other Design	

Subject breakdown									
Normal	X	Patients		Young		Elderly		Renal	
								Hepatic	X

	Subject type	Normals				Group	N=	M=	F=
Weight (lb)	Mean	160.6	Range	139	188	Group	N= 8	M= 5	F= 3
Age	Mean	52.5	Range	40	65	Group	N=	M=	F=
	Subject type	Hepatic				Group	N=	M=	F=
Weight (lb)	Mean	180.3	Range	146	238	Group	N= 16	M= 11	F= 5
Age	Mean	58.2	Range	41	67	Group	N=	M=	F=

Treatment group	Dose	Dosage Form	Strength	Lot#	Lot size
Normal	tid	FCT	5 mg	0130FCT003 B001	30,000
Hepatic	tid	FCT	5 mg	0130FCT003 B001	30,000

<b>Sampling Times</b>	
Plasma	With respect to morning dose: predose, 1, 2, 3, 4, 6, and 8 hours on Days 1 and 8, predose on Days 2 and 7
Urine	NA
Feces	NA

Assay method	HPLC with tandem mass spectrometric detection
Assay Sensitivity	0.10 ng of cyclobenzaprine per mL of plasma
Assay Accuracy	Ranged from 98.0 - 106.0% over the concentration range of 0.10-50.00 ng/mL

Labeling claims from study	See a doctor before using this product.
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Cyclobenzaprine Hepatic Insufficiency Study  
D.M. #1105, M.A. #007-00

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**Table 4**  
Study Demographics

Subject	Gender	Age	Ht (in.)	Wt (lb.)	Race	Acetaminophen Administration
<b>Patients with hepatic insufficiency</b>						
1	F	67	61	174	Caucasian	None
2	F	60	63	172	Caucasian	None
3	F	65	63	167	Hispanic	None
4	F	47	65	200	Black	None
5	F	52	63	146	Black	None
9	M	42	67	175	Hispanic	None
11	M	59	69	195	Black	None
12	M	55	67	166	Hispanic	None
13	M	48	65	161	Caucasian	None
14	M	52	72	195	Caucasian	None
15	M	54	64	152	Caucasian	325 mg Day 1 and 500 mg Day 7
16	M	52	72	225	Caucasian	325 mg Day 1 and Day 6
17	M	60	65	159	Hispanic	None
18	M	41	72	238	Caucasian	None
19	M	54	71	184	Hispanic	500 mg Day 5 and Day 6
24	M	60	70	175	Caucasian	2x325 mg Day 1 and 325 mg Day 2
Mean		54.3	66.8	180.3		
S.D.		7.5	3.7	25.2		
<b>Age-matched healthy subjects</b>						
6	F	46	64	149	Hispanic	None
7	F	65	62	139	Caucasian	None
8	F	65	62	168	Caucasian	None
10	M	40	67	155	Hispanic	None
20	M	46	70	153	Caucasian	None
21	M	56	72	174	Hispanic	None
22	M	43	72	159	Hispanic	None
23	M	59	72	188	Caucasian	325 mg Day 7
Mean		52.5	67.6	160.6		
S.D.		10.0	4.5	15.5		

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Cyclobenzaprine Hepatic Insufficiency Study  
D.M. #1105, M.A. #007-00

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Table 7

Peak Plasma Concentration and Time to Peak Plasma Concentration of  
Cyclobenzaprine After the First and Last Dose

Subject	C <sub>max</sub> , ng/ml		T <sub>max</sub> , h	
	Day 1	Day 8	Day 1	Day 8
<u>Patients with hepatic insufficiency</u>				
1	5.7	34.7	6	4
2	5.2	41.2	4	3
3	3.5	21.2	6	6
4	5.2	41.4	2	3
5	5.6	47.4	4	6
9	5.7	49.5	4	4
11	8.0	56.3	6	1
12	4.3	27.4	8	8
13	7.0	44.9	3	3
14	4.2	22.1	4	2
15	5.5	27.0	4	2
16	2.9	11.1	3	3
17	3.2	28.0	8	4
18	3.9	27.7	8	3
19	3.0	15.3	3	3
24	3.2	24.0	4	2
Mean	4.8	32.5	4.8	3.6
S.D.	1.5	13.0	1.9	1.8
<u>Age-matched healthy subjects</u>				
6	8.1	31.5	3	4
7	7.2	44.8	2	8
8	4.5	32.2	8	4
10	3.2	11.1	3	4
20	2.8	7.9	4	3
21	2.7	14.3	6	6
22	6.0	18.0	4	3
23	2.5	12.2	4	4
Mean	4.6	21.5	4.3	4.5
S.D.	2.2	13.1	1.9	1.7

Cyclobenzaprine Hepatic Insufficiency Study  
D.M. #1105, M.A. #007-00

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Table 8

Area Under the Plasma Concentration-Time Curve of Cyclobenzaprine Over the First and Last Dosing Interval and the Corresponding Accumulation Ratio (R)

Subject	AUC <sub>0-24</sub> , ng <sup>2</sup> /ml		R
	Day 1	Day 8	
<u>Patients with hepatic insufficiency</u>			
1	33.1	262.6	7.9
2	36.0	290.1	8.1
3	20.5	138.6	6.8
4	26.4	264.9	10.0
5	31.4	298.8	9.5
9	36.3	336.4	9.3
11	34.9	426.4	12.2
12	22.3	206.4	9.3
13	43.9	306.2	7.0
14	26.4	154.2	5.8
15	30.1	189.9	6.3
16	15.5	68.3	4.4
17	14.7	197.1	13.4
18	20.9	198.4	9.5
19	16.6	105.5	6.4
24	18.9	161.5	8.5
Mean	26.7	225.3	8.2*
S.D.	8.7	93.3	(4.4-13.4) <sup>b</sup>
<u>Age-matched healthy subjects</u>			
6	41.9	239.5	5.7
7	46.6	315.3	6.8
8	22.9	241.4	10.5
10	18.1	81.0	4.5
20	16.9	55.5	3.3
21	11.9	104.2	8.8
22	33.6	128.8	3.8
23	13.2	85.5	6.5
Mean	25.6	156.4	6.0*
S.D.	13.4	95.4	(3.3-10.5) <sup>b</sup>

\*Geo. Mean <sup>b</sup>Range

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Cyclobenzaprine Hepatic Insufficiency Study  
D.M. #1105, M.A. #007-00

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Table 9

Effective Half-Life, Predicted Steady-State Trough Concentration  $C_{min}(ss)$  and Percent of Steady State (%SS) Achieved Based on Monoexponential Fit of Cyclobenzaprine Trough Concentrations

Subject	$t_{1/2}$ , h	$C_{min}(SS)$ , ng/ml	%SS
<u>Patients with hepatic insufficiency</u>			
1	89.3	42.8	73
2	68.9	37.7	82
3	33.5	13.9	97
4	97.0	48.0	70
5	45.4	34.7	92
9	188.0	98.4	46
11	63.2	53.3	84
12	38.9	27.6	95
13	76.9	46.9	78
14	29.6	15.5	98
15	60.3	23.0	86
16	22.4	6.6	100
17	29.0	22.9	98
18	54.9	23.4	88
19	36.3	12.4	96
24	37.1	16.3	96
Mean	46.2 <sup>a</sup>	32.7	86
Range	(22.4-188)	(6.6-98.4)	(46-100)
<u>Age-matched healthy subjects</u>			
6	44.8	25.9	93
7	49.6	37.8	91
8	51.2	28.9	90
10	26.5	9.8	99
20	10.7	5.2	100
21	26.9	11.0	99
22	13.7	13.5	100
23	24.0	9.2	99
Mean	23.1 <sup>a</sup>	17.7	96
Range	(10.7-51.2)	(5.2-37.8)	(90-100)

<sup>a</sup> Harmonic Mean

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**Dissolution Results for Cyclobenzaprine Hydrochloride 5-mg Tablets Used in  
Clinical Studies**

Batch Number (Batch Size)	Time (min)	% Label Claim Dissolved
0130 FCT 003 B001 (30,000 tablets)	10	
	15	
	20	
	30	102, 102, 103, 101, 102, 104 Avg=102% (RSD 1.0%)
0130 FCT 003 B002 (150,000 tablets)	10	
	15	
	20	
	30	100, 103, 100, 101, 103, 102 Avg=102% (RSD 1.0%)
0130 FCT 007 B003 (3,200,000 tablets)	10	71, 48, 83, 99, 51, 60 Avg=69% (RSD 28.7%)
	15	
	20	102, 103, 99, 100, 103, 103 Avg=102% (RSD 1.7%)
	30	103, 104, 98, 100, 103, 103 Avg=102% (RSD 2.3%)
	60	102, 104, 92, 100, 103, 103 Avg=101% (RSD 4.4%)
0130 FCT 007 B004 (330,000 tablets)	10	101, 92, 97, 100, 98, 87 Avg=96% (RSD 5.6%)
	15	
	20	107, 101, 100, 97, 103, 102 Avg=102% (RSD 3.3%)
	30	107, 101, 100, 97, 104, 102 Avg=102% (RSD 3.4%)
0130 FCT 007 B005 (330,000 tablets)	10	98, 94, 86, 101, 101, 95 Avg=96% (RSD 5.9%)
	15	
	20	98, 102, 103, 102, 102, 100 Avg=101% (RSD 1.8%)
	30	98, 102, 103, 102, 101, 101 Avg=101% (RSD 1.7%)

RSD = Residual standard deviation.

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