CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-777

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-777, N-000 (BZ/MR)	Submission Date(s): 8/8/2006
Brand Name	Amrix
Generic Name	Cyclobenzaprine HCl modified release capsules
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Rheumatology Products
Sponsor	ECR Pharmaceuticals, Richmond, VA
Relevant IND(s)	62,261
Submission Type; Code	Complete Response; 3S
Formulation; Strength(s)	Modified Release Capsules; 15 and 30 mg
Indication	As an adjunct to rest and physical therapy for the relief of muscle spasm associated with acute, painful muscoskeletal conditions
Proposed Dosage Regimen	The recommended adult dose for most patients is one AMRIX 15 mg capsule taken once daily. Some patients may require up to 30 mg/day, given as two 15 mg capsules or one AMRIX 30 mg capsule taken once daily.

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1 Executive Summary

1.1 Recommendation

The sponsor has adequately addressed the clinical pharmacology related deficiencies identified in the Agency's approvable letter dated 2/28/2005. The submission is acceptable from a Clinical Pharmacology perspective provided that a mutually satisfactory agreement is reached between the Agency and the Sponsor regarding the language in the package insert.

1.2 Phase IV Commitments

None

1.3 Summary of CPB Findings

NDA 21-777, originally submitted on 04/30/2004, received approvable action on 2/28/2005. Current submission is a complete response to the deficiencies identified in that action. This submission does not contain any new Clinical Pharmacology data. Rather, Sponsor used previous data in responding to the Clinical Pharmacology related deficiencies. See Clinical Pharmacology review dated 2/22/2005 by Dr. Abimbola Adebowale for a complete assessment of the originally submitted Clinical Pharmacology data. Meeting was held between the Agency and Sponsor on 05/04/2005 to discuss the deficiencies in the approvable letter (see meeting minutes dated 05/17/2005 for further details on the discussions in this meeting). Further, letter dated 09/12/2005 contains Agency's response to the guidance requested by the sponsor in resolving the Clinical Pharmacology related deficiencies (see Clinical Pharmacology review by Dr. Abimbola Adebowale dated 08/09/2005 for further details).

Deficiencies 2 and 3 are Clinical Pharmacology related while deficiency 4 is related to dissolution specifications for the product. ONDQA is addressing deficiency 4. Deficiencies 2 and 3 (as stated in the letter and identified here in bold text) and Agency's assessment of sponsor's responses to these are as follows;

> ***Deficiency 2: As a 505(b)(2) application, reliance of prior findings of safety for this application were predicated on similar exposure for Amrix and the reference listed product under conditions of use. However, comparable bioavailability between Amrix and the reference listed product has not been demonstrated for either the initial single-day dosing or steady state. The data suggest that the bioavailability of Amrix may be greater than that of the reference listed product.***

A great deal of uncertainty existed around the condition (intact or crushed) of the Reference Listed Drug used in Study # 1107 conducted to fulfill 505(b)(2) relative bioavailability requirement. Study # 1107 was "A relative bioavailability study comparing cyclobenzaprine levels following administration of single-dose 30 mg Amrix or 10 mg cyclobenzaprine immediate release tablet (Flexeril, TID dosing for one day) in 36 subjects". Division of Scientific Investigation review dated 10-27-2005 clarified the prevailing confusion - "The inspection revealed that Flexeril was administered in intact

tablet form and not ground and encapsulated as initially reported in the NDA study report." As such, the conclusions reached in the original Clinical Pharmacology review that the systemic exposure of cyclobenzaprine (AUC and Cmax) is similar between the single dose of Amrix 30 mg capsules and three Flexeril tablets administered as TID regimen, stands. This satisfactorily addresses the comparable exposure between single dose of Amrix and equivalent total daily dose of Flexeril.

With respect to the exposure differences between Amrix and Flexeril at steady state from study 1104, sponsor has adequately addressed this issue by taking into account the difference in asymmetrical dosing regimen (6h, 6h, 12 h dosing vs every 8 hour dosing) with accompanying missing doses (last two) of Flexeril and similar pre-dose levels between Amrix and Flexeril.

In study # 1104, Flexeril was administered TID between 6 to 7 PM, 6 to 7 AM, and 12 to 1 PM in order to be consistent with the likely dosing of the Flexeril in patients. The Flexeril dosing regimen used in this study resulted in two 6-hour dosing intervals and one 12-hour dosing interval. Hence, there were irregular dosing intervals for the Flexeril in this study. On Day 7, the 6 to 7 PM dose of both ER 30 mg and the Flexeril were administered. However, on Day 8, the 6 to 7 AM dose (second daily dose) and the 12 to 1 PM dose (third daily dose) of Flexeril were inadvertently not administered (completion of seventh treatment day). Amrix treated subjects were to receive 2 placebo capsules as their second and third dose, so this error did not affect the dose of cyclobenzaprine received for Amrix. The omission of the 2nd and 3rd dose, however, did affect the dose of Flexeril with only 1/3 of the dose being administered during the final 24 hour period compared to the full dose of Amrix. Because of this reason, as was concluded in the original Clinical Pharmacology review of Dr. Abimbola Adebowale, the steady state comparison of the IR formulation and Amrix (i.e, Cmax and AUC values at steady state) is inappropriate. The higher Cmax and AUC values seen (Figure 1) at steady state for Amrix relative to Flexeril are not truly representative of steady state values that would have been seen if Flexeril was dosed appropriately.

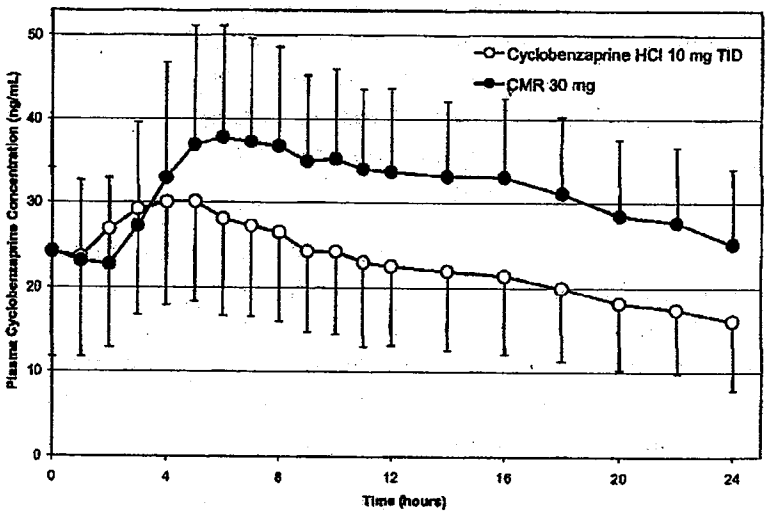

Figure 1: Mean (SD) of plasma levels of cyclobenzaprine in subjects receiving immediate-release cyclobenzaprine and Amrix 30 mg on Day 8

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Based on what was seen with single dose comparative data from study 1107, the steady-state exposure of Amrix and Flexeril would have been comparable if Flexeril dosing was appropriate. This can be seen from the following figure where the pre-dose (or Cmin) concentrations for both treatments were similar on all days except on day 8 (24 hours after the dose administration on day 7) where the pre-dose concentrations of Flexeril are significantly lower. Based on this, if both the 6 to 7 AM and dose and the 12 to 1 PM dose were administered, it is more than likely that the pre-dose concentrations on day 8 would have been similar.

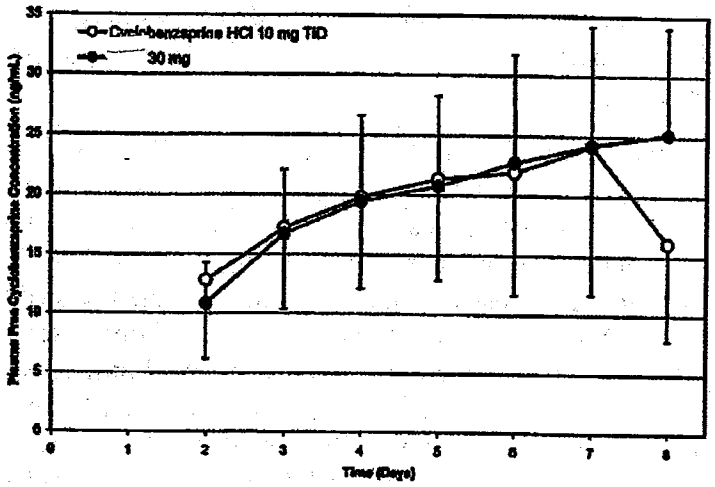

Figure 2: Mean (SD) trough cyclobenzaprine plasma concentration over time (days).

Overall, based on similar exposure seen at single dose and similar pre-dose concentrations seen at multiple doses, it is reasonable to expect similar exposures at steady state.

> ***Deficiency 3: The half life of Amrix in the elderly is substantially prolonged compared to younger subjects. The pharmacokinetic 2characteristics of Amrix were not evaluated in patients with hepatic insufficiency, although it is known from the reference listed prod2uct that patients with hepatic insufficiency have increased exposure to cyclobenzaprine. The proposed dosing recommendations for elderly patients and for patients with impaired hepatic function are not adequate to ensure safe use in these populations.***

In response, the sponsor has changed the relevant labeling sections

t. However, use of Amrix is not recommended in subjects with mild, moderate or severe hepatic impairment, considering

a) a two-fold higher cyclobenzaprine plasma levels in subjects with mild hepatic impairment, as compared to healthy subjects, following administration of immediate-release cyclobenzaprine and

b) because there is limited dosing flexibility with Amrix.

In addition, use of Amrix is not recommended in elderly, considering a 40% increase in cyclobenzaprine plasma levels following administration of immediate-release cyclobenzaprine and a 56% increase in plasma half-life following administration of Amrix in elderly subjects as compared to young adults.

Upon submission of the complete response dated 8/7/2006, Agency issued the following information request to the sponsor on 10/9/2006 with respect to the alcohol interaction potential of the product:

> **"Provide data on in vitro drug release using the test procedure described in the NDA but with the media containing varying amounts of ethyl alcohol. Choose the media containing 0, 4, 20, and 40 % alcohol and the time points sufficient to cover the entire release profile from initial time to the time when asymptote is reached.**
>
> **Alternatively, provide a rationale that in the setting of ingesting alcohol, any resultant rapid release of cyclobenzaprine from this modified-release formulation would not result in a serious adverse event."**

Following data shows the *in vitro* dissolution of Amrix tablets in the NDA media containing alcohol;

Table 1
PF312EA004, 15mg capsules

Reported Average (and Range) % Released for N=6 vessels								
	Timepoint (hours)							
% EtOH	0.25	0.5	0.75	1	2	4	6	8
0*					20 (18-23)	45 (42-47)		65 (61-68)
4	1 (1–3)	2 (2-3)	3 (3-4)	6 (5-7)	32 (31-33)	56 (54-58)	67 (66-69)	74 (72-77)
20	1 (0-2)	8 (6-11)	23 (19-28)	35 (30-41)	58 (52-65)	78 (72-83)	86 (80-91)	92 (86-96)
40	4 (3-5)	6 (5-8)	11 (8-13)	22 (19-26)	63 (59-69)	86 (83-93)	94 (90-102)	99 (94-108)

Table 2
PF313EA004, 30mg capsules

Reported Average (and Range) % Released for N=6 vessels								
	Timepoint (hours)							
% EtOH	0.25	0.5	0.75	1	2	4	6	8
0*					24 (23-26)	49 (47-51)		68 (65-70)
4	1 (0-1)	1 (1-2)	3 (2-3)	6 (5-6)	33 (33-34)	57 (55-58)	68 (66-69)	75 (73-76)
20	1 (1-1)	16 (13-19)	37 (35-39)	49 (47-51)	68 (66-70)	84 (81-86)	91 (87-93)	95 (92-97)
40	3 (2-4)	6 (5-8)	10 (9-11)	24 (21-27)	67 (64-69)	88 (86-90)	95 (93-98)	99 (97-102)

It is to be noted that the sponsor did not evaluate dissolution of Amrix in a 0% EtOH medium at all time points; instead, these results were taken from a 24-month stability testing. The tables above include results only through the 8-hour sampling point for the 0% samples. An additional time point at 16 hours was also collected as per the NDA test method but not reported above as no 16 hour sample was collected for media with alcohol. For completeness of results, the 16 hour results for the 0% alcohol are included below:
PF312EA004 16 hour result = 79% avg. (range 74 – 84)
PF313EA004 16 hour result = 82% avg. (range 78 – 85)

The data shown in the above table indicates that up to the first 1 hour, the 20% alcohol containing dissolution medium causes faster and greater release of cyclobenzaprine from Amrix 15 and 30 mg capsules compared to the release noted with 40% alcohol or 4% alcohol. However, the extent of drug release is similar between 20% and 40% alcohol containing media after 2 hours time point, with lower drug release noted with 4% alcohol containing medium.

Although, *in vitro* data suggest a potential for dose dumping with alcohol, no *in vivo* study was requested by the review team in view of the known risk/benefit of cyclobenzaprine and proposed labeling language (in **WARNINGS** and **PRECAUTIONS**, Information of Patients, Drug Interactions, **OVERDOSAGE** sections) discourages the consumption of alcohol from a pharmacodynamic interaction perspective.

2 Labeling

(Strikeouts and highlighted underlined text reflect this reviewer's deletions and additions to sponsor proposed langauge)

CLINICAL PHARMACOLOGY

Pharmcodynamics
Cyclobenzaprine relieves skeletal muscle spasm of local origin without interfering with muscle function. Cyclobenzaprine has not been shown to be effective in muscle spasm due to central nervous system disease. In animal models, cyclobenzaprine reduced or abolished skeletal muscle hyperactivity. Animal studies indicate that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. Such studies show that cyclobenzaprine acts primarily within the central nervous system at the brain stem as opposed to the spinal cord level, although an overlapping action on the latter may contribute to its overall skeletal muscle relaxant activity. Evidence suggests that the net effect of cyclobenzaprine is a reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems. Pharmacological studies in animals demonstrated a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

Pharmacokinetics

Absorption

In a single-dose study comprised of healthy adult males (n=15), the dose adjusted ratios of the arithmetic means of AUC_{0-168} and $AUC_{0-\infty}$ indicated that exposure of the AMRIX 30 mg was about 16% and 10% higher than that of AMRIX 15 mg, respectively. The dose-adjusted ratios of the arithmetic means of C_{max} indicated that the peak plasma concentration of AMRIX 30 mg was about 20% higher than that of AMRIX 15 mg.

The half-lives and time to peak plasma cyclobenzaprine concentration were similar for both AMRIX 15 mg and 30 mg. These data are summarized below.

Table 1 **SUMMARY OF PHARMACOKINETIC PARAMETERS IN HEALTHY ADULT SUBJECTS**

Parameter/Statistic	15 mg (N = 15) Mean ± SD	30 mg (N = 14) Mean ± SD
AUC_{0-168} (ng·hr/mL)	318.3 ± 114.7	736.6 ± 259.4
$AUC_{0-\infty}$ (ng·hr/mL)	354.1 ± 119.8	779.9 ± 277.6
C_{max} (ng/mL)	8.3 ± 2.2	19.9 ± 5.9
T_{max} (hrs)	8.1 ± 2.9	7.1 ± 1.6
$t_{1/2}$ (hrs)	33.4 ± 10.3	32.0 ± 10.1

A food effect study conducted in healthy adult subjects (n=15) utilizing a single dose of AMRIX 30 mg demonstrated a statistically significant increase in bioavailability when AMRIX 30 mg was given with food relative to the fasted state. There was a 35% increase in peak plasma cyclobenzaprine concentration (C_{max}) and a 20% increase in exposure (AUC_{0-168} and $AUC_{0-\infty}$) in the presence of food. No effect, however, was noted in T_{lag}, T_{max}, or the shape of the mean plasma cyclobenzaprine concentration versus time profile. Cyclobenzaprine in plasma was first detectable in both the fed and fasted states at 1.5 hours.

In a multiple-dose study utilizing AMRIX 30 mg administered once daily for 7 days in a group of healthy adult volunteers (n=35) a 2.5-fold accumulation of plasma cyclobenzaprine levels

Metabolism/Elimination

Cyclobenzaprine is extensively metabolized and is excreted primarily as glucuronides via the kidney. Cytochromes P-450 3A4, 1A2, and, to a lesser extent, 2D6, mediate N-demethylation, one of the oxidative pathways for cyclobenzaprine. Cyclobenzaprine has an elimination half-life of (range 8-37 hours; n=18); plasma clearance is 0.7 L/min.

Although there were no notable differences in C_{max}. or T_{max}, cyclobenzaprine plasma AUC is increased by 40% and the plasma half life of cyclobenzaprine is prolonged

Pharmacokinetic characteristics of cyclobenzaprine following multiple dose administration of Amrix in elderly was not evaluated.

Note to sponsor:

Summary of Pharmacokinetic Parameters of Amrix 30 mg Extended Release Capsules,

by Age Group

Parameter Mean ± SD	18 to 45 years (N=18) Amrix 30 QD	65 to 75 years (N=17) Amrix 30 QD
AUC_{0-168} (ng·hr/mL)	715.1 ± 264.2	945.9 ± 255.2
$AUC_{0-\infty}$ (ng·hr/mL)	751.2 ± 271.5	1055.2 ± 301.9
C_{max} (ng/mL)*	19.2 ± 5.6	19.2 ± 5.1
T_{max} (hrs)*	6.8 ± 1.9	8.5 ± 2.3
$T_{1/2}$ (hrs)	32.4 ± 8.1	49.0 ± 8.3

* - measured over the entire 24 hour dosing period
SD = standard deviation

Hepatic Impairment

In a pharmacokinetic study sixteen subjects with hepatic impairment (15 mild, 1 moderate per Child-Pugh score), both AUC and C_{max} were approximately double the values seen in the healthy control group

Pharmacokinetics of cyclobenzaprine in subjects with severe hepatic impairment is not known.

WARNINGS

...

Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke. may enhance the effects of alcohol, barbiturates, and other CNS depressants.

As a result of a two-fold higher cyclobenzaprine plasma levels in subjects with mild hepatic impairment, as compared to healthy subjects, following administration of immediate-release cyclobenzaprine and because there is limited dosing flexibility with Amrix, use of Amrix is not recommended in subjects with mild, moderate or severe hepatic impairment.

As a result of a 40% increase in cyclobenzaprine plasma levels and a 56% increase in plasma half-life following administration of Amrix in elderly subjects as compared to young adults, use of Amrix is not recommended in elderly.

PRECAUTIONS

General

Because of its atropine-like action, should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

Information for Patients

_____ especially when used with alcohol or other CNS depressants, may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle _____

Drug Interactions

_____ may have life-threatening interactions with MAO inhibitors. (See CONTRAINDICATIONS.) _____ may enhance the effects of alcohol, barbiturates, and other CNS depressants. Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds. Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol (ULTRAM® [tramadol HCl tablets, Ortho-McNeil Pharmaceutical] or ULTRACET® [tramadol HCl and acetaminophen tablets, Ortho-McNeil Pharmaceutical]).

...

OVERDOSAGE

Although rare, deaths may occur from overdosage with _____. Multiple drug ingestion (including alcohol) is common in deliberate cyclobenzaprine overdose.

DOSAGE AND ADMINISTRATION

The recommended adult dose for most patients is one (1) AMRIX 15 mg capsule taken once daily. Some patients may require up to 30 mg/day, given as one (1) AMRIX 30 mg capsule taken once daily~~. or as two (2) AMRIX 15 mg capsules taken once daily~~.

It is recommended that doses be taken at approximately the same time each day.

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3 Appendix

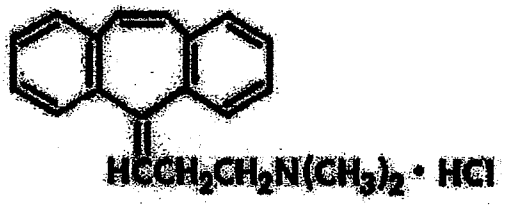
3.1 Proposed labeling

Rx Only

AMRIX®
(Cyclobenzaprine HCl Extended Release Capsules)

DESCRIPTION

The active ingredient in AMRIX® extended release capsules is cyclobenzaprine hydrochloride, USP. Cyclobenzaprine hydrochloride (HCl) is a white, crystalline tricyclic amine salt with the empirical formula $C_{20}H_{21}N{\cdot}HCl$ and a molecular weight of 311.9. It has a melting point of 217°C, and a pK_a of 8.47 at 25°C. It is freely soluble in water and alcohol, sparingly soluble in isopropanol, and insoluble in hydrocarbon solvents. If aqueous solutions are made alkaline, the free base separates. Cyclobenzaprine HCl is designated chemically as 3-(*5H*-dibenzo[*a,d*] cyclohepten-5-ylidene)-*N,N*-dimethyl-1-propanamine hydrochloride, and has the following structural formula:



AMRIX extended release capsules for oral administration are supplied in 15 and 30 mg strengths. AMRIX capsules contain the following inactive ingredients: sugar spheres N F (20-25 mesh), Opadry® Clear YS-1-7006, ethylcellulose NF (Ethocel Standard 10 Premium), diethyl phthalate NF, titanium oxide, and gelatin. AMRIX 15 mg capsules also contain red iron oxide and yellow iron oxide. AMRIX 30 mg capsules also contain FD&C blue #1, FD&C blue #2, FD&C red #40, and FD&C yellow #6.

CLINICAL PHARMACOLOGY

Cyclobenzaprine relieves skeletal muscle spasm of local origin without interfering with muscle function. Cyclobenzaprine has not been shown to be effective in muscle spasm due to central nervous system disease. In animal models, cyclobenzaprine reduced or abolished skeletal muscle hyperactivity. Animal studies indicate that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. Such studies show that cyclobenzaprine acts primarily within the central nervous system at the brain stem as opposed to the spinal cord level, although an overlapping action on the latter may

contribute to its overall skeletal muscle relaxant activity. Evidence suggests that the net effect of cyclobenzaprine is a reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems. Pharmacological studies in animals demonstrated a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

Pharmacokinetics

In a single dose study comprised of healthy adult males (n=15),

The dose adjusted ratios of the arithmetic means of $AUC_{0\text{-}168}$ and $AUC_{0\text{-}\infty}$ indicated that exposure of the AMRIX 30 mg was about 16% and 10% higher than that of AMRIX 15 mg, respectively. The dose-adjusted ratios of the arithmetic means of C_{max} indicated that the peak plasma concentration of AMRIX 30 mg was about 20% higher than that of AMRIX 15 mg. The half-lives and time to peak plasma cyclobenzaprine concentration were similar for both AMRIX 15 mg and 30 mg. These data are summarized below.

SUMMARY OF PHARMACOKINETIC PARAMETERS IN HEALTHY ADULT SUBJECTS

Parameter	15 mg (N = 15) Mean ± SD	30 mg (N = 14) Mean ± SD
$AUC_{0\text{-}168}$ (ng·hr/mL)	318.3 ± 114.7	736.6 ± 259.4
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$t_{1/2}$ (hrs)	33.4 ± 10.3	32.0 ± 10.1

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A food effect study conducted in healthy adult subjects (n=15) utilizing a single dose of AMRIX 30 mg demonstrated a statistically significant increase in bioavailability when AMRIX 30 mg was given with food relative to the fasted state. There was a 35% increase in peak plasma cyclobenzaprine concentration (C_{max}) and a 20% increase in exposure (AUC_{0-168} and $AUC_{0-\infty}$) in the presence of food. No effect, however, was noted in T_{lag}, T_{max}, or the shape of the mean plasma cyclobenzaprine concentration versus time profile. Cyclobenzaprine in plasma was first detectable in both the fed and fasted states at 1.5 hours.

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Summary of Pharmacokinetic Parameters of Amrix 30 mg Extended Release Capsules.

by Age Group

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$T_{1/2}$ (hrs)	32.4 ± 8.1	49.0 ± 8.3

* - measured over the entire 24 hour dosing period
SD = standard deviation

Hepatic Impairment

In a pharmacokinetic study sixteen subjects with hepatic impairment (15 mild, 1 moderate per Child-Pugh score), both AUC and C_{max} were approximately double the values seen in the healthy control group.

Clinical Studies

with

INDICATIONS AND USAGE

is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, limitation of motion,

should be used only for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is

generally of short duration and specific therapy for longer periods is seldom warranted.

[redacted] has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.

CONTRAINDICATIONS

- Hypersensitivity to any component of this product.
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation.
- Hyperpyretic crisis seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.
- During the acute recovery phase of myocardial infarction, and in patients with arrhythmias, heart block conduction disturbances, or congestive heart failure.
- Hyperthyroidism.

WARNINGS

[redacted] is closely related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. In short term studies for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm, some of the more serious central nervous system reactions noted with the tricyclic antidepressants have occurred (see WARNINGS, below, and ADVERSE REACTIONS).

Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke. [redacted] may enhance the effects of alcohol, barbiturates, and other CNS depressants.

PRECAUTIONS

General

Because of its atropine-like action, [redacted] should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

Information for Patients

[redacted], especially when used with alcohol or other CNS depressants, may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. [redacted]

Drug Interactions

_____ may have life-threatening interactions with MAO inhibitors. (See CONTRAINDICATIONS.) _____ may enhance the effects of alcohol, barbiturates, and other CNS depressants. Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds. Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol (ULTRAM® [tramadol HCl tablets, Ortho-McNeil Pharmaceutical] or ULTRACET® [tramadol HCl and acetaminophen tablets, Ortho-McNeil Pharmaceutical]).

Carcinogenesis, Mutagenesis, Impairment of Fertility
In rats treated with cyclobenzaprine for up to 67 weeks at doses of approximately 5 to 40 times the maximum recommended human dose, pale, sometimes enlarged, livers were noted and there was a dose-related hepatocyte vacuolation with lipidosis. In the higher dose groups, this microscopic change was seen after 26 weeks and even earlier in rats that died prior to 26 weeks; at lower doses, the change was not seen until after 26 weeks. Cyclobenzaprine did not affect the onset, incidence, or distribution of neoplasia in an 81-week study in the mouse or in a 105-week study in the rat. At oral doses of up to 10 times the human dose, cyclobenzaprine did not adversely affect the reproductive performance or fertility of male or female rats. Cyclobenzaprine did not demonstrate mutagenic activity in the male mouse at dose levels of up to 20 times the human dose.

A battery of mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenic effects have provided no evidence for a mutagenic potential for cyclobenzaprine. An *in vivo* mouse bone micronucleus assay, an assessment of chromosomal aberrations (Chinese hamster ovary), and a mammalian microsome reverse mutation assay were negative.

Pregnancy
Pregnancy Category B: Reproduction studies have been performed in rats, mice, and rabbits at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyclobenzaprine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because cyclobenzaprine is

closely related to the tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when _____ is administered to a nursing woman.

Pediatric Use

Use in the Elderly

ADVERSE REACTIONS

	AMRIX 15 mg N=127	AMRIX 30 mg N=126	Placebo N=128
Dry mouth	6%	14%	2%
Dizziness	3%	6%	2%
Fatigue	3%	3%	2%
Constipation	1%	3%	0%
Somnolence	1%	2%	0%
Nausea	3%	3%	1%
Dyspepsia	0%	4%	1%

In a postmarketing surveillance program (7607 patients treated with cyclobenzaprine 10 mg TID), the adverse reactions reported most frequently were drowsiness, dry mouth, and dizziness. The incidence of these common adverse reactions was lower in the surveillance program than in the controlled clinical studies:

	Clinical Studies cyclobenzaprine 10 mg TID	Surveillance Program cyclobenzaprine 10 mg TID
Drowsiness	39%	16%
Dry Mouth	27%	7%
Dizziness	11%	3%

Among the less frequent adverse reactions, there was no appreciable difference in incidence in controlled clinical studies or in the surveillance program. Adverse reactions which were reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion. The following adverse reactions have been reported in post-marketing experience or with an incidence of less than 1% of patients in clinical trials with the 10 mg TID tablet:

Body as a Whole: Syncope; malaise.
Cardiovascular: Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension.
Digestive: Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice, and cholestasis.
Hypersensitivity: Anaphylaxis; angioedema; pruritus; facial edema; urticaria; rash.
Musculoskeletal: Local weakness.
Nervous System and Psychiatric: Seizures, ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; psychosis, abnormal thinking and dreaming; hallucinations; excitement; paresthesia; diplopia.
Skin: Sweating.
Special Senses: Ageusia; tinnitus.
Urogenital: Urinary frequency and/or retention.

Causal Relationship Unknown
Other reactions, reported rarely for cyclobenzaprine under circumstances where a causal relationship could not be established or reported for other tricyclic drugs, are listed to serve as alerting information to physicians:

Body as a whole: Chest pain; edema.
Cardiovascular: Hypertension; myocardial infarction; heart block; stroke.
Digestive: Paralytic ileus, tongue discoloration; stomatitis; parotid swelling.
Endocrine: Inappropriate ADH syndrome.
Hematic and Lymphatic: Purpura; bone marrow depression; leukopenia; eosinophilia; thrombocytopenia.
Metabolic, Nutritional and Immune: Elevation and lowering of blood sugar levels; weight gain or loss.
Musculoskeletal: Myalgia.

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Nervous System and Psychiatric: Decreased or increased libido; abnormal gait; delusions; aggressive behavior; paranoia; peripheral neuropathy; Bell's palsy; alteration in EEG patterns; extrapyramidal symptoms.
Respiratory: Dyspnea.
Skin: Photosensitization; alopecia.
Urogenital: Impaired urination; dilatation of urinary tract; impotence; testicular swelling; gynecomastia; breast enlargement; galactorrhea.

DRUG ABUSE AND DEPENDENCE

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when cyclobenzaprine is administered, even though they have not been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration rarely may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE

Although rare, deaths may occur from overdosage with [redacted]. Multiple drug ingestion (including alcohol) is common in deliberate cyclobenzaprine overdose. **As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment.** Signs and symptoms of toxicity may develop rapidly after cyclobenzaprine overdose; therefore, hospital monitoring is required as soon as possible. The acute oral LD_{50} of cyclobenzaprine is approximately 338 and 425 mg/kg in mice and rats, respectively.

MANIFESTATIONS
The most common effects associated with cyclobenzaprine overdose are drowsiness and tachycardia. Less frequent manifestations include tremor, agitation, coma, ataxia, hypertension, slurred speech, confusion, dizziness, nausea, vomiting, and hallucinations. Rare but potentially critical manifestations of overdose are cardiac arrest, chest pain, cardiac dysrhythmias, severe hypotension, seizures, and neuroleptic malignant syndrome. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of cyclobenzaprine toxicity. Other potential effects of overdosage include any of the symptoms listed under ADVERSE REACTIONS.

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MANAGEMENT

General

As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment.

In order to protect against the rare but potentially critical manifestations described above, obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line, and initiate gastric decontamination. Observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. Monitoring of plasma drug levels should not guide management of the patient. Dialysis is probably of no value because of low plasma concentrations of the drug.

Gastrointestinal Decontamination

All patients suspected of an overdose with [illegible] should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage and emesis is contraindicated.

Cardiovascular

A maximal limb-lead QRS duration of 0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and hyperventilation (as needed), should be instituted for patients with dysrhythmias and/or QRS widening. A pH >7.60 or a pCO_2 <20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

CNS

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a poison control center.

PSYCHIATRIC FOLLOW-UP

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

PEDIATRIC MANAGEMENT

The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION

The recommended adult dose for most patients is one (1) AMRIX 15 mg capsule taken once daily. Some patients may require up to 30 mg/day, given as [redacted]. It is recommended that doses be taken at approximately the same time each day.

Use of AMRIX for periods longer than two or three weeks is not recommended (see INDICATIONS AND USAGE).

Dosage Considerations for Special Patient Populations: Amrix should not be used [redacted] in the elderly [redacted] patients with impaired hepatic function [redacted]

HOW SUPPLIED

AMRIX [redacted] release capsules are available in 15 and 30 mg strengths, packaged in bottles of 60 capsules. AMRIX 15 mg capsules (NDC 00095-0150-06) are orange/orange, are embossed "ECR 15" on each half and bear a single white band. AMRIX 30 mg capsules (NDC 00095-0300-06) are blue/orange, are embossed "ECR 30" on each half and bear two white bands. Physician samples (AMRIX 15 mg capsules, NDC 00095-0150-09; AMRIX 30 mg capsules, NDC 00095-0300-09) are packaged in individual blisters.

Dispense in a tight, light-resistant container as defined in the USP/NF.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. IN CASE OF ACCIDENTAL OVERDOSE, SEEK PROFESSIONAL ASSISTANCE OR CONTACT A POISON CONTROL CENTER IMMEDIATELY.

Manufactured for and distributed by
ECR Pharmaceuticals, Richmond, Virginia 23255
Manufactured by Eurand America, Vandalia, Ohio 45377

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MI 0150/300 Rev. 07/2006

3.2 Division of Scientific Investigations Memo

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 10/21/05

TO: Paul Z. Balcer, Regulatory Project Manager
Christine Fang, M.D., Clinical Reviewer
Division of Anesthesia, Analgesia, and Rheumatology Drug Products, HFD-170

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Dianne D. Tesch
Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: #21-777

APPLICANT: ECR Pharmaceuticals

DRUG: Amrix ® (cyclobenzaprine 15 and 30 mg modified release CMR)

CHEMICAL CLASSIFICATION: 3S

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Muscle Relaxant

CONSULTATION REQUEST DATE: August 30, 2005

ACTION GOAL DATE: 10/30/05

PDUFA DATE: 2/28/06

I. BACKGROUND:

In this NDA, the report for Study 1107 indicated that ground and encapsulated Flexeril was used

as the comparator product in the above referenced study. The sponsor now contends that the investigator used intact Flexeril and not product that was ground and encapsulated. The Division of Anesthesia, Analgesia, and Rheumatology Products requests a site visit to determine the manner in which Flexeril was used during this study.

This was a Phase I safety and PK study. Dr. Gutierrez was the only researcher for Study 1107. She enrolled approximately 36 subjects. She is a high volume researcher, with 120 studies listed in the Clinical Investigator System (CIS) data base. Dr. Gutierrez has three prior inspections performed by the Good Laboratory Practices/Bioequivalence Branch, in 2000, 2002, and 2004. One inspection was classified NAI, and the other two were VAI. According to the FDA inspector, deficiencies noted at prior inspections have been resolved.

II. RESULTS (by protocol/site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Maria J. Gutierrez	Ft. Lauderdale	FL	8/30/05	10/19/05	NAI
Eurand, Inc.	Vandalia	OH	8/30/05	1024/05	NAI

A. Protocol CMR 1107: "A Randomized Open-Label, Two-Period Crossover Study to Compare the Safety and Pharmacokinetics of Cyclobenzaprine HCl Modified Release (CMR) 30 mg Once Daily and Cyclobenzaprine HCl 10 mg Three Times Daily in Healthy Volunteers"

1. Site #1 Maria Gutierrez, M.D., Fort Lauderdale, FL. The data are acceptable.

   a. The inspection revealed that Flexeril was administered in intact tablet form and not ground and encapsulated as initially reported in the NDA study report. The investigational drug Amrix® was administered in capsule form. 65 subjects were screened, thirty six enrolled, and 2 withdrew consent. 12 of 36 records were reviewed in depth for data integrity and adherence to protocol.

   b. No limitations were encountered.

   c. There was no evidence of under reporting of adverse events or other violations that might have affected data integrity.

2. Site #2 Eurand, Inc., Vandalia, OH. The data and information were acceptable.

   a. The firm manufactured three lots of cyclobenzaprine HCl Modified Release capsules and placebo capsules for the study. The firm sent the batches to

   b. No limitations were encountered.

   c. There was no evidence of manufacturing irregularities.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

There were no significant problems found at either Dr. Gutierrez's site or at the manufacturing site. According to Dr. Gutierrez and her staff intact Flexeril tablets were used at her site. The manufacturer, Eurand, says that ground and encapsulated Flexeril was shipped to the ——— ——— A separate investigation of the ——— site was not ordered.

Dianne D. Tesch
GCPB Reviewer Name
Title

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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CSO

Leslie Ball
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MEDICAL OFFICER

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3.3 Alcohol-Amrix Dissolution Report

Evaluation of the Drug Release Rate of Cyclobenzaprine Hydrochloride Extended-Release Capsules [Amrix] in the Presence of Varying Amounts of Ethyl Alcohol

Michael Markham
Asst. Director R&D Analytical
Eurand, Inc.
845 Center Drive
Vandalia, OH 45377

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In a letter from the Agency related to NDA 21-777 dated 10/9/2006 the following comment/request was made; "Due to the potential for dose-dumping in controlled-release formulations in the presence of alcohol, we need you to provide the following information about your product. Provide data on in vitro drug release using the test procedure described in the NDA [900 mL 0.1N HCl] but with the media containing varying amounts of ethyl alcohol. Choose the media containing 0, 4, 20, and 40% alcohol and the time points sufficient to cover the entire release profile from initial time to the time when asymptote is reached. Alternatively, provide a rationale that in the setting of ingesting alcohol, any resultant rapid release of cyclobenzaprine from this modified-release formulation would not result in a serious adverse event." This report provides a brief summary of the testing and results related to the various alcohol dissolution tests that were performed.

As requested, the test procedure utilized was the NDA procedure except the dissolution media contained varying amounts of alcohol. Additionally, for media containing alcohol, early time points were taken and analyzed to enable proper dissolution profiling. Specific dissolution conditions are noted below. Dissolution testing was performed on two lots of capsules; PF312EA0004 (15 mg) and PF313EA0004 (30 mg). The actual capsules tested were taken from the 25°C/60% RH stability samples. The "0%" alcohol media testing reported in Tables 1 and 2 were taken from the 24-month stability testing and hence the dissolution profiles in this condition did not include the early time points that were included in the alcohol dissolution runs. Six replicate vessels were analyzed for each lot of material.

Dissolution profiles for both lots of drug product (15 and 30 mg) in each dissolution media are summarized in Tables 1 and 2 below. The data are graphically displayed in Figures 1 and 2 below.

Dissolution Conditions:

- Media: 0.1 N HCl containing 0, 4, 20, or 40% ethyl alcohol
- Volume: 900 mL
- Temperature: 37.0 ± 0.5°C
- USP Apparatus 2 at 50 rpm's
- Time points (for media containing alcohol): 15, 30, 45, and 60 minutes, 2,4,6, and 8 hours
- Time points (for media without alcohol): 2, 4, and 8 hours
- 1.5 mL sampled at each time point

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Table 1

PF312EA004, 15mg capsules

Reported Average (and Range) % Released for N=6 vessels								
	Timepoint (hours)							
% EtOH	0.25	0.5	0.75	1	2	4	6	8
0*					20 (18-23)	45 (42-47)		65 (61-68)
4	1 (1–3)	2 (2-3)	3 (3-4)	6 (5-7)	32 (31-33)	56 (54-58)	67 (66-69)	74 (72-77)
20	1 (0-2)	8 (6-11)	23 (19-28)	35 (30-41)	58 (52-65)	78 (72-83)	86 (80-91)	92 (86-96)
40	4 (3-5)	6 (5-8)	11 (8-13)	22 (19-26)	63 (59-69)	86 (83-93)	94 (90-102)	99 (94-108)

Table 2

PF313EA004, 30mg capsules

Reported Average (and Range) % Released for N=6 vessels								
	Timepoint (hours)							
% EtOH	0.25	0.5	0.75	1	2	4	6	8
0*					24 (23-26)	49 (47-51)		68 (65-70)
4	1 (0-1)	1 (1-2)	3 (2-3)	6 (5-6)	33 (33-34)	57 (55-58)	68 (66-69)	75 (73-76)
20	1 (1-1)	16 (13-19)	37 (35-39)	49 (47-51)	68 (66-70)	84 (81-86)	91 (87-93)	95 (92-97)
40	3 (2-4)	6 (5-8)	10 (9-11)	24 (21-27)	67 (64-69)	88 (86-90)	95 (93-98)	99 (97-102)

*0% EtOH results taken from 24-month stability testing. The tables above include results only through the 8-hour sampling point for the 0% samples. An additional time point at 16 hours was also collected as per the approve test method but not reported above as no 16 hour sample was collected for media with alcohol. For completeness of results the 16 hour results for the 0% alcohol are included below.

PF312EA004 16 hour result = 79% avg. (range 74 – 84)
PF313EA004 16 hour result = 82% avg. (range 78 – 85)

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Figure 1

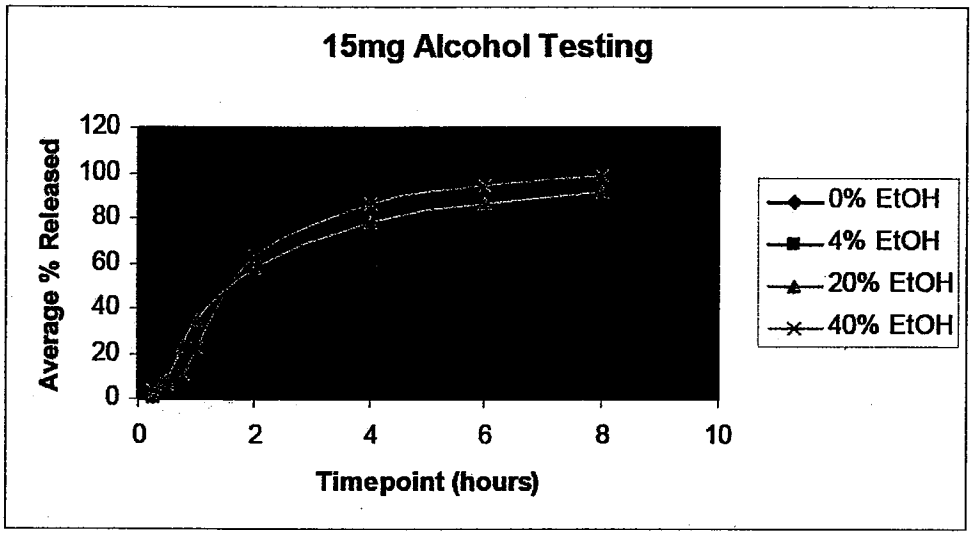
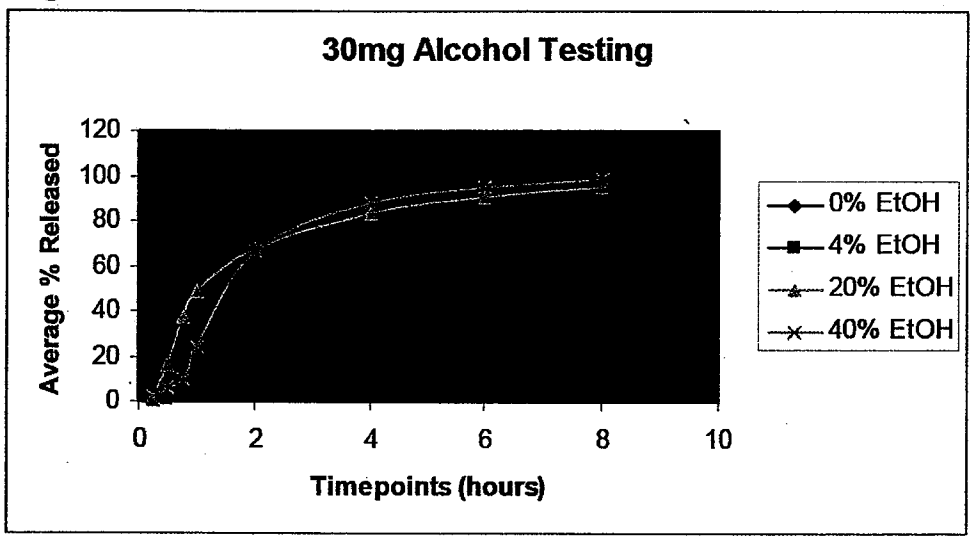


Figure 2



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Office of Clinical Pharmacology and Biopharmaceutics Review

NDA #:	21-777
Stamped Receipt Date(s):	30th April, 2004 and, 29th December, 2004
Brand Name	AMRIX ®
Generic Name	Cyclobenzaprine HCl
Reviewer	Abimbola Adebowale Ph.D.
Team Leader	Dennis Bashaw Pharm.D.
OCPB Division	DPE III
OND division	HFD-550
Applicant	ECR Pharmaceuticals, Richmond, VA 23255
Submission Type; Code	Original NDA 505 (b) (2)
Formulation; Strength(s)	Modified Release Capsules, 15 and 30 mg
Relevant IND # (s)	62, 261
Indication	As an adjunct to rest and physical therapy for the relief of muscle spasm associated with acute, painful muscoskeletal conditions

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1. Executive Summary

This NDA is a 505 (b) (2) application for Amrix ® capsules, a new modified release (MR) formulation of cyclobenzaprine hydrochloride (HCl). The reference listed drug (RLD) product is Flexeril® 10 mg tablets (NDA 17-821, approved prior to January 1 1982), an immediate release (IR) formulation. There are also Flexeril® 5 mg tablets, available as single source products. Currently, there is no approved modified release formulation of cyclobenzaprine HCl available.

The applicant is seeking the same indication as Flexeril® tablets for Amrix ® capsules, i.e., as an adjunct to rest and physical therapy for the relief of muscle spasm associated with acute, painful muscoskeletal conditions There are two proposed dosage strengths for Amrix ® capsules, 15 and 30 mg capsules. The dosing regimen recommendation for the Amrix ® capsules will be once per day, compared to three times per day currently approved for the Flexeril® tablets.

1.1 Recommendation (s):

The clinical pharmacology and biopharmaceutics data submitted for Amrix® capsules adequately characterized the pharmacokinetic performance of this new modified release formulation for cyclobenzaprine HCl. However, the data submitted did not provide a comparable systemic exposure bridge of the Amrix ® capsules to the currently approved Flexeril® tablets. The implications of this are that the applicant cannot rely on the safety findings (especially the long term safety) of the currently approved IR drug product.

Therefore, from a clinical pharmacology and biopharmaceutics perspective the applicant has not met the requirements outlined in 21 CFR 320 and, their application is not acceptable because additional studies will be required.

General Comments for the Medical Officer:

Although the relative bioavailability of the Amrix® capsules to encapsulated Flexeril ® tablet was demonstrated to be bioequivalent, the relevance of this finding of equivalence is unknown since the "reference" product used in this study was modified from the approved product. Also in this study the intact approved Flexeril® tablet was not compared to the encapsulated Flexeril® tablet.

In addition, the information provided did not demonstrate that the systemic exposure of this encapsulated Flexeril® tablet was comparable to the intact approved Flexeril ® tablet therefore it did not provide a comparable systemic exposure bridge.

Comments to be conveyed to the Applicant:

1. If the applicant pursues the development of this product, they would need to conduct a relative bioavailability study of the to be marketed formulation of the Amrix®

capsules versus the approved intact Flexeril ® tablet, administered according to the dosage recommendations in the label.

2. It is also recommended that the applicant revise their 4-hr and 8-hr proposed dissolution acceptance criteria as follows:

	Applicant's Proposed specifications	**Revised Recommended Specifications**
Time (hrs)		
2		
4		
8		
16		

Labeling Recommendation:

Specific labeling recommendations for the Clinical Pharmacology sections of the label are deferred pending the completion of a successful clinical development program. The following feedback on the special populations section is being provided to the applicant so that they can better address these issues in a subsequent labeling proposal

General Comments (Internal):
At this time the intended action by the clinical division is approvable due to a lack of efficacy and inadequate safety information.

1.2 Phase IV Commitments:

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

To support the human pharmacokinetics (PK) and biopharmaceutics requirements, Amrix ® capsules was studied in a total of 5 *in vivo* PK studies. A dissolution method and specifications were also proposed. Among these studies, 4 studies (#'s 1102, 1103, 1104 and 1107) were considered pivotal and were reviewed in detail. Study # 1101, a pilot relative bioavailability study, was not reviewed in detail because the formulation used was different from the final to be marketed formulation (Synopses is attached in Appendix 4.3 for reference purposes). In this submission the applicant used the following terms as synonyms "CMR (cyclobenzaprine HCl modified release)" and, "Amrix® capsules".
The *in vivo* PK studies primarily evaluated the following:

- The pharmacokinetics after single and multiple dosing in healthy subjects
- The effect of food on the highest strength after a single dose
- Dose proportionality assessments
- The relative bioavailability of Amrix ® capsules (30 mg) once daily to encapsulated 10 mg immediate release (IR) tablets TID after single and multiple dosing in healthy subjects
- The pharmacokinetics of cyclobenzaprine in elderly subjects

Regulatory Background:

The applicant used an encapsulated approved Flexeril ® 10 mg tablets as its Reference Listed Drug (RLD) in the PK studies (except 1101) and its active control in the clinical studies. For all these studies the immediate release capsules consisted of Flexeril ® 10 mg tablets that were ground to a powder and the appropriate weight (— mg) of powder equivalent to 10 mg of active was filled into size —gelatin capsules. The applicant stated that no additional materials were added during the encapsulation of tablets into capsule and all other variables remained constant. These were used in the clinical studies for blinding purposes however it is not clear why they were used in the PK studies.

Previously, on March 15th, 2002 the applicant submitted their PK protocols to the Agency for review (reviewed by Dr. J. Lee). Although the sponsor indicated that they were going to use Flexeril ® capsules in the PK protocols they did not indicate that these capsules were going to be in any way different from the approved product.

In this submission, the applicant did not study the bioequivalence of the encapsulated Flexeril® tablets to the approved product neither did they include data demonstrating that altering the Flexeril® tablets would not affect its systemic exposure. A request for this information was sent out to the sponsor on December 8th, 2004. A response was received from the sponsor on December 23rd, 2004.

In the response, the applicant provided in vitro dissolution data and an in vivo cross study comparison of two studies conducted by them. A review of the data by this reviewer indicated that the in vitro data suggests similar dissolution profiles however, the in vivo comparison data indicates that the encapsulated Flexeril® tablets has a higher exposure (up to ~ 38%) than the approved Flexeril® tablets. Consequently, the relative bioavailability studies were conducted with a product that is not approved and, the information submitted did not provide a bridge to the approved product.

Therefore the primary focus of the clinical pharmacology and biopharmaceutics summary of finding discussed below will be the characterization of Amrix ® capsules with limited references to the encapsulated IR product for comparison purposes only where necessary.

Single Dose Pharmacokinetics

Absorption:

Absorption of cyclobenzaprine was slower from Amrix ® capsules compared to the encapsulated immediate release (IR) formulation The data from a single-dose crossover study (1107) comparing 30 mg CMR and 10 mg cyclobenzaprine IR (TID dosing for one day) in 36 subjects aged 18-75 years old under fasting conditions illustrates this difference in release rates. The plasma cyclobenzaprine concentrations were detected earlier in subjects who received the IR formulation than those who received Amrix ® capsules. Only 38 % (13/34) of the subjects administered Amrix ® capsules had quantifiable cyclobenzaprine concentrations at 2 hrs, while all subjects administered the encapsulated IR formulation had quantifiable concentrations at 2 hrs.

Consistent with its extended release characteristics, the mean Tmax of Amrix® 30 mg was longer than that following the first dose of the encapsulated IR formulation (mean Tmax =7.6 vs. 4.7 hrs, respectively). In the pilot study (#1101) that characterized the PK of approved Flexeril ® tablets in 12 healthy male subjects, the mean Tmax was 4.6 hrs similar to that obtained for the encapsulated IR tablet. The longer mean Tmax for the Amrix® capsules compared to the IR formulation reflects its controlled release characteristic.

In another single dose study (#1103) comparing Amrix 30mg capsules (fed vs. fasted), a mean lag time (Tlag) of 2.1 and 1.8 hrs was reported for the fed and fasted treatments, respectively. This lag time appears to be formulation related.

Excretion:
Cyclobenzaprine is eliminated slowly. Following a single dose of Amrix® 15mg and 30mg capsules the mean half life in healthy volunteers (aged ~18-45 years old) was 33.4 and 32 hrs respectively (Study 1102 and 1107). Elderly subjects have a more prolonged elimination half-life of approximately 50hrs (see below).

Dose Proportionality

Amrix ® Capsules are intended to be administered as one or two 15 mg capsules or one 30 mg capsule taken once daily. Dose proportionality (relative bioavailability comparisons) of the 15 mg and 30 mg capsules was evaluated in a single-dose study (#1102) which consisted of 16 healthy subjects aged 18-37 years old. The dose-adjusted ratios of the arithmetic means of AUC inf, $AUC_{0\text{-}168}$ and C_{max} indicated that exposure of the 30 mg capsule was about 10 %, 16 % and 20 % higher than that of the 15 mg capsule, respectively. Therefore this suggests that AUC and C_{max} do not increase proportionally with dose. Graphical representation of the individual dose-normalized C_{max} and AUC_{0}-inf values showed that for most subjects (except 2) there was no difference in mean ratios. This suggests that the difference in mean ratios may be due to variability between subjects and not differences between the two formulations.

Food Effect
A single dose food effect study (# 1103) following the administration of Amrix® 30 mg capsule was studied in healthy adult subjects. Results from the study demonstrated that food increases the rate and extent of absorption of cyclobenzaprine after a single dose of Amrix ® 30 mg capsules. The $C_{max,}$ and $AUC_{0\text{-}168 \text{ and } 0\text{-}inf}$ of cyclobenzaprine increased 35% and 20%,

respectively in the presence of food. The clinical significance of the food effect is unknown. There was no effect observed on $T_{max,}$ or lag time (Tlag) suggesting that dose dumping did not occur.

Multiple Dose Pharmacokinetics:

In Study 1104 which consisted of thirty-six healthy volunteers aged between 19-59 years old, the steady state pharmacokinetics of Amrix ® 30 mg capsules was characterized. Cyclobenzaprine accumulates following administration of Amrix® capsules 30 mg once daily, with the mean $Cmax_{ss}$ being about two-fold higher than after a single dose (41.1 vs. 19.2 ng/mL). The mean AUC_{ss}, $Tmax_{ss}$ and half-life ($t_{1/2}$) were similar to that obtained after a single dose. The mean AUC_{ss} was 753.1 vs. $AUC_{0\text{-}inf}$ (single dose) = 751.2 ng.hr/mL, $Tmax_{ss}$ was 8 vs. 7.6 hrs and, $t_{1/2}$ at steady state was 34.8 vs. 32.1 hrs, respectively. The mean $C_{av\ ss}$ was 31.4 ng/mL and the mean CL/F was 44.3 L/hr.

Please note that for the multiple dose study (#1104), encapsulated Flexeril 10 mg tablets were also evaluated in comparison to Amrix® capsules. However, the PK parameters of the encapsulated tablets could not be accurately estimated from the area under the curve because the subjects took only one of the required three doses on the last day of dosing. In addition the dosing intervals were asymmetrical, therefore, estimates of PK parameters within one dosing interval could not be extrapolated to the others.

Exposure-Response Relationships:

There was no exposure-response relationship established for efficacy. In terms of safety, data from the Phase III studies and clinical pharmacology and biopharmaceutics studies suggested that patients/subjects in the Amrix ® 30 mg capsule group had a higher incidence of drug-related adverse events than patients in the Amrix ® 15 mg subgroup (See medical review for details).

Intrinsic Factors (Elderly):

A subgroup analysis of the exposure data obtained in study 1107, a single dose bioavailability study of the 30 mg capsule demonstrated differences in the $AUC_{0\text{-}168}$, $AUC_{0\text{-}inf}$ and half life ($t_{1/2}$) obtained between subgroups aged 18-45 years old and 65 to 75 years old. The mean $AUC_{0\text{-}168}$, $AUC_{0\text{-}inf}$ and $t_{1/2}$ were 32 %, 40 %, and 50 % respectively higher, in the 65-75 year old subjects compared to the 18 – 45 year old subjects. There were no notable differences in Cmax and Tmax between the age subgroups. These findings were not formulation dependent because similar findings were also observed for the encapsulated Flexeril ® tablets. It should also be noted that the currently approved Flexeril® package insert contains results of a PK study in elderly subjects showing a similar increase in AUC and recommending that dosing should be initiated with a 5 mg dose and titrated upwards.

Relative Bioavailability:

Between Amrix® capsules and encapsulated Flexeril ® tablets

In study 1107, Amrix® 30 capsules administered once daily were shown to be bioequivalent to 10 mg of encapsulated Flexeril® tablets TID. The 90 % CI for the geometric mean ratio for AUC $_{0\text{-}168}$ (87-95%), AUC $_{0\text{-}inf}$ (88-96%) and Cmax (98-110%) were within the acceptance criteria of 80 % to 125 % for all subjects as well as for subjects stratified by age group (18-45 years and 65-75 years of age).

The observed T_{max} values were different. Amrix® capsules had a much earlier mean T_{max} (7.6 hrs) compared to the encapsulated Flexeril ® tablets (mean T_{max} =18.5 hrs). The clinical significance of this is unknown.

Between encapsulated Flexeril ® tablets and the approved Flexeril ® tablets
The single point in vitro dissolution comparison indicated similarity in dissolution for the encapsulated Flexeril® and the intact Flexeril® tablets (mean % dissolved was 102 vs. 99 % , respectively) at the 0.5 hour sampling point. The cross comparison pharmacokinetic analysis of subjects receiving Flexeril® 10 mg tablets in the applicant's pilot study # 1101 and a similar aged group of subjects (i.e. $\leq$ 40 years old) receiving encapsulated Flexeril® 10 mg in study #1107 demonstrated that an increase in exposure for the encapsulated tablet. The Cmax, AUC $_{0\text{-}168}$ and AUC $_{0\text{-}inf}$ were increased by 34.6 %, 38.3 % and 34.8 % respectively, for the encapsulated tablet (study 1107) relative to the intact tablet (study 1101).

Therefore, the applicant has not provided a comparable systemic exposure bridge of their encapsulated (IR) drug products to the approved (IR) drug product.

Dissolution:

The proposed dissolution method is acceptable. The dissolution specifications are not acceptable because they are too wide to ensure batch to batch quality. Based on the dissolution profile data for both the 15 mg and 30 mg capsules, the following revised dissolution specifications are recommended (proposed changes are in bolded italic):

	Applicant's Proposed specifications	**Revised Recommended Specifications**
Time (hrs)		
2		
4		
8		
16		

Signatures

Reviewer:

Abimbola Adebowale, Ph.D.

Clinical Pharmacology and Biopharmaceutics Reviewer
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Team Leader Concurrence:

Dennis Bashaw Pharm.D.
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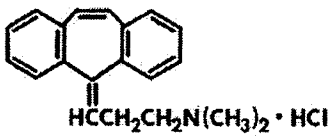
2. Question – Based Review (QBR)

2.1 General Attributes

Physicochemical Properties of the Drug Substances

The active ingredient in Amrix® capsule is cyclobenzaprine hydrochloride (HCl), USP. Cyclobenzaprine HCl is designated chemically as 3 - (*5H*-dibenzo [*a,d*] cyclohepten-5-ylidene)-*N,N*-dimethyl-1-propanamine hydrochloride, and has the following structural formula:



Cyclobenzaprine hydrochloride (HCl) is a white, crystalline tricyclic amine salt with the empirical formula $C_{20}H_{21}N{\cdot}HCl$ and a molecular weight of 311.9. It has a melting point of 217 °C and a pK_a of 8.47 at 25°C. It is freely soluble in water and alcohol, sparingly soluble in isopropanol, and insoluble in hydrocarbon solvents.

Therapeutic Indications and Mechanism of Drug Action

Cyclobenzaprine is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Cyclobenzaprine relieves skeletal muscle spasm of local origin (i.e. cervical or lumbar) associated with local pain,

tenderness, limitation of motion, and restrictions in the activities of daily living, without interfering with muscle function. Cyclobenzaprine has not been shown to be effective in muscle spasm due to central nervous system disease. In animal models, cyclobenzaprine reduced or abolished skeletal muscle hyperactivity. Animal studies indicate that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. These studies suggests that the net effect of cyclobenzaprine is a reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems.

Proposed Dosage and Route of Administration

The recommended adult dose for most patients is one (1) Amrix® 15 mg capsule taken once daily. Some patients may require up to 30 mg/day, given as two (2) 15 mg capsules taken once daily or as one (1) Amrix® 30 mg capsule taken once daily. It is recommended that doses be taken at approximately the same time each day.

2.2 General Clinical Pharmacology

Q. What were the design features of the pivotal clinical trials used to support dosing and labeling?

The applicant collected the important efficacy and safety information in studies 1105 and 1106. These two studies were of identical-design, randomized, double-blind, active-controlled, placebo-controlled, parallel-group, multi-center 4-arm studies in subjects with pain due to muscle spasms of local origin (i.e. cervical or lumbar) associated with local pain, tenderness, limitation of motion, and restrictions in the activities of daily living. The 4-arms of the study were Amrix® 15mg, or 30 mg once daily, encapsulated Flexeril® (cyclobenzaprine) 10 mg tablets TID or Placebo. The duration of the treatments was for 14 days. There were a total of 254 subjects (study 1105) and 250 subjects (study 1106) studied with approximately equal number of subjects (ranged from 61-64) per treatment arm.

Q. What is the basis of selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers?

Subjects had to be experiencing acute painful muscle spasm of local origin (i.e. cervical or lumbar), associated with local pain, tenderness, limitation of motion, and restrictions in the activities of daily living to enter the study. The co-primary efficacy endpoints were based on the subject's rating of medication helpfulness (SRMH) and a physician's clinical global assessment (PCGA) on Day 4. SRMH was measured on days 2 through 14 using a 5-point rating scale (0= poor, 1=fair, 2= good, 3= very good, 4= excellent). The PCGA was measured on days 4, 8, and 14 using a 5-point rating scale (1= worse, 2=no change, 3 = slight improvement, 4 =moderate improvement, 5 = marked improvement). Presence of muscle spasm, presence of local pain, limitation of range of motion, and limitation of activities of daily living were the basis of the physician's clinical global assessment. There were no surrogate endpoints or biomarkers used in any of the clinical trials.

<u>Exposure-Response Relationships</u>

Q. What are the characteristics of the exposure-response relationships for efficacy?

None, the applicant stated that there were no statistically significant differences in the distribution of responses in subject's rating of medication helpfulness and physician's clinical global assessment between the Amrix® groups (15 mg and 30 mg) and the Cyclobenzaprine HCl 10 mg TID at Days 4, 8, or 14 in the Phase 3 trials (see medical review for details).

Q. What are the characteristics of the exposure-response relationships for safety?

Data from the clinical studies suggests that subjects in the Amrix® 30 mg capsule group had a higher incidence of drug-related AE's than patients in the Amrix® 15 mg capsule group (the medical reviewer is currently reviewing this data in detail).

In the Phase III studies 1105 and 1106, the applicant stated that most of the treatment-emergent adverse events (AEs) reported by subjects in the Amrix® 30 mg capsules and the Cyclobenzaprine HCl 10 mg TID (82.6% and 82.9 %, respectively) were considered drug-related. In the Amrix® 15 mg capsules and placebo groups, the percentage of treatment-emergent AEs considered drug-related were 53.8 % and 56.5 %, respectively.

In the single dose Phase I studies the applicant stated that the highest incidence of somnolence occurred in subjects receiving Amrix® 30 mg capsules and Cyclobenzaprine HCl 10 mg TID. The percentages of subjects reporting drug-related dizziness, pain in limb, and insomnia were higher in the Amrix® 30 mg group than in the other groups.

In the multiple-dose Study 1104, the applicant stated that somnolence, dry mouth, headache, and dizziness were the most frequently reported drug-related AEs reported by subjects receiving both cyclobenzaprine HCl 10 mg TID and Amrix® 30 mg capsules. The incidence of AE's appeared similar for both treatments. There were 125 treatment-emergent AEs (96.8 % drug-related) reported in 34 subjects receiving cyclobenzaprine HCl 10 mg TID and, 142 treatment-emergent AEs (95.8 % drug-related) in 36 subjects receiving Amrix® 30 mg capsules.

Q. Were the active moieties in plasma appropriately identified and measured?

Yes, the applicant measured the appropriate moieties in the human pharmacokinetics and bioavailability studies. Total cyclobenzaprine was measured in all the studies. See Analytical section 2.6 for more details.

<u>Pharmacokinetic (PK) Characteristics</u>

Q. What are the single and multiple dose PK parameters following administration of cyclobenzaprine?

Single Dose Administration

In study (1102) which consisted of sixteen healthy subjects (7 males and 9 females) aged 18-37 years old, the PK of a single dose of Amrix ® 15 mg and 30 mg were evaluated. These data are summarized in the table below.

Table 1. Summary of the Pharmacokinetic Parameters [Mean ± SD] in Healthy Adult Subjects following a Single Dose

Parameter	15 mg [Mean ± SD (N = 15)]	30 mg [Mean ± SD (N = 14)]
AUC_{0-168} (ng·hr/mL)	318.3 ± 114.7	736.6 ± 259.4
$AUC_{0-\infty}$ (ng·hr/mL)	354.1 ± 119.8	779.9 ± 277.6
C_{max} (ng/mL)	8.3 ± 2.2	19.9 ± 5.9
T_{max} (hrs)	8.1 ± 2.9	7.1 ± 1.6
$t_{1/2}$ (hrs)	33.4 ± 10.3	32.0 ± 10.1

Multiple Dose Administration

In study (1104) which consisted of thirty-six healthy volunteers (13 males and 23 females) aged between 19-59 years old, the PK of multiple doses (seven day treatment) of Amrix ® 30 mg administered once daily compared with encapsulated Flexeril ® 10 mg administered TID was evaluated. The Amrix ® 30mg PK data are summarized in the table below.

Table 2. Summary of the Pharmacokinetic Parameters [Mean ± SD] in Healthy Adult Subjects following Multiple Doses

Parameter	30 mg [Mean ± SD (N = 35)]
$AUC_{0-t_{ss}}$ (ng·hr/mL)	753.1 ± 232.9
C_{maxss} (ng/mL)	41.1 ± 13.3
$C_{min\ ss}$ (ng/mL)	21.4 ± 8.7
$C_{av\ ss}$ (ng/mL	31.4 ± 9.7
T_{maxss} (hrs)	8.0 ± 3.9
$t_{1/2}$ (hrs)	34.8 ± 8.1
CL/F (L/h)	44.3 ± 17.1
λ_z (1/h)	0.021 ± 0.005
Fluctuation Index [FI] (%)	64.0 ± 17.3
Accumulation Ratio (Rac)	2.65 ± 0.48

A comparison of the data in table 2 with that in table 1 above indicates that cyclobenzaprine accumulates when the CMR 30mg is dosed once daily for 7 days, with Cmax at steady state being about two-fold higher than after a single dose However, the exposure (AUC), Tmax and half life were similar following multiple and single dosing

Reviewer's Comments
Pharmacokinetic parameters for the IR formulation could not be accurately estimated from the AUC in Study 1104 because the subjects took only one of the required IR doses. The AUC 0-tss was estimated using a simulation based on results from Study 1107. Any potential error in this simulation impacted not only the AUC 0-tss but also the Cavss and the CL/F. The evaluation of the pharmacokinetic performance of the CMR 30 mg formulation at steady state was not compromised since the doses missed were placebos. Therefore only the data for the CMR 30 mg are summarized above.

Q. What are the characteristics of cyclobenzaprine absorption?

Cyclobenzaprine was absorbed slower from the Amrix ® 30mg formulation compared to the encapsulated Flexeril ® 10 mg formulation. The data from a single-dose crossover study (1107) comparing 30 mg CMR and 10 mg cyclobenzaprine IR (TID dosing for one day) in 36 subjects [seventeen aged 18-45 years old and seventeen aged 55-75 years old] illustrates this difference in release rates. Consistent with its controlled release characteristics, the mean T_{max} of Amrix ® 30mg capsules was longer than that of the encapsulated Flexeril ® 10 mg formulation (mean Tmax was 7.6 vs. 4.6 hrs). The mean data from this study are summarized in the figure and table below:

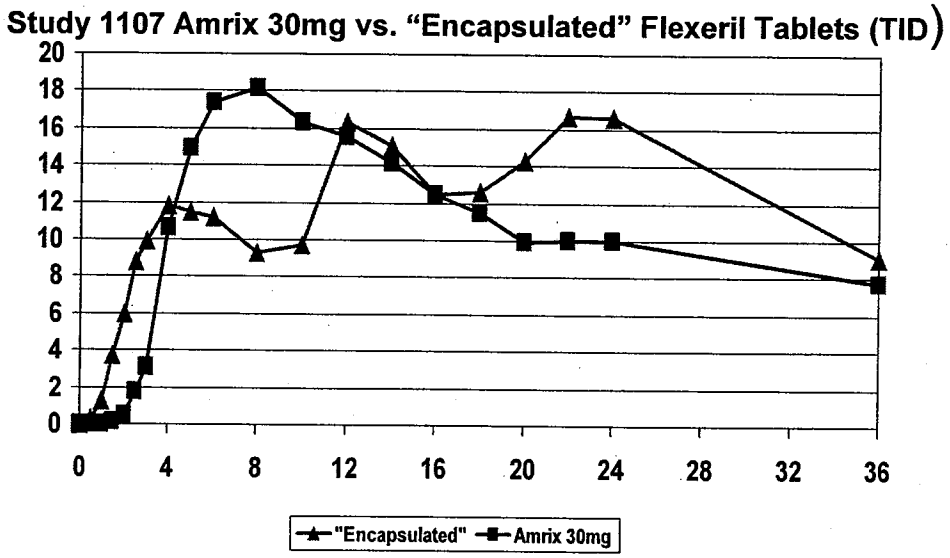


Table 4:

Parameter	Cyclobenzaprine HCl 10 mg TID n = 35	CMR 30 mg n = 35
AUC_{0-168} (ng·hr/mL)	914.4 ± 311.7	827.2 ± 281.5
$AUC_{0-\infty}$ (ng·hr/mL)	987.4 ± 352.5	898.9 ± 321.7
$C_{max\,(first)}$ (ng/mL)[a]	12.6 ± 3.7	6.4 ± 1.8
C_{max} (ng/mL)[b]	18.3 ± 4.4	19.2 ± 5.3
$T_{max\,(first)}$ (hrs)[a]	4.7 ± 1.3	7.6 ± 2.2
T_{max} (hrs)[b]	18.5 ± 5.4	7.6 ± 2.2
$t_{1/2}$ (hrs)	39.0 ± 11.9	40.5 ± 11.7

[a] Estimated using plasma levels after the first dose and before second dose for cyclobenzaprine 10 mg TID; for CMR 30 mg, the entire study period was used and the value was dose-adjusted to a 10-mg dose.
[b] Estimated using plasma levels during the entire study period for both study medications.

In the pilot study (#1101) that characterized the PK of approved Flexeril ® tablets in 12 healthy male subjects, the mean Tmax following a dosing interval of 8 hrs was 4.6 hrs similar to that obtained for the encapsulated IR tablet.

The data in the table above shows that the Tmax using the plasma levels over the 24 hr dosing intervals were different (mean Tmax =18.5 vs. 7.6 hrs).

Q. What are the characteristics of cyclobenzaprine excretion?

Cyclobenzaprine is eliminated slowly from Amrix® capsules with a mean (SD) half life = 32.4 (8.1) hrs in healthy volunteers aged 18-45 years old (Study 1107, N =18) and a clearance of 44.3 (17.1) L/hr (=0.74 (0.29) L/min) in healthy volunteers aged 18-45 years old [Study 1104, N = 35]. Cyclobenzaprine is excreted primarily as glucuronides via the kidney and it is subject to enterohepatic circulation. (Flexeril tablets PI).

Q. Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the cyclobenzaprine dose-concentration relationship?

Study 1102 provided information on the dose proportionality of the Amrix® capsules following single dose administration of the 15 mg and 30 mg strengths. The dose-adjusted ratios of the arithmetic means of $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}168}$ indicated that exposure of the 30 mg Amrix® capsules was about 10 % and 16 % higher than that of the 15 mg Amrix® capsules, respectively. The dose-adjusted ratios of the arithmetic means of Cmax indicated that the 30 mg Amrix® capsules was about 20 % higher than that of the 15 mg capsules, respectively. Therefore, this data demonstrated that the bioavailability of cyclobenzaprine does not increase in a dose proportional manner following administration of Amrix® capsules 15 mg and 30 mg. The only difference between the 15 mg and 30mg Amrix® capsules is the _____ Thus the increases noted in the pharmacokinetic parameters are highly unlikely to be due to formulation factors.

Graphical representation of the individual dose normalized C_{max} and $AUC_{0\text{-}inf}$ values (see below) showed that, for most subjects (except 2 subjects), there was no difference between formulations. The plots indicate that the difference in mean ratios is probably driven by the results from 2 subjects for each parameter which may be due to intra-subject variability.

Figure 3: Comparisons of Individual Subject Dose Normalized C_{max} Values – Pharmacokinetic Population

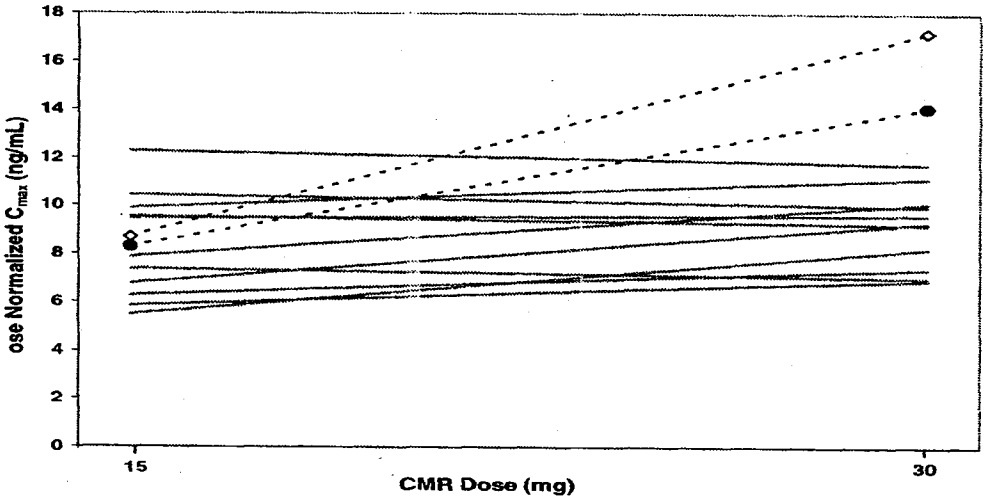
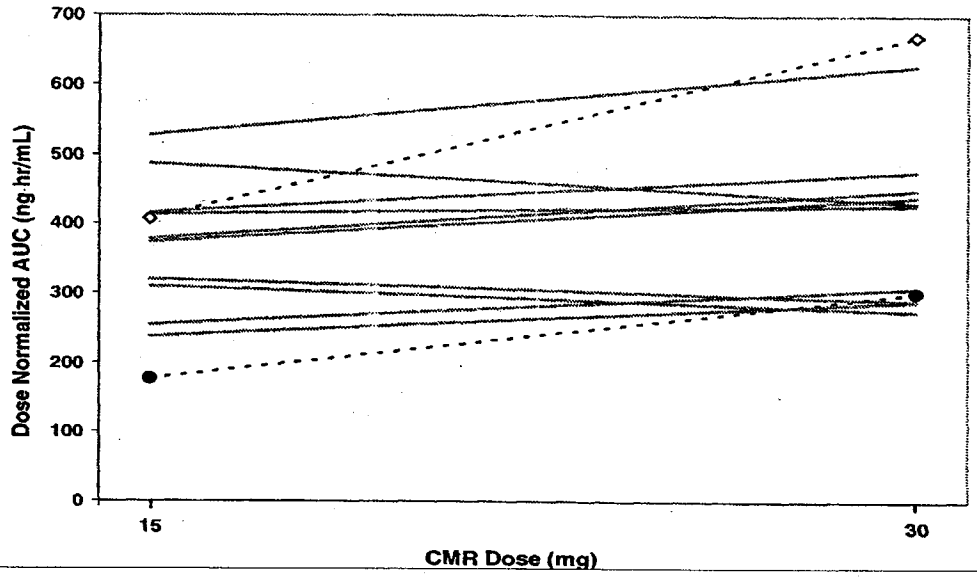


Figure 4: Comparisons of Individual Subject Dose Normalized $AUC_{0-\infty}$ Values – Pharmacokinetic Population

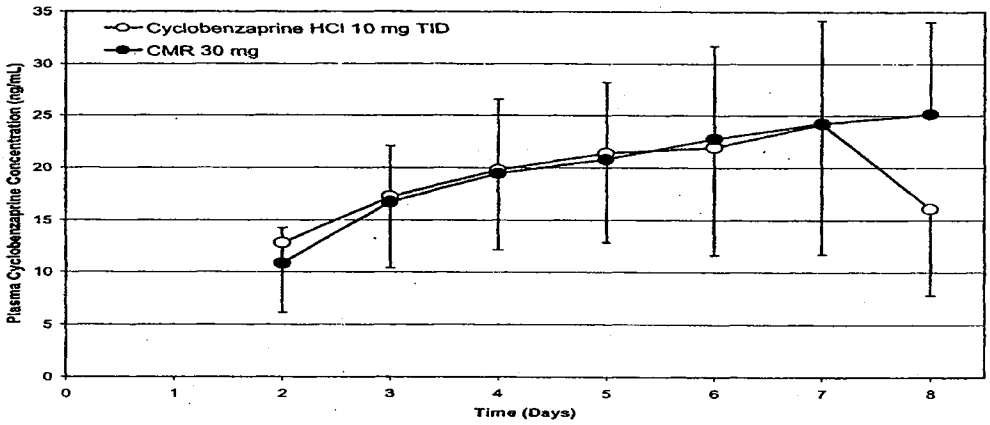


In Figure 3, subjects # 01-0010 (◊) and #01-0016 (•) have larger differences in mean normalized Cmax values compared to other subjects. In Figure 4, subjects # 01-0010 (◊) and # 01-0003 (•) have larger differences in mean normalized AUC 0-inf values compared to other subjects.

Q. How do cyclobenzaprine pharmacokinetic parameters change with time following chronic dosing?

Pre-dose plasma concentration data obtained from healthy volunteers who received Amrix ® 30 mg capsules once daily in Study 1104 indicate that cyclobenzaprine steady state concentrations were achieved before day 7. A graphical representation of the mean trough cyclobenzaprine plasma concentration over time is shown in the table below:

Figure 2: Mean (± SD) Trough Cyclobenzaprine Plasma Concentration Over Time – Safety Population



Reviewer's Comments: Applicant could not assess subjects receiving cyclobenzaprine HCL 10 mg TID for steady state attainment due to the missed doses on Day 8.

Q. What is the inter-subject and intra-subject variability of cyclobenzaprine in volunteers and what are the sources of variability?

Data are not available to determine the intra-subject variability. Following single doses of Amrix® 30 mg capsules, the inter-subject variability of the PK parameters was approximately 25 -37 % in healthy volunteers aged 18 – 45 years old and 17-29 % in healthy volunteers aged 65-75 years old. Variability may be due to CYP3A4 activity and pre-systemic metabolism. Estimates of mean oral bioavailability of cyclobenzaprine range from 33 % to 55 % (Flexeril tablets PI).

2.3. Intrinsic Factors

Q. What intrinsic factors influence exposure or response to cyclobenzaprine? What is the impact of these factors on exposure and response?

The applicant evaluated the effect of old age (elderly) on the exposure to Amrix ® 30 mg capsules. The applicant did not evaluate the effect of hepatic impairment on the capsules

Q. Based on what is known about exposure-response relationships, what dosage regimen adjustments, if any, are recommended for each subgroup listed below?

Elderly

In study 1107, conducted to measure the bioavailability of a single dose of Amrix ® 30 mg in healthy subjects a subgroup analysis for subjects aged 18 to 45 years old and 65 to 75 years old demonstrated differences in the pharmacokinetic parameters between the groups. There were notable differences between the age subgroups in AUCs and half-life ($t_{1/2}$). The mean AUC_{0-168}, $AUC_{0-\infty}$, and $t_{1/2}$ were 32%, 40%, and 51% higher, respectively, in subjects 65 to 75 years old compared to subjects 18 to 45 years old. There were no notable differences in C_{max} or T_{max} between the age subgroups. These data are summarized in the table below;

Table 5: Summary of CMR 30 mg PK Parameters by Age Group

Parameter/Statistic	18 to 45 years (N = 18) Mean ± SD	65 to 75 years (N = 17) Mean ± SD
AUC_{0-168} (ng·hr/mL)	**715.1 ± 264.2**	**945.9 ± 255.2**
$AUC_{0-\infty}$ (ng·hr/mL)	**751.2 ± 271.5**	**1055.2 ± 301.9**
C_{max} (ng/mL)*	19.2 ± 5.6	19.2 ± 5.1
T_{max} (hrs)*	6.8 ± 1.9	8.5 ± 2.3
$t_{1/2}$ (hrs)	**32.4 ± 8.1**	**49.0 ± 8.3**

*-measured over the entire 24 hour dosing period, SD = standard deviation

The larger AUCs are attributable to the increased $t_{1/2}$ in elderly subjects and not a change in absorption since C_{max} and T_{max} were comparable in both age subgroups.
The notable differences in PK parameters were independent of the formulation. Similar differences between the subgroups were obtained for the Flexeril ® 10 mg treated subjects For these subjects, the mean AUC_{0-168}, $AUC_{0-\infty}$, and $t_{1/2}$ were 26%, 35%, and 55% greater, respectively, in subjects 65 to 75 years old compared to subjects 18 to 45 years old.

Hepatic Impairment:

Cyclobenzaprine is extensively metabolized and, is excreted primarily as glucuronides via the kidney. Cytochromes P-450 3A4, 1A2, and, to a lesser extent, 2D6, mediate N-demethylation, one of the oxidative pathways for cyclobenzaprine (PI for Flexeril® tablet).

2.4. Extrinsic Factors

Q. What are the extrinsic factors that influence exposure or response?

The applicant evaluated the effect of food on Amrix® 30mg capsules. Administration with food increases the exposure (Cmax and AUC) of cyclobenzaprine (See section 2.5). The applicant did not evaluate the effects of drug-drug interactions on the Amrix® capsules but

included language in the Amrix ® label on drug-drug interactions taken from the Flexeril ® 10 mg tablet label. The proposed label is as follows:

No subtitle was included in label*:

*

Drug Interactions
Cyclobenzaprine may have life-threatening interactions with MAO inhibitors. (See CONTRAINDICATIONS.) 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. Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol (ULTRAM® [tramadol HCl tablets, Ortho-McNeil Pharmaceutical] or ULTRACET® [tramadol HCl and acetaminophen tablets, Ortho-McNeil Pharmaceutical]).

Reviewer's Comments: The label above is similar in wording and location to that of Flexeril tablets with the exception of the change in name from "Flexeril" to "Cyclobenzaprine" and the inclusion of the Ultram and Ultracet brand names of tramadol. The applicant needs to include the "Drug Interactions" title on the first paragraph for clarity.

2.5. General Biopharmaceutics

Q. What is the quantitative composition of the to-be-marketed formulation?

Amrix ® capsules were manufactured in 15 and 30 mg strengths. Both strengths of the capsules are comprised of the same The difference between the 15 mg and 30 mg capsules was that Inserted below is a table of the quantitative composition of both strengths of the CMR capsules.

3.3 Quantitative Composition

Components	15 mg		30 mg	
	Target per Capsule (mg)	% per Capsule (w/w)	Target per Capsule (mg)	% per Capsule (w/w)
Cyclobenzaprine Hydrochloride USP	15.0	[redacted]	30.0	[redacted]
Sugar Spheres NF, 20-25 mesh	[redacted]			
Opadry® Clear YS-1-7006				
Ethylcellulose NF (Ethocel Standard 10 Premium)				
Diethyl Phthalate NF				
[redacted]				
[redacted]				
Total Fill Weight				
[redacted] Gelatin Capsules				
[redacted]				
Total Capsule Weight				

* Removed during processing

Q. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation(s)?

The formulations used in all the pharmacokinetic studies (with the exception of the pilot Study # 1101) and, the Phase III clinical trials were of the same composition and came from the same [redacted] sizes, with similar production sizes [redacted] as the to-be-marketed formulation.

Q. What is the effect of food on the bioavailability of cyclobenzaprine and what dosing recommendations should be made regarding administration in relation to meals?

A food effect study (# 1103) that was conducted in healthy adult subjects (n=15) utilizing a single dose of Amrix ® 30 mg capsules demonstrated an increase in bioavailability when Amrix® 30 mg capsule was given with food relative to the fasted state. There was a 35% increase in C_{max} and a 20% increase in exposure ($AUC_{0\text{-}168}$ and $AUC_{0\text{-}\infty}$) in the presence of food. No effect, however, was noted on T_{lag}, T_{max}, or $t_{1/2}$.

Table 6: Summary of Fed/Fasted Pharmacokinetic Parameters in Healthy Adult Subjects

Parameter	30 mg Fed (N = 15) Mean ± SD [Range]	30 mg Fasted (N = 16) Mean ± SD [Range]	Ratio[a] [90% CI] (n = 15)
AUC_{0-168} (ng·hr/mL)	673.6 ± 230.1 [309.4 – 980.5]	538.5 ± 174.2 [294.6 – 907.9]	1.5 [1.11, **1.32**]
$AUC_{0-\infty}$ (ng·hr/mL)	710.3 ± 240.2 [331.4 – 1005.3]	585.7 ± 183.5 [318.9 – 975.1]	1.20 [1.11, **1.31**]
C_{max} (ng/mL)	25.4 ± 9.9 [12.0-47.4]	18.2 ± 5.3 [10.9-30.8]	1.36 [1.17, **1.57**]
T_{lag} (hrs)	2.1 ± 0.7 [1 – 3]	1.8 ± 0.6 [1 – 3]	NA
T_{max} (hrs)	7.4 ± 2.1 [5 – 12]	6.6 ± 1.5 [5 – 10]	NA
$t_{1/2}$ (hrs)	33.4 ± 8.6 [18.6 – 50.8]	32.42 ± 7.2 [19.9 – 48.2]	NA

[a]Ratio is the LS ratio of geometric means of CMR 30 mg-Fed to CMR 30 mg-Fasted. CI = Confidence Intervals

Q. What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The applicant did not propose any dosing or labeling recommendations regarding administration of CMR 15 and 30 mg in relation to meals or meal types. The higher AUC and C_{max} values obtained in the presence of food are still within the range of AUC (range = 300.7 – 1585.2 ng h/mL) and Cmax values (14.2 -86.40 ng/mL) obtained at steady state for Amrix ® 30 mg capsules. Therefore the effect of food may not be a safety concern when this product is dosed to steady state. The medical reviewer Dr. Fang informed me that the capsules were administered without regard to the timing of meals in the Phase 3 trials.

Q. Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

The dissolution method is acceptable but the specification is not acceptable.
Proposed Dissolution Method

Apparatus: USP 2 (Paddles)
Speed: 50 RPM
Temperature: 37 ± 0.5 °C
Drug Release Media: 900 mL of 0.1N HCl
Sampling Times: 1, 2, 4, 6, 8, 12 and 16 hours
Sample Volume: 1-2 mL

The applicant stated that the drug release media (0.1N HCl) was chosen based on the USP monograph for cyclobenzaprine tablets. The agitation speed and temperature is also the same as that of the USP monograph for cyclobenzaprine tablets.

Dissolution profiles were generated for clinical batches of both strengths in four different media (0.1N HCl, pH 4.5 buffer, pH 6.8 buffer, USP water). The result of the release data for the 15 mg and 30 mg capsules in different media is reproduced in the table below.

Table 7: Dissolution Data for the 15 mg Capsules

	% Dissolved Mean [Range]			
Time (hours)	**0.1 N HCL**	**pH 4.5 Buffer**	**pH 6.8 Buffer**	**USP H_2O**
1	4 [2-6]	5 [4-6]	4 [3-5]	4 [3-6]
2	23 [20-28]	26 [24-28]	20 [18-23]	25 [22-28]
4	49 [45-53]	52 [51-54]	43 [40-48]	49 [44-54]
6	62 [60-66]	65 [64-66]	57 [51-64]	62 [57-67]
8	70 [68-74]	73 [72-74]	66 [60-74]	69 [64-75]
12	80 [77-84]	82 [80-84]	76 [70-83]	78 [73-85]
16	84 [80-88]	88 [86-91]	81 [75-88]	84 [78-91]
18	ND*	ND	83 [78-90]	ND
24	ND*	ND	87 [83-92]	ND

* Not determined

Table 8: Dissolution Data for the 30 mg capsules

	% Dissolved Mean [Range]			
Time (hours)	**0.1 N HCL**	**pH 4.5 Buffer**	**pH 6.8 Buffer**	**USP H_2O**
1	4 [0-5]	5 [4-6]	4 [3-5]	4 [3-5]
2	28 [25-30]	29 [28-30]	24 [22-25]	27 [25-29]
4	51 [47-55]	54 [53-56]	48 [44-50]	52 [49-53]
6	65 [61-68]	69 [66-71]	62 [59-65]	65 [62-66]
8	73 [69-75]	76 [74-79]	70 [67-73]	72 [70-73]
12	84 [80-87]	87 [85-88]	80 [75-83]	80 [77-82]
16	90 [84-93]	91 [89-94]	87 [83-93]	87 [85-89]
24	ND*	ND	91 [86-97]	ND

* Not determined

The f2 values between the 15 mg and 30 mg strengths, in each media, were all above 50 (ranging from 69.1 to 78.4) indicating similar dissolution profiles between the 15 mg and 30 mg strengths of CMR capsules.

Reviewer's Comments: Comparative dissolution data indicated that the dissolution of both strengths in the 0.1 N HCl was somewhat lower than that of the pH 4.5 media and somewhat higher than that of the pH 6.8 and water alone however, the differences were minimal. The applicant chose the 0.1 N HCL. This is acceptable.

<u>Drug Release Proposed Acceptance Criteria:</u>

2 hour:
4 hour:
8 hour:
16 hour:

The proposed acceptance criteria are not acceptable. The time point specification range at the 4 and 8 hr deviates by > ±10 % from the mean dissolution profile obtained for these batches and the variability at these time points ranges from 2 -2.4. It is recommended that

the applicant tighten the acceptance criteria for the 4 hr and 8 hr time point to allow for a better assessment of batch-to-batch quality.

The applicant conducted comparative dissolution studies on the Lots (# PF306EA001, 30 mg and Lot # PF307EA002, 15 mg) of both strengths used in the pivotal BE studies (1102, 1103, 1104 and 1107. Inserted below are the tables showing the mean dissolution data for the pivotal clinical supplies of the 15 mg and 30 mg Cyclobenzaprine HCl Modified Release (CMR) Capsules.

TABLE 6.18: DISSOLUTION DATA FOR PIVOTAL CLINICAL BATCHES OF CMR CAPSULES

Date of Test	Strength (mg)	Lot Number	Dissolution Apparatus	Media/ Temperature	Speed (rpm)	Units Tested (N)	Time (hours)	% Dissolved		
								Mean	Range	Standard Deviation
4-3-02	30 mg	PF306EA001	USP 2	900 ml 0.1 N HCl 37°C ± 5°C	50	12	1	4	0-5	1.4
							2	28	25-30	1.2
							4	51	47-55	2.4
							6	65	61-68	2.0
							8	73	69-75	1.8
							12	84	80-87	2.2
							16	90	84-93	2.8
4-29-02	15 mg	PF307EA002	USP 2	900 ml 0.1 N HCl 37°C ± 5°C	50	12	1	4	2-6	1.1
							2	23	20-28	2.3
							4	49	45-53	2.3
							6	62	60-66	2.1
							8	70	68-74	2.2
							12	80	77-84	1.9
							16	84	80-88	2.2

Based on the above data, this reviewer recommends the following revised proposed acceptance criteria (proposed *changes are in bold italics*):

2 hour:
4 hour:
8 hour:
16 hour:

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Q. What is the relative bioavailability of Amrix® capsules to encapsulated IR drug product?

In study # 1107 an evaluation of the bioequivalence between the Amrix® 30 mg capsule and the encapsulated IR formulation, demonstrated that the 90% CI for the geometric mean ratio for AUC 0-168, AUC 0-∞, and Cmax fell within the 80% to 125 % BE limit (see table 9 below) indicating that the Amrix® 30 mg is bioequivalent to the encapsulated Flexeril 10 mg TID tablets.

Table 9:

PK Parameter	Ratio [90% CI] (n = 34)
AUC 0-168 (ng.hr/mL)	0.910 [0.874, 0.949]
AUC 0-∞ (ng.hr/mL)	0.919 [0.880, 0.959]
Cmax (ng/mL)	1.042 [0.984, 1.104]

However, the T_{max} using the plasma concentrations during the entire study period for both medications was different. The Amrix® capsules had a much earlier mean T_{max} (7.6 hrs) compared to the encapsulated Flexeril ® tablets (mean T_{max} =18.5 hrs). Since the "reference" product in this study was modified from the approved product the relevance of this finding of equivalence is unknown.

Q. Does the encapsulated IR drug product have comparable exposure or is it bioequivalent to the approved intact IR drug product?

No, the altered approved product has a higher exposure (up to ~38%) than the approved product. In this submission, the applicant did not conduct a study to evaluate the bioequivalence of the encapsulated Flexeril tablets. The applicant provided in vitro dissolution data and an in vivo cross study comparison of two studies (#1101 and 1107) conducted by them to support a possible comparable exposure between the two formulations.

A review of the data by this reviewer indicated that the in vitro dissolution data demonstrated similarity in dissolution for the encapsulated Flexeril® and the intact Flexeril® tablets (mean % dissolved was 102 vs. 99 % , respectively) at the 0.5 hour sampling point.

The cross comparison pharmacokinetic analysis of subjects receiving intact Flexeril® 10 mg tablets in the applicant's pilot study # 1101 and a similar aged group of subjects (i.e. ≤ 40 years old) receiving encapsulated Flexeril® 10 mg in study #1107 demonstrated an increase in exposure for the encapsulated tablet. The Cmax, AUC 0-168 and AUC 0-inf were increased by 34.6 %, 38.3 % and 34.8 % respectively, for the encapsulated tablet (study 1107) relative to the intact tablet (study 1101). Reproduced in the table below is a summary of the PK assessment following three doses (0-24 hrs).

Table 10: Comparison of Flexeril 10 mg PK Parameters by Study in Subjects Aged ≤ 40 years old

PK Parameter	Study 1101 (tablet) Male Subjects only	Study 1107 (capsule) Male Subjects only	Study 1107 (capsule) Males and Females
	Mean ± SD [range] (N = 12)	Mean ± SD [range] (N = 8)	Mean ± SD [range] (N = 11)
AUC_{0-168} (ng·hr/mL)	504 ± 206 [214-752]	697 ± 304 [270-1192]	693 ± 265.2 [270-1192]
$AUC_{0-\infty}$ (ng·hr/mL)	534 ± 215.3 [228-817]	720 ± 305 [291-1213]	718 ± 267.5 [291-1213]
C_{max} (ng/mL)	12.4 ± 3.6 [6.3-17.8]	16.7 ± 4.8 [7.6-24.7]	16.4 ± 4.2 [7.6-24.7]
T_{max} (hrs)	17.7 ± 7.6 [4.0-24.0]	17.3 ± 5.8 [12.0-24.0]	16.7 ± 5.5 [12.0-24.0]

T_{max} was similar for both formulations. The inclusion of the female data in Study 1107 did not change the conclusions obtained from evaluating males only. However, due to the differences in the PK of cyclobenzaprine between the young and elderly populations, an analysis in subjects aged ≤ 40 years old does not provide a complete picture of the systemic exposure for both formulations.

Reviewer's Comments: The overall implication of the above findings is that the applicant has not provided a systemic exposure bridge of their encapsulated (IR) drug product to the approved (IR) drug product and so clinically we cannot rely on the safety findings of the approved IR drug product especially in terms of long term exposure.

2.6. Analytical

Q. Were the analytical methods used for the determination of cyclobenzaprine in biological fluids acceptable?

Yes, the applicant used high-performance liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) to determine the concentrations of total (free and unbound) unconjugated (as free base) cyclobenzaprine in plasma. Adequate documentation of method validation and in-study validation was provided (see Table below).

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Table 11: Method Validation

Compound	Cyclobenzaprine
Internal Standard	[redacted]
Matrix	Human Plasma
Accuracy (%) ***Between-Day***	[redacted]
Precision (CV %) ***Between-Day***	5 % to 6 %
Standard curve range	0.5 to 50 ng/mL R> = 0.991 (N = 36)
Sensitivity (LOQ)	0.5 ng/ml (% CV = 7%, Accuracy = 87 %)
Selectivity	No interfering peaks at the retention times of interest (sponsor did not provide chromatograms, just blank plasma cyclobenzaprine concentrations)
Mean Recovery % (%CV)	92 %
Stability	There was [redacted] degradation following 3 freeze-thaw cycles and [redacted] % degradation @ -5 °C storage for 37 days
Conclusions	Method validation is acceptable

3. Labeling Recommendation:

Specific labeling recommendations for the Clinical Pharmacology sections of the label are deferred pending the completion of a successful clinical development program. The following feedback on the special populations section is being provided to the applicant so that they can better address these issues in a subsequent labeling proposal

4. Appendix

4.1. Consult Review: None

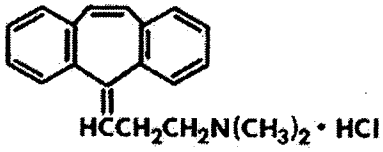
4.2. Proposed Package Insert

Rx Only

AMRIX®
(Cyclobenzaprine HCl Modified Release Capsules)

DESCRIPTION

The active ingredient in AMRIX® capsules is cyclobenzaprine hydrochloride, USP. Cyclobenzaprine hydrochloride (HCl) is a white, crystalline tricyclic amine salt with the empirical formula $C_{20}H_{21}N{\cdot}HCl$ and a molecular weight of 311.9. It has a melting point of 217°C, and a pK_a of 8.47 at 25°C. It is freely soluble in water and alcohol, sparingly soluble in isopropanol, and insoluble in hydrocarbon solvents. If aqueous solutions are made alkaline, the free base separates. Cyclobenzaprine HCl is designated chemically as 3-(*5H*-dibenzo[*a*,*d*] cyclohepten-5-ylidene)-*N*,*N*-dimethyl-1-propanamine hydrochloride, and has the following structural formula:



AMRIX capsules for oral administration are supplied in 15 and 30 mg strengths. AMRIX capsules contain the following inactive ingredients: sugar spheres NF (20-25 mesh), Opadry® Clear YS-1-7006, ethylcellulose NF (Ethocel Standard 10 Premium), diethyl phthalate NF, titanium oxide, and gelatin. AMRIX 15 mg capsules also contain red iron oxide and yellow iron oxide. AMRIX 30 mg capsules also contain FD&C blue #1, FD&C blue #2, FD&C red #40, and FD&C yellow #6.

CLINICAL PHARMACOLOGY

Cyclobenzaprine relieves skeletal muscle spasm of local origin without interfering with muscle function. Cyclobenzaprine has not been shown to be effective in muscle spasm due to central nervous system disease. In animal models, cyclobenzaprine reduced or abolished skeletal muscle hyperactivity. Animal studies indicate that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. Such studies show that cyclobenzaprine acts primarily within the central nervous system at the brain stem as opposed to the spinal cord level, although an overlapping action on the latter may contribute to its overall skeletal muscle relaxant activity. Evidence suggests that the net effect of cyclobenzaprine is a reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems. Pharmacological studies in animals demonstrated a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

Pharmacokinetics

Cyclobenzaprine is extensively metabolized and is excreted primarily as glucuronides via the kidney. Cytochromes P-450 3A4, 1A2, and, to a lesser extent, 2D6, mediate N-demethylation, one of the oxidative pathways for cyclobenzaprine. Cyclobenzaprine [illegible] an effective half-life of [illegible] hours (range 8-37 hours; n=18); plasma clearance is 0.7 L/min.

In a single dose study comprised of healthy adult males (n=15),

The dose adjusted ratios of the arithmetic means of AUC_{0-168} and $AUC_{0-\infty}$ indicated that exposure of the AMRIX 30 mg was about 16% and 10% higher than that of AMRIX 15 mg, respectively. The dose-adjusted ratios of the arithmetic means of C_{max} indicated that the peak plasma concentration of AMRIX 30 mg was about 20% higher than that of AMRIX 15 mg. The half-lives and time to peak plasma cyclobenzaprine concentration were similar for both AMRIX 15 mg and 30 mg. These data are summarized below.

SUMMARY OF PHARMACOKINETIC PARAMETERS IN HEALTHY ADULT SUBJECTS

Parameter/Statistic	15 mg (N = 15) Mean ± SD	30 mg (N = 14) Mean ± SD
AUC_{0-168} (ng·hr/mL)	318.3 ± 114.7	736.6 ± 259.4
$AUC_{0-\infty}$ (ng·hr/mL)	354.1 ± 119.8	779.9 ± 277.6
C_{max} (ng/mL)	8.3 ± 2.2	19.9 ± 5.9
T_{max} (hrs)	8.1 ± 2.9	7.1 ± 1.6
$t_{1/2}$ (hrs)	33.4 ± 10.3	32.0 ± 10.1

A food effect study conducted in healthy adult subjects (n=15) utilizing a single dose of AMRIX 30 mg demonstrated a statistically significant increase in bioavailability when AMRIX 30 mg was given with food relative to the fasted state. There was a 35% increase in

peak plasma cyclobenzaprine concentration (C_{max}) and a 20% increase in exposure (AUC_{0-168} and $AUC_{0-\infty}$) in the presence of food. No effect, however, was noted in T_{lag}, T_{max}, or the shape of the mean plasma cyclobenzaprine concentration versus time profile. Cyclobenzaprine in plasma was first detectable in both the fed and fasted states at 1.5 hours.

A multiple-dose study utilizing AMRIX 30 mg administered once daily for 7 days in a group of healthy adult volunteers (n=35)

Elderly

SUMMARY OF AMRIX 30 MG PK PARAMETERS BY AGE GROUP

Parameter/Statistic	18 to 45 years (N = 18) Mean ± SD	65 to 75 years (N = 17) Mean ± SD
AUC_{0-168} (ng·hr/mL)	715.1 ± 264.2	945.9 ± 255.2
$AUC_{0-\infty}$ (ng·hr/mL)	751.2 ± 271.5	1055.2 ± 301.9
C_{max} (ng/mL)*	19.2 ± 5.6	19.2 ± 5.1
T_{max} (hrs)*	6.8 ± 1.9	8.5 ± 2.3
$t_{1/2}$ (hrs)	32.4 ± 8.1	49.0 ± 8.3

*-measured over the entire 24 hour dosing period
SD = standard deviation

Hepatic Impairment
In a pharmacokinetic study of sixteen subjects with hepatic impairment (15 mild, 1 moderate per Child-Pugh score), both AUC and C_{max} were approximately double the values seen in the healthy control group.

1 Page(s) Withheld

✓ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1

INDICATIONS AND USAGE

is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, limitation of motion.

should be used only for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.

has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.

CONTRAINDICATIONS

- Hypersensitivity to any component of this product.
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation.
- Hyperpyretic crisis seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.
- During the acute recovery phase of myocardial infarction, and in patients with arrhythmias, heart block conduction disturbances, or congestive heart failure.
- Hyperthyroidism.

WARNINGS

_____ is closely related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. In short term studies for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm, some of the more serious central nervous system reactions noted with the tricyclic antidepressants have occurred (see WARNINGS, below, and ADVERSE REACTIONS).

Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke. _____ may enhance the effects of alcohol, barbiturates, and other CNS depressants.

PRECAUTIONS

General

Because of its atropine-like action, _____ should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

Information for Patients

_____ especially when used with alcohol or other CNS depressants, may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. _____

Drug Interactions

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[redacted] may have life-threatening interactions with MAO inhibitors. (See CONTRAINDICATIONS.) [redacted] may enhance the effects of alcohol, barbiturates, and other CNS depressants. Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds. Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol (ULTRAM® [tramadol HCl tablets, Ortho-McNeil Pharmaceutical] or ULTRACET® [tramadol HCl and acetaminophen tablets, Ortho-McNeil Pharmaceutical]).

Carcinogenesis, Mutagenesis, Impairment of Fertility
In rats treated with cyclobenzaprine for up to 67 weeks at doses of approximately 5 to 40 times the maximum recommended human dose, pale, sometimes enlarged, livers were noted and there was a dose-related hepatocyte vacuolation with lipidosis. In the higher dose groups, this microscopic change was seen after 26 weeks and even earlier in rats that died prior to 26 weeks; at lower doses, the change was not seen until after 26 weeks. Cyclobenzaprine did not affect the onset, incidence, or distribution of neoplasia in an 81-week study in the mouse or in a 105-week study in the rat. At oral doses of up to 10 times the human dose, cyclobenzaprine did not adversely affect the reproductive performance or fertility of male or female rats. Cyclobenzaprine did not demonstrate mutagenic activity in the male mouse at dose levels of up to 20 times the human dose.

A battery of mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenic effects have provided no evidence for a mutagenic potential for cyclobenzaprine. An *in vivo* mouse bone micronucleus assay, an assessment of chromosomal aberrations (Chinese hamster ovary), and a mammalian microsome reverse mutation assay were negative.

Pregnancy
Pregnancy Category B: Reproduction studies have been performed in rats, mice, and rabbits at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyclobenzaprine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because cyclobenzaprine is closely related to the tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when [redacted] is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of [redacted] in pediatric patients [redacted] have not been established.

Use in the Elderly
The plasma concentration of cyclobenzaprine is increased in the elderly (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Elderly).*

ADVERSE REACTIONS

Incidence of the most common adverse reactions (occurring in ≥ 3% of subjects in any treatment group) in two Phase III, double-blind AMRIX trials:

	AMRIX 15 mg N=127	AMRIX 30 mg N=126	Placebo N=128
Dry mouth	6%	14%	2%
Dizziness	3%	6%	2%
Fatigue	3%	3%	2%
Constipation	1%	3%	0%
Somnolence	1%	2%	0%
Nausea	3%	3%	1%
Dyspepsia	0%	4%	1%

In a postmarketing surveillance program (7607 patients treated with cyclobenzaprine 10 mg TID), the adverse reactions reported most frequently were drowsiness, dry mouth, and dizziness. The incidence of these common adverse reactions was lower in the surveillance program than in the controlled clinical studies:

	Clinical Studies cyclobenzaprine 10 mg TID	Surveillance Program cyclobenzaprine 10 mg TID
Drowsiness	39%	16%
Dry Mouth	27%	7%
Dizziness	11%	3%

Among the less frequent adverse reactions, there was no appreciable difference in incidence in controlled clinical studies or in the surveillance program. Adverse reactions which were reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion. The following adverse reactions have been reported in post-marketing experience or with an incidence of less than 1% of patients in clinical trials with the 10 mg TID tablet:

Body as a Whole: Syncope; malaise.

Cardiovascular: Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension.
Digestive: Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice, and cholestasis.
Hypersensitivity: Anaphylaxis; angioedema; pruritus; facial edema; urticaria; rash.
Musculoskeletal: Local weakness.
Nervous System and Psychiatric: Seizures, ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; psychosis, abnormal thinking and dreaming; hallucinations; excitement; paresthesia; diplopia.
Skin: Sweating.
Special Senses: Ageusia; tinnitus.
Urogenital: Urinary frequency and/or retention.

Causal Relationship Unknown
Other reactions, reported rarely for cyclobenzaprine under circumstances where a causal relationship could not be established or reported for other tricyclic drugs, are listed to serve as alerting information to physicians:

Body as a whole: Chest pain; edema.
Cardiovascular: Hypertension; myocardial infarction; heart block; stroke.
Digestive: Paralytic ileus, tongue discoloration; stomatitis; parotid swelling.
Endocrine: Inappropriate ADH syndrome.
Hematic and Lymphatic: Purpura; bone marrow depression; leukopenia; eosinophilia; thrombocytopenia.
Metabolic, Nutritional and Immune: Elevation and lowering of blood sugar levels; weight gain or loss.
Musculoskeletal: Myalgia.
Nervous System and Psychiatric: Decreased or increased libido; abnormal gait; delusions; aggressive behavior; paranoia; peripheral neuropathy; Bell's palsy; alteration in EEG patterns; extrapyramidal symptoms.
Respiratory: Dyspnea.
Skin: Photosensitization; alopecia.
Urogenital: Impaired urination; dilatation of urinary tract; impotence; testicular swelling; gynecomastia; breast enlargement; galactorrhea.

DRUG ABUSE AND DEPENDENCE

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when _____ is administered, even though they have not been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration rarely may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE

Although rare, deaths may occur from overdosage with ———— Multiple drug ingestion (including alcohol) is common in deliberate cyclobenzaprine overdose. **As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment.** Signs and symptoms of toxicity may develop rapidly after cyclobenzaprine overdose; therefore, hospital monitoring is required as soon as possible. The acute oral LD_{50} of cyclobenzaprine is approximately 338 and 425 mg/kg in mice and rats, respectively.

MANIFESTATIONS

The most common effects associated with cyclobenzaprine overdose are drowsiness and tachycardia. Less frequent manifestations include tremor, agitation, coma, ataxia, hypertension, slurred speech, confusion, dizziness, nausea, vomiting, and hallucinations. Rare but potentially critical manifestations of overdose are cardiac arrest, chest pain, cardiac dysrhythmias, severe hypotension, seizures, and neuroleptic malignant syndrome. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of cyclobenzaprine toxicity. Other potential effects of overdosage include any of the symptoms listed under ADVERSE REACTIONS.

MANAGEMENT

General

As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment.

In order to protect against the rare but potentially critical manifestations described above, obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line, and initiate gastric decontamination. Observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. Monitoring of plasma drug levels should not guide management of the patient. Dialysis is probably of no value because of low plasma concentrations of the drug.

Gastrointestinal Decontamination

All patients suspected of an overdose with ———— should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage and emesis is contraindicated.

Cardiovascular

A maximal limb-lead QRS duration of 0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and hyperventilation (as needed), should be instituted for patients with dysrhythmias and/or QRS widening. A pH >7.60 or a pCO_2 <20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

CNS
In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a poison control center.

PSYCHIATRIC FOLLOW-UP
Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

PEDIATRIC MANAGEMENT
The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION

The recommended adult dose for most patients is one (1) AMRIX 15 mg capsule taken once daily. Some patients may require up to 30 mg/day, given as two (2) 15 mg capsules taken once daily or as one (1) AMRIX 30 mg capsule taken once daily. It is recommended that doses be taken at approximately the same time each day.

Use of AMRIX for periods longer than two or three weeks is not recommended (see INDICATIONS AND USAGE).

HOW SUPPLIED

AMRIX release capsules are available in 15 and 30 mg strengths, packaged in bottles of 60 capsules. AMRIX 15 mg capsules (NDC 00095-0150-06) are orange/orange, are embossed "ECR 15" on each half, and bear a single white band. AMRIX 30 mg capsules (NDC 00095-0300-06) are blue/orange, are embossed "ECR 30" on each half, and bear two white bands. Physician samples (AMRIX 15 mg capsules, NDC 00095-0150-09; AMRIX 30 mg capsules, NDC 00095-0300-09) are packaged in individual blisters.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. IN CASE OF ACCIDENTAL OVERDOSE, SEEK PROFESSIONAL ASSISTANCE OR CONTACT A POISON CONTROL CENTER IMMEDIATELY.

Dispense in a tight, light-resistant container as defined in the USP/NF.

; [see USP Controlled Room Temperature].

Manufactured by Eurand America, Vandalia, Ohio 45377

Manufactured for and distributed by
ECR Pharmaceuticals, Richmond, Virginia 23255

4.3. Individual Study Reviews

Study Number: 1104

Title of Study: A Randomized, Double-Blind, Two-Period Crossover Study to Assess the Safety and Bioavailability of Multiple Dosing of Cyclobenzaprine HCI Modified-Release (CMR) 30 mg and Cyclobenzaprine HCI 10 mg TID in Healthy Volunteers
Principal Investigator (s): Maria J. Gutierrez, MD
Study Center (s): Comprehensive NeuroScience, Inc., Ft. Lauderdale, FL
Objectives: The primary objective of this double-blind, single-center, two-period crossover study was to assess the safety and bioavailability of multiple dosing of CMR 30 mg once daily compared with cyclobenzaprine HCI 10 mg TID in healthy volunteers.
Methodology: Subjects were randomly assigned to one of 2 possible treatment sequences, approximately 18 subjects in each group. The study consisted of a screening visit, the first 7-day treatment period with CMR or cyclobenzaprine with study assessments, a 14-day washout period, and the second 7-day treatment period with study assessments. Each assessment period consisted of blood collection during the second through seventh day of multiple dosing for trough levels and for 4 days after the seventh dose for pharmacokinetic (PK) parameter estimation, as well as safety assessments.
Study Period: 01 July 2002 -07 August 2002
Study Population Demographics: Planned: 36; Randomized: 36; Safety: 36; Completed PK: 34. Subjects were healthy males or non-pregnant females between 18 and 75 years of age with body weight within ±20% of their ideal weight for height. Two subjects dropped out after the first dosing period. The demographic characteristics (mean(SD)) of the study population is as follows: *Age*: 37.3 (10.33) [Range = 19-59], 5 subjects were aged > 45 years old; *Gender*: 13 M and 23 F; *Race*: All Caucasian; *Height* 163.6 (7.37) cm [Range = 152-178 cm]; *Weight*: 68.7 (9.35) k [53-90]
Investigational Product (s): Cyclobenzaprine HCL Modified-Release (CMR) 30 mg (Batch No: PF306EA00I) Reference Therapy: Cyclobenzaprine HCI Dose: 10 mg (Batch No: PF304EA001)
Dosing Regimen, Mode of Administration and Treatment Duration: Two treatment periods of 7 days each (7 days of CMR 30 mg once daily (6-7 PM) and 7 days of cyclobenzaprine HCL 10 mg TID (6-7 AM, 12-1 PM and 6-7 PM), separated by 14 days of washout. *Reviewer's comments: The IR dosing regimen used in this study resulted in two 6-hour dosing intervals and one 12-hour dosing interval. This non symmetrical dosing may complicate estimates of PK parameters at SS, because they will be a function of the particular dosing interval. Ideally this should be 0-24 hrs and this should not be a problem since the difference at SS resides mainly in the troughs. The implication of the irregular dosing and non-symmetrical areas under the curve is that the total area under the curve cannot simply be split into three equal areas (e.g. the first 12-hour dosing interval would not necessarily be half of the total 24-hour AUC).*
PK Sampling Scheme: On days 2-7 and 22-27: One sample prior to evening dose for trough determination On days 7 and 27: Pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22 24, 48,72 and 96 hours after the last dose

Analytical Methods:LC/MS/MS

Compound	Cyclobenzaprine
Internal Standard	[redacted]
Matrix	Plasma
Accuracy (%) ***Between-Day***	[redacted]
Precision (CV %) ***Between-Day***	[redacted]
Standard curve range	0.5 to 50 ng/mL R> = 0.998 (N = 37)
Sensitivity (LOQ)	0.5 ng/ml (CV% = 1.2)
Selectivity	No interfering peaks @ retention time of cyclobenzaprine

PK data Analysis: The steady state PK parameters calculated included: Cmaxss, Cav ss, CL/F, K, t ½, Rac (steady state accumulation ratio, and Fluctuation index (Cmax –Cmin/Cav).

Since the second and third daily doses of cyclobenzaprine HCL 10 mg TID were inadvertently omitted on Day 8 of each study period, therefore the AUC0-tss for the IR capsule is only measurable for the first 12 hours of the 24 hour dosing cycle. This prohibited the estimation of AUC $_{0\text{-}T\ ss}$ and AUC $_{0\text{-}T\ ss}$ over a 24-hour period for the IR formulation. As recommended by the FDA (e-mail communication March 31, 2003) the report focused on clearance and elimination rate that are independent of the dosing interval, instead of AUC $_{0\text{-}t\ SS}$.

OCPB's response sent by e-mail on March 31st, 2003 was as follows:
With regards to the dosing error that occurred on the last day of study 1104, while it will decrease the utility of the trial by not providing final dosing interval profile, the data to be gained from the trial should still be sufficient to provide a relevant PK steady-state performance comparison. The data analysis plan should be modified to include comparison of Cl values and elimination rate as primary steady state parameters, replacing or down grading AUC at this point.

The applicant stated that the Cavss was used in place of the AUC $_{0\text{-}tss}$ for inferential statistics since it required no further manipulation and represented the time averaged AUC $_{0\text{-}tss}$

Statistical Analysis:

To compare bioavailability, PK parameters were transformed to the natural log scale. Analysis of variance (ANOVA) was performed using a model that included fixed effects for treatment, period, sequence, and subject nested in sequence. Least-squares (LS) means for each treatment, between-treatment group differences in LS means, and the corresponding 90% CI's were calculated from the model and transformed back to the arithmetic scale.

Results: Subjects receiving CMR 30 mg appeared to reach steady state by Day 7 (p=0.098). Subjects receiving cyclobenzaprine HCI 10 mg TID could not be assessed for steady state attainment due to the missed doses on Day 8. The dosing error was discovered after unblinding and additional PK parameters were calculated.

Pre-dose Plasma Concentrations following Cyclobenzaprine ER (30 mg daily)

	Day 2 post dose	Day 3 post dose	Day 4 Post dose	Day 5 post dose	Day 6 post dose	Day 7 post dose
Cyclobenzaprine HCl 10 mg TID	12.785 (6.6498)	17.238 (6.8604)	19.767 (7.6653)	21.361 (8.5385)	21.928 (10.3076)	24.156 (12.465)
CMR 30 mg	10.821 (3.4319)	16.737 (5.3335)	19.429 (7.1344)	20.775 (7.4696)	22.757 (8.9506)	24.239 (9.9158)

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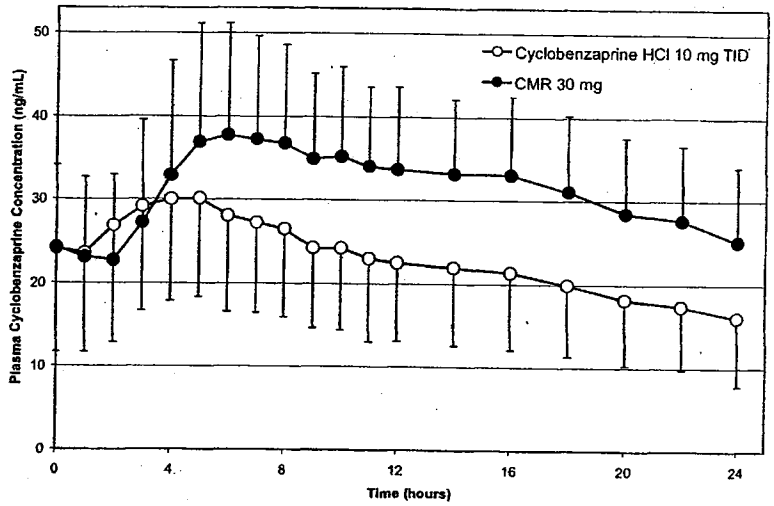
Figure 4: Mean (± SD) Plasma Cyclobenzaprine Concentration Over Time (24 hours) – Safety Population



Mean (±SD) pharmacokinetic parameters are presented for subjects in the Safety Population in the following table.

Parameter/Statistic	Cyclobenzaprine HCl 10 mg TID n = 34	CMR 30 mg n = 35
CL/F (L/hr)	56.1 ± 25.3	44.3 ± 17.1
λ_z (1/hr)	0.022 ± 0.005	0.021 ± 0.005
$C_{av\,ss}$ (ng/mL)	26.4 ± 10.9	31.4 ± 9.7
$C_{max\,ss}$ (ng/mL)	32.4 ± 13.6	41.1 ± 13.3
$T_{max\,ss}$ (hr)	4.4 ± 2.3	8.0 ± 3.9
$C_{min\,ss}$ (ng/mL)	20.4 ± 9.6	21.4 ± 8.7
$T_{min\,ss}$ (hr)	7.1 ± 5.1	4.9 ± 7.4
$t_{1/2}$	34.1 ± 9.4	34.8 ± 8.1
$AUC_{0\text{-}t\,ss}$ (ng·hr/mL)	316.2 ± 130.8	753.1 ± 232.9
F_i (%)	48.0 ± 17.8	64.0 ± 17.3
R_{ac}	–	2.65 ± 0.48

AUC 0-t = 0-6 for IR and 0-24 for MR, not right comparison in terms of dosing interval

The information provided for CMR 30 mg describes the performance of the CMR formulation at steady state (24 hr tau), but not that of the IR formulation. The CMR formulation was demonstrated to have a slower controlled absorption input than the IR formulation (Mean Tmax ss = 8 vs. 4 hr). The t 1/2 was virtually identical in cyclobenzaprine HCI 10 mg TID treated subjects and CMR 30 mg treated subjects. The Cmin SS for CMR 30 mg was similar to cyclobenzaprine HCI 10 mg TID. In contrast, the Cmaxss was 27% higher in CMR30mg treated subjects compared with cyclobenzaprine HCI 10 mg TID treated subjects, the clinical relevance of this was evaluated in the clinical trials. This result led to a slightly larger Fi in CMR 30 mg treated subjects compared to cyclobenzaprine HCI 10 mg TID treated subjects. A larger apparent Cavg, SS ratio was a result of the observed lower CL/F in CMR 30 mg treated subjects compared with cyclobenzaprine HCL 10 mg TID treated subjects. The estimated CL/F in CMR 30 mg treated subjects was approximately 20% less than that estimated for cyclobenzaprine HCI 10mg TID treated subjects. In concurrence, the observed Cavgss was approximately 20% higher in CMR 30 mg treated subjects compared with cyclobenzaprine HCI 10 mg TID treated subjects.

The summary of the ANOVA for CL/F, λ_z, $C_{av\,SS}$, and $C_{max\,SS}$ are presented for subjects in the Bioavailability population in the following table.

Parameter/Statistic	Cyclobenzaprine HCl 10 mg TID n = 34	CMR 30 mg n = 34	Ratio n = 34
CL/F (L/hr)			
LS mean	51.8	42.0	0.81
90% CI	48.671, 55.169	39.431, 44.696	0.741, 0.885
λ_z (1/hr)			
LS mean	0.021	0.020	0.98
90% CI	0.0201, 0.0218	0.0197, 0.0214	0.924, 1.038
$C_{av\,SS}$ (ng/mL)			
LS mean	24.1	29.8	1.23
90% CI	22.666, 25.694	27.963, 31.698	1.129, 1.348
$C_{max\,SS}$ (ng/mL)			
LS mean	29.8	38.8	1.30
90% CI	27.837, 31.857	36.285, 41.524	1.185, 1.434

The LS mean ratio of K. was approximately one, indicating that elimination was formulation independent.

Reviewer's Comments:
Generally the statistical analysis in the table above indicates that the CMR formulation has a lower clearance and a higher exposure than the IR formulation. Interestingly, since the cyclobenzaprine was ground and then encapsulated one would expect it to have somewhat of a higher exposure (since dissolution will not be rate limiting). However, one should treat the information with caution due to the incompleteness of the IR data.

Although the data provides the steady state information on the CMR highest strength (30 mg) enough information was not provided to allow a comparison of the systemic exposure of the ER drug product to that of the IR product at SS. The implications of this are that comparative labeling claims in relation to the approved IR product cannot really be used for the ER product.

Safety:
There were 125 treatment-emergent AEs reported in 34 subjects receiving cyclobenzaprine HCI 10 mg TID and 142 treatment-emergent AEs in 36 subjects receiving CMR 30 mg. Most of the AEs were considered mild in intensity. The most common AEs reported by subjects receiving both cyclobenzaprine HCL 10 mg TID and CMR 30 mg were somnolence, dry mouth, dizziness, and headache. Almost all the AEs were considered related to study drug.

Study Number: 1107

Title of Study: A Randomized, Open-Label, Two-Period Crossover Study to Compare the Safety and Pharmacokinetics of Cyclobenzaprine HCl Modified-Release (CMR) 30 mg Once Daily and Cyclobenzaprine HCI 10 mg Three Times Daily in Healthy Volunteers

Principal Investigator (s): Maria J. Gutierrez, MD

Study Center (s): Comprehensive NeuroScience, Inc., Ft. Lauderdale, FL

Objectives: To compare the safety and pharmacokinetics (PK) of CMR 30 mg once daily and cyclobenzaprine HCL 10 mg three times daily (TID) in healthy subjects.

Study Design: This was a randomized, open-label, two-period crossover study designed to compare the safety and PK of a single oral dose of CMR 30 mg and TID dosing of cyclobenzaprine HCl 10 mg in healthy young adult (18 to 45 years) and elderly (65 to 75 years) subjects.

Study Period: 19 September 2002 to 4 November 2002

Study Population Demographics: 36 Caucasian Subjects (Enrolled), 34 subjects (18 to 45 years: 17 subjects; 65 to 75 years, 17 subjects) completed the study. Two subjects withdrew before their second randomized dose. Subject #01-0011 (received only Cyclobenzaprine HCl 10 mg TID) due to family concerns and #01-0030 (received only CMR 30mg) due to work-related problems. Inserted below is a table of the demographic characteristics of the subjects

Parameter/Statistic	**18 to 45 Years (N = 18)**	**65 to 75 Years (N = 18)**	**Total (N = 36)**
Age (years) Mean ± SD Range	33.9 ± 7.83 21 - 43	69.4 ± 2.89 65 - 73	51.7 ± 18.89 21 - 73
Gender: Male / Female	9 / 9	3 / 15	12 / 24
Height (cm) Mean ± SD Range	166.7 ± 8.82 152 - 180	157.2 ± 9.55 142 - 178	162.0 ± 10.27 142 - 180
Weight (kg) Mean ± SD Range	68.6 ± 8.38 53 - 80	70.7 ± 10.05 54 - 91	69.6 ± 9.18 53 - 91

Investigational Product (s): Test: Cyclobenzaprine HCl Modified-Release (CMR) Dose: 30 mg, Batch/Lot No: PF306EAOOI. **Reference:** Cyclobenzaprine HCl Dose: 10 mg TID, Batch/Lot No: 2090845

Dosing Regimen, Mode of Administration and Treatment Duration: Subjects were randomly assigned to one of 2 possible treatment sequences, 18 subjects in each treatment sequence. The study consisted of two treatment periods of 7 days each separated by 14 days of washout. Following an 11-hr fasting period, each subject received one capsule of CMR 30 mg or one tablet of cyclobenzaprine 10 mg according to the randomization schedule. Subjects in the cyclobenzaprine 10 mg TID group received their subsequent 2 doses of cyclobenzaprine HCl 8 hrs (4-4:42 PM) and 16 hrs (12 midnight to 12:42 AM) later, following a 4.5-hr fasting period. There was a 14-day washout period between study drug administrations.

PK Sampling Scheme: Pre-dose (8-12 hrs prior to dosing), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 36, 48, 72, 96, 120, 144, and 168 hrs after dosing

Analytical Methods: Total (free and unbound) unconjugated (as free base) was measured by LC/MS/MS. LOQ = 0.5 ng/mL

Compound	Cyclobenzaprine
Internal Standard	[redacted]
Matrix	Plasma
Accuracy (%) ***Between-Day***	[redacted]
Precision (CV %) ***Between-Day***	[redacted]
Standard curve range	0.5 to 50 ng/mL R> = 0.991 (N = 36)
Sensitivity (LOQ)	0.5 ng/ml (CV% = 0.9)
Selectivity	No info (check other studies)
Mean Recovery % (%CV)	No Info (check other studies)
Stability	No Info (check other studies)
Conclusions	Method validation acceptable?

PK data Analysis: The following PK parameters were derived from the plasma concentration time data: AUC 0-168, AUC 0-inf, Cmax (first), Cmax, Tmax (first), T max, t1/2.

Reviewer's Comments: the two additional parameters Cmax (first) and Tmax (first) were estimated based on the plasma levels obtained following the first dose of cyclobenzaprine HCl 10 mg TID. For comparative purposes CMR 30 mg, Cmax during the entire study period was dose-adjusted (to a 10mg dose) to calculate Cmax (first), which represents the expected Cmax if a 10 mg CMR formulation was administered. This was because the Cmax and Tmax for the TID formulation (covering all 3 doses) may have been based on the plasma levels that occurred after a subject's second or third dose which would not be analogous to the single-dose parameters determined for the CMR formulation

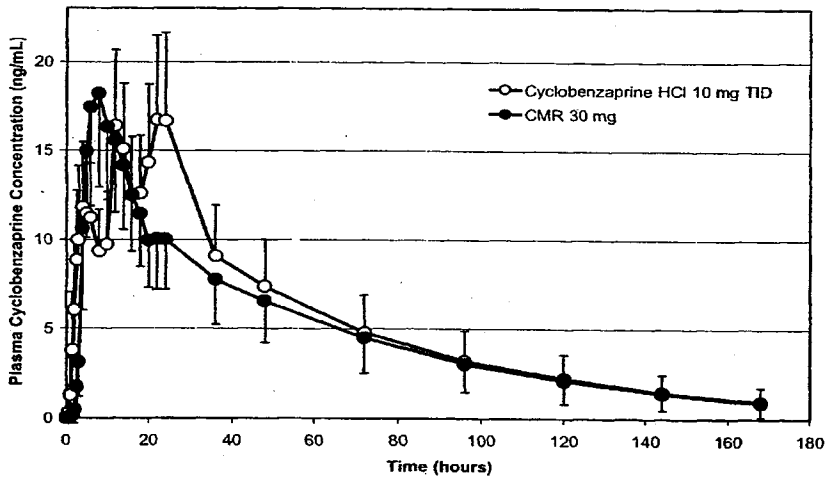
Statistical Analysis: A comparative analysis was performed on log-transformed values of AUC 0-168, AUC 0-inf, Cmax (first), and Cmax. An ANOVA with treatment, period, sequence, and subject nested within treatment sequence as fixed effects was performed. The following statistics were produced: least-squares (LS) means and corresponding 90% confidence intervals (CIs) for each treatment; and the treatment group ratio based on the LS mean and the related 90% CI, with cyclobenzaprine HCl 10 mg TID treatment as the reference. Subgroup analyses for age subgroups 18 to 45 years and 65 to 75 years were performed. The LS means, ratios, and 90% CIs were transformed back to the arithmetic scale.

Results:

Plasma Concentrations:

Inserted below is a figure that presents the mean (SD) plasma cyclobenzaprine concentration over time for all subjects

Figure 2: Mean (± SD) Plasma Cyclobenzaprine Concentration Over Time – All Subjects – Safety Population



Reviewer's Comments: Although not very clear due to the scale used on the x-axis, the graph is supposed to indicate that the TID dosing produced three peaks in plasma cyclobenzaprine concentrations with distinct troughs between the peaks.

The shape of the plasma profiles were similar in both age groups studied but plasma cyclobenzaprine levels tended to be higher in subjects 65 to 75 years old compared to subjects 18 to 45 years old, particularly between hours 36 and 168 after initial dosing.

PK parameters:

Inserted below are summaries of the mean (SD) PK parameters for all subjects:

in the elderly population.

Parameter	Cyclobenzaprine HCl 10 mg TID n = 35	CMR 30 mg n = 35
AUC_{0-168} (ng·hr/mL)	914.4 ± 311.7	827.2 ± 281.5
$AUC_{0-\infty}$ (ng·hr/mL)	987.4 ± 352.5	898.9 ± 321.7
$C_{max\,(first)}$ (ng/mL)[a]	12.6 ± 3.7	6.4 ± 1.8
C_{max} (ng/mL)[b]	18.3 ± 4.4	19.2 ± 5.3
$T_{max\,(first)}$ (hrs)[a]	4.7 ± 1.3	7.6 ± 2.2
T_{max} (hrs)[b]	18.5 ± 5.4	7.6 ± 2.2
$t_{1/2}$ (hrs)	39.0 ± 11.9	40.5 ± 11.7

[a] Estimated using plasma levels after the first dose and before second dose for cyclobenzaprine 10 mg TID; for CMR 30 mg, the entire study period was used and the value was dose-adjusted to a 10-mg dose.
[b] Estimated using plasma levels during the entire study period for both study medications.

The AUC 0-168, AUC 0-∞, and t 1/2 were similar for cyclobenzaprine HCl 10 mg TID and CMR 30 mg treated subjects. The Cmax (first) in cyclobenzaprine HCl 10 mg TID treated subjects (12.6 ng/mL) was lower than the Cmax in CMR 30 mg treated subjects (19.2 ng/mL). Interestingly, the Cmax was similar for both treatments (18.3 ng/mL for cyclobenzaprine HCl 10 mg TID [after 3 doses] and 19.2 ng/mL for CMR 30 mg). In cyclobenzaprine HCl 10 mg TID treated subjects, Tmax (first) occurred earlier (4.7 hrs) than in CMR 30 mg treated subjects (7.6 hrs).

Mean PK (SD) parameters for subjects aged 18 to 45 years old

Parameter	Cyclobenzaprine HCl 10 mg TID n = 17	CMR 30 mg n = 18
AUC_{0-168} (ng·hr/mL)	805.4 ± 330.7	715.1 ± 264.2
$AUC_{0-\infty}$ (ng·hr/mL)	837.4 ± 340.2	751.2 ± 271.5
$C_{max\,(first)}$ (ng/mL)[a]	13.0 ± 4.6	6.4 ± 1.9
C_{max} (ng/mL)[b]	18.1 ± 5.4	19.2 ± 5.6
$T_{max\,(first)}$ (hrs)[a]	4.3 ± 1.0	6.8 ± 1.9
T_{max} (hrs)[b]	17.2 ± 5.7	6.8 ± 1.9
$t_{1/2}$ (hrs)	30.4 ± 7.1	32.4 ± 8.1

[a] Estimated using plasma levels after the first dose and before second dose for cyclobenzaprine 10 mg TID; for CMR 30 mg, the entire study period was used and the value was dose-adjusted to a 10-mg dose.
[b] Estimated using plasma levels during the entire study period for both study medications.

Mean PK (SD) parameters for subjects aged 65 to 75 years old
the safety population.

Parameter	Cyclobenzaprine HCl 10 mg TID n = 18	CMR 30 mg n = 17
AUC_{0-168} (ng·hr/mL)	1017.4 ± 261.3	945.9 ± 255.2
$AUC_{0-\infty}$ (ng·hr/mL)	1129.1 ± 309.6	1055.2 ± 301.9
$C_{max\,(first)}$ (ng/mL)[a]	12.2 ± 2.6	6.4 ± 1.7
C_{max} (ng/mL)[b]	18.5 ± 3.3	19.2 ± 5.1
$T_{max\,(first)}$ (hrs)[a]	5.0 ± 1.4	8.5 ± 2.3
T_{max} (hrs)[b]	19.7 ± 5.0	8.5 ± 2.3
$t_{1/2}$ (hrs)	47.1 ± 9.4	49.0 ± 8.3

[a] Estimated using plasma levels after the first dose and before second dose for cyclobenzaprine 10 mg TID; for CMR 30 mg, the entire study period was used and the value was dose-adjusted to a 10-mg dose.
[b] Estimated using plasma levels during the entire study period for both study medications.

There were no notable differences in Cmax or Tmax between the age subgroups in either treatment group. However, there were notable differences between the age subgroups in AUCs and t ½ in both treatment groups. In cyclobenzaprine HCl 10 mg treated subjects 65 to 75 years compared with subjects 18 to 45 years the AUC 0-168, AUC 0-∞, and t ½ were 26 %, 35 % and 55 % greater, respectively. In CMR 30 mg treated subjects 65 to 75 years compared with subjects 18 to 45 years, the AUC 0-168, AUC 0-∞, and t ½ were 32 %, 40 % and 51 % greater, respectively.

Statistical Analysis:
Table 1: Summary of Analysis of Variance on Pharmacokinetic Parameters - All Subjects

Parameter	**Cyclobenzaprine HCl 10 mg TID(n = 34) LS mean**	**CMR 30 mg (n = 34) LS Mean**	**Ratio[b] [90% CI] (n = 34)**
AUC 0-168 (ng.hr/mL)	861.1	784.0	0.910 [0.874, 0.949]
AUC 0-∞ (ng.hr/mL)	923.7	848.9	0.919 [0.880, 0.959]
Cmax (first) (ng/mL)[c]	12.1	6.2	0.512 [0.480, 0.546]
Cmax (ng/mL)[d]	17.8	18.6	1.042 [0.984, 1.104]

See Footnote explanation below (bottom of Table 3)

Reviewer's Comments: The 90% CI for the geometric mean ratio for AUC0-168, AUC0-∞, and Cmax fell within the 80% to 125 % BE limit indicating that the CMR 30 mg is BE to the Cyclobenzaprine HCl 10 mg TID tablets.

Table 2: Summary of Analysis of Variance on Pharmacokinetic Parameters – Age Group 18 to 45 Years

Parameter	**Cyclobenzaprine HCl 10 mg TID (n = 17) LS mean**	**CMR 30 mg (n = 17) LS Mean**	**Ratio[b] [90% CI] (n = 17)**
AUC 0-168 (ng.hr/mL)	737.7	674.3	0.914 [0.852, 0.981]
AUC 0-∞ (ng.hr/mL)	769.6	712.0	0.925 [0.862, 0.993]
Cmax (first) (ng/mL)[c]	12.1	6.2	0.512 [0.463, 0.566]
Cmax (ng/mL)[d]	17.3	18.7	1.076 [0.989, 1.171]

See Footnote explanation below (bottom of Table 3)

Table 3: Summary of Analysis of Variance on Pharmacokinetic Parameters – Age Group 65 to 75 Years

Parameter/Statistic	**Cyclobenzaprine HCl**	**CMR 30 mg (n = 17)**	**Ratio[b] [90% CI] (n = 17)**

	10 mg TID (n = 17) LS Mean	LS Mean	
AUC 0-168 (ng.hr/mL)	1000.8	908.7	0.908 [0.861, 0.957]
AUC 0-∞ (ng.hr/mL)	1104.2	1009.7	0.914 [0.863, 0.969]
Cmax (first) (ng/mL)[c]	11.9	6.1	0.514 [0.468, 0.565]
Cmax (ng/mL)[d]	18.3	18.4	1.005 [0.925,1.092]

LS mean = least-squares mean; GI = confidence interval.
[a]LS mean and 90% GI calculated from ANOVA on log-transformed parameter with subject (nested in sequence), period, sequence, and treatment as fixed effects. All LS means and CIs are displayed on the arithmetic scale.
[b]Ratio is the LS ratio of geometric means of CMR 30 mg to cyclobenzaprine HCI 10 mg TID.
[c]Estimated using plasma levels after the first dose and before the second dose of cyclobenzaprine HCI 10mgTID. For CMR 30mg,the entire study period was used and the value was dose-adjusted to a 10-mg dose.
[d]Estimated using plasma levels during the entire study period for both study medications.

Reviewer's Comments: *In both age subgroups, the 90% CIs for the geometric mean ratios for AUC 0-168, AUC 0-∞ and Cmax fell within the 80% to 125% limits indicating that CMR 30mg and Cyclobenzaprine 10 mg TID are bioequivalent within the subgroups.*

Applicant's Study Conclusions:
As expected, the TID dosing of cyclobenzaprine HCI 10 mg produced 3 peaks in plasma cyclobenzaprine concentrations with distinct troughs between the peaks. In contrast, subjects who received CMR 30 mg did not exhibit multiple peaks and troughs in plasma cyclobenzaprine levels over the 24-hour treatment period. In CMR 30 mg treated subjects, a small inflection in the plasma cyclobenzaprine concentration curve around Hour 22 is presumed to be due to enterohepatic recycling.

Cyclobenzaprine HCI 10 mg TID and CMR 30 mg were bioequivalent; the 90% CIs for the LS mean ratios for AUCO-168, AUCO-., and Cmax fell within the 80% to 125% limits. The bioequivalence of Cmax was fortuitous and was most likely due to the long half-life of cyclobenzaprine resulting in only a small fraction of the drug being systemically eliminated (with both formulations) at the time the Cmax occurred. As expected, the Tmax (first) occurred earlier in cyclobenzaprine HCI 10 mg TID treated subjects compared to CMR 30 mg treated subjects. This difference reflects the slower controlled-release of cyclobenzaprine from the CMR 30 mg formulation. The tl/2 was similar in both cyclobenzaprine HCI 10 mg TID treated subjects and CMR 30 mg treated subjects.

There were notable differences between the age subgroups in AUCs and tl/2 for both formulations of cyclobenzaprine. The AUCs were 26% to 40% larger and t l/2 were 51 % to 55% longer in subjects 65 to 75 years compared to subjects 18 to 45 years. The larger AUCs are attributable to the increased t l/2 in elderly subjects and not a change in absorption, since the Cmax and Tmax were similar in both age subgroups. Winchell et al[2] reported that after 7 days of dosing with cyclobenzaprine HCl, elderly subjects (54 to 79 years) who received 5 mg TID had significantly higher plasma cyclobenzaprine concentrations compared to young adult subjects (22 to 40 years) who received 5 mg TID. In addition, the elderly subjects who received 7 days of dosing with 5 mg TID had similar cyclobenzaprine plasma concentrations as young adult subjects who received 10 mg TID. They attributed the differences in steady-state plasma concentration between elderly and young adult subjects to reduced clearance of cyclobenzaprine. The results of the current study further support the existence of differences in the PK of cyclobenzaprine in elderly and young adult subjects.

Safety: 6 subjects who received cyclobenzaprine HCl 10 mg TID reported 9 AEs and 8 subjects who received CMR 30 mg reported 13 AEs. Most AE's were mild in intensity and considered related to study medication. The most common treatment-emergent AE in both age subgroups was somnolence (This is currently being reviewed by the clinical reviewer).

Study Number: 1102

Title of Study:
A Randomized Double-Blind Two-period Crossover Study to Assess the Safety and Bioavailability of Cyclobenzaprine HCI Modified-Release (CMR) 15 mg and 30 mg in Healthy Volunteers.

Principal Investigator (s): Maria J. Gutierrez, MD

Study Center (s): Comprehensive NeuroScience, Inc., Ft. Lauderdale, FL

Objectives; The primary objectives of this randomized, double-blind, two-period crossover study were to assess the safety and bioavailabilty of CMR 15 mg and 30 mg in healthy adult subjects.

Study Population Demographics: 16 healthy male and female subjects as shown in the table below:

Parameter/Statistic	**(N = 16)**
Age (years)Mean ± SD Range	30.2 ± 6.75 18 – 37
Gender: Male / Female	7 / 9
Ethnic Origin Black Caucasian	 3 13
Height (cm)Mean ± SD Range	169.1 ± 8.54 152 – 183
Weight (kg) Mean ± SD Range	70.7 ± 12.18 48 – 91

15 subjects (8 in period 1 and 7 in period 2) received CMR 15 mg and 14 subjects (8 subjects during period 1 and 6 subjects during period 2) received CMR 30 mg

Study Design: This was a randomized, double-blind, two-period, crossover, single center study that compared the safety and bioavailability of CMR 15 mg and 30 mg. Sixteen healthy male and non-pregnant female subjects were randomly assigned to one of 2 possible treatment sequences. Eight subjects were randomly assigned to each sequence (CMR 30 mg followed by CMR 15 mg or CMR 15 mg followed by CMR 30 mg). There was a 14-day washout period between doses. *Check if one subject dropped out?*

Study Period: 29 April 2002 - 31 May 2002

Investigational Product (s): Cyclobenzaprine HCI Modified-Release (CMR) Dose: 15 mg, Batch No: PF307EA002 Dose: 30 mg Batch No, PF306EA001

Drug Administration: In the morning (between 8:30 AM and 9:05 AM), following a 4-hr fasting period, each subject received one capsule of CMR 15 mg and one capsule of CMR 30mg with 180 mL of room temperature water, according to the randomization schedule

PK Sampling Scheme: Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 36, 48, 72, 96, 120, 144, 168 hours post dose

Analytical Methods:LC/MS/MS. LOQ = 0.5 ng/mL

Compound	Cyclobenzaprine
Internal Standard	[redacted]
Matrix	Plasma
Accuracy (%) ***Between-Day***	[redacted]
Precision (CV %) ***Between-Day***	[redacted]
Standard curve range	0.5 to 50 ng/mL R> = 0.998 (N = 37)
Sensitivity (LOQ)	0.5 ng/ml (CV% = 1.2)
Conclusions	Method validation acceptable

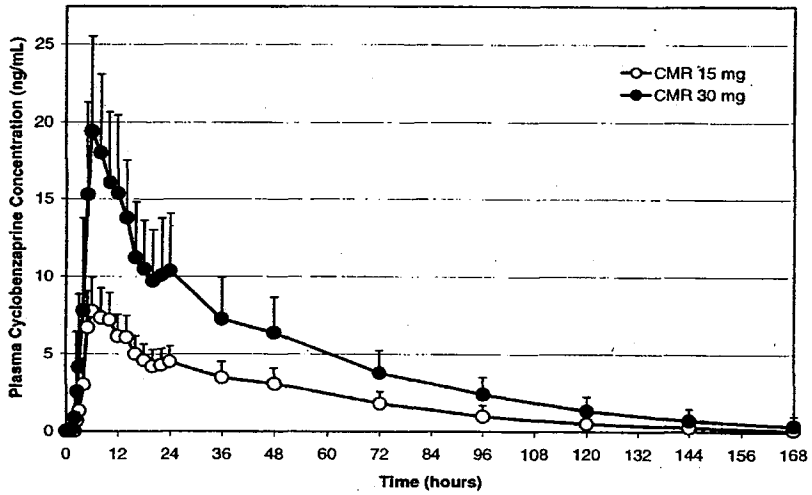
PK data Analysis: Peak plasma cyclobenzaprine concentration (Cmax), time to peak plasma cyclobenzaprine concentration (Tmax), area under the plasma cyclobenzaprine concentration versus time curve to the last measurable time point (AUC 0-168), total area under the plasma cyclobenzaprine concentration versus time curve extrapolated to infinity (AUC 0-inf), and terminal elimination half-life ($t_{1/2}$) of cyclobenzaprine were observed or calculated from the plasma data.

Statistical Analysis: A comparative analysis was performed on log-transformed values of Cmax and both AUC parameters. The ANOVA model had fixed effects for treatment, period, sequence, and subject (treatment sequence). The following statistics were produced: least-squares (LS) means for each treatment, between-treatment differences in LS means, the corresponding 95% confidence intervals (CIs), and the P-value for the treatment effect. The LS means, LS mean differences, and 95% CIs were transformed back to the arithmetic scale. Graphical presentations of dose –adjusted AUC inf and Cmax are provided as evidence of dose proportionality.

Results:

Plasma Concentration vs. Time profile:

Figure 2: Mean (± SD) Plasma Cyclobenzaprine Concentration Over Time – Safety Population



Slight increases in the mean plasma cyclobenzaprine concentrations at about 24 hours post dosing was presumed to be due to enterohepatic recycling. Cyclobenzaprine in plasma was first detectable in the CMR 15 mg treated subjects at Hour 2.5 and in the CMR 30 mg treated subjects at Hour 1.5. (***Hard to see in the graph due to the compressed X axis).***

As expected, the CMR 30 mg dose produced significantly higher plasma cyclobenzaprine concentrations than the 15 mg dose as reflected by AUC 0-168, AUC 0-inf -, and Cmax. The magnitude of the increase in AUC 0-168, AUC 0-inf, and Cmax were somewhat greater than 2-fold.

SUMMARY OF PHARMACOKINETIC PARAMETERS IN HEALTHY ADULT SUBJECTS

Parameter/Statistic	15 mg (N = 15) Mean ± SD	30 mg (N = 14) Mean ± SD
$AUC_{0\text{-}168}$ (ng·hr/mL)	318.3 ± 114.7	736.6 ± 259.4
$AUC_{0\text{-}\infty}$ (ng·hr/mL)	354.1 ± 119.8	779.9 ± 277.6
C_{max} (ng/mL)	8.3 ± 2.2	19.9 ± 5.9
T_{max} (hrs)	8.1 ± 2.9	7.1 ± 1.6
$t_{1/2}$ (hrs)	33.4 ± 10.3	32.0 ± 10.1

Table: Summary of Analysis of Variance on Pharmacokinetic Parameters –

Parameter/Statistic[a]	CMR 15 mg (n = 17) LS mean	CMR 30 mg (n = 13) LS Mean	Ratio[b] [95% CI] (n = 17)
AUC 0-168 (ng.hr/mL)	294.6	714.3	2.4 [2.1, 2.8] $p < 0.001$[c]
AUC 0-∞ (ng.hr/mL)	330.3	755.1	2.3 [2.0, 2.6] $p < 0.001$
Cmax (ng/mL)	8.1	19.7	2.4 [2.1, 2.8] $p < 0.001$

LS mean = least-squares mean; CI = confidence interval
[a]LS mean and 95% CI calculated from ANOVA on log-transformed parameter with subject (nested in sequence), period, sequence, and treatment as fixed effects. All LS means and CIs are displayed on the arithmetic scale.
[b]Ratio is the ratio of LS geometric means of CMR 30 mg to CMR 15 mg.
[c]P-value from same ANOVA model for effect of treatment.

A ratio of 2 for Cmax and AUC dose adjusted mean ratios would indicate dose proportionality between the 15 and 30 mg formulations. The 95 % CI s of the ratios do not include the value of 2 indicating that a statistical difference exists between the 15 and 30 mg CMR formulations with respect to AUC and Cmax. The ratios of the LS means when adjusted for dose suggested approximately 15-20 % difference between the 15 and 30 mg formulations for both AUC and Cmax.
Although the 30 mg CMR had slightly higher values than the 15 mg formulation, graphical representation of the individual dose normalized Cmax and AUC 0-inf values (see below) showed that, for most subjects (except 2 subjects), there was no difference between formulations. The plots indicate that the difference in mean ratios is probably driven by the results from 2 subjects for each parameter which may be due to intra-subject variability.

Figure 3: Comparisons of Individual Subject Dose Normalized C_{max} Values – Pharmacokinetic Population

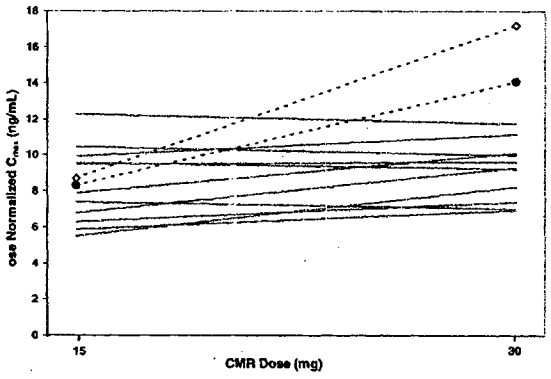
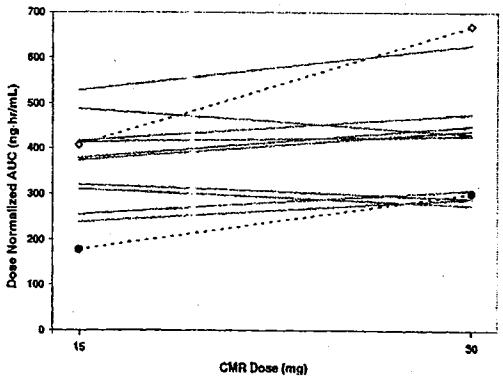


Figure 4: Comparisons of Individual Subject Dose Normalized $AUC_{0-\infty}$ Values – Pharmacokinetic Population



In Figure 3, subjects # 01-0010 (◊) and #01-0016 (•) have larger differences in mean normalized Cmax values compared to other subjects. In Figure 4, subjects # 01-0010 (◊) and # 01-0003 (•) have larger differences in mean normalized AUC 0-inf values compared to other subjects.
Study Conclusions: The treatments were statistically significantly different from each other as values (dose unadjusted) for AUC's and Cmax, were higher for the 30 mg formulation compared to the CMR 15 mg formulation. The dose unadjusted exposure of the CMR 30 mg formulation was slightly higher than 2-fold relative to the CMR 15 mg formulation. The LS mean ratio of CMR 30 mg/CMR 15 mg was 2.4 for AUC 0-168, 2.3 for AUC 0-inf, and 2.4 for Cmax. For most subjects, there was no difference between formulations for the AUC and Cmax, values when normalized for dose. The similarity between the formulations for dose normalized AUC0-inf and Cmax (with the exception of 2 subjects) in conjunction with the fact that the only difference between the dose formulations was in the _____ suggested that the dosage formulations were dose proportional. The time to observed maximal plasma cyclobenzaprine concentration and observed peak plasma cyclobenzaprine concentration reflected similar release performance between the 15 and 30 mg formulations. The elimination half-lives were similar for the CMR 15 mg and 30 mg formulations and was somewhat similar to values reported in the literature for immediate release cyclobenzaprine formulations [PDR (Cyclobenzaprine 10mg IR, mean effective half life = 18 hours (range = 8 - 37 hours, n=18)]

Safety: There were no deaths, SAEs or discontinuations due to AEs reported during this study. A total of 7 treatment-emergent AEs, all mild in intensity, were reported in 7 subjects (5 subjects who received CMR 15 mg and 2 subjects who received CMR 30 mg). Only 2 of the AEs (glossodynia in a subject receiving CMR 15 mg and somnolence in a subject receiving CMR 30 mg) were considered related to study medication by the Investigator. (The medical reviewer is currently reviewing this data).

Study Number: 1103

Title of Study: A Randomized, Open-label, Two-period Crossover Study to Assess the Effect of Food on the Bioavailability of Cyclobenzaprine HCI Modified-release (CMR) 30 mg in Healthy Volunteers

Principal Investigator (s): Maria J. Gutierrez, MD

Study Center (s): Comprehensive NeuroScience, Inc., Ft. Lauderdale, FL

Objectives: To assess the effect of food on the bioavailability of CMR 30 mg in healthy adult subjects.

Study Population Demographics: 16 subjects were enrolled, 15 completed PK portion. A summary of the demographics of the subjects is shown in the table below:

Parameter/Statistic	**(N = 16)**
Age (years)Mean ± SD Range	29.7 ± 7.36 19 - 39
Gender: Male / Female	8 / 8
Ethnic Origin Black Caucasian	 3 13
Height (cm)Mean ± SD Range	168.8 ± 9.84 155 - 191
Weight (kg) Mean ± SD Range	70.3 ± 12.56 51 - 99

One subject in the fasted/fed treatment sequence did not complete the study, therefore 16 subjects received CMR 30 mg in the fasted state and 15 subjects received CMR 30 mg in the fed state.

Study Period: 29 April 2002 - 31 May 2002

Study Design: This was a randomized, single-center, open-label, two-period crossover study designed to assess the effect of food on the bioavailability of single oral doses of CMR 30 mg. 16 healthy male and female subjects were randomly assigned to one of 2 possible treatment sequences. Eight subjects were randomly assigned to each sequence (CMR 30 mg in the fasted state followed by CMR 30 mg in the fed state or CMR 30 mg in the fed state followed by CMR 30 mg in the fasted state). There was a 14-day washout period between doses.

Investigational Product (s): Cyclobenzaprine HCI Modified-release (CMR) Dose: 30 mg, Batch No.- PF306EAOOI

Dosing Regimen, Mode of Administration and Treatment Duration: Subjects received one 30 mg CMR capsule with 180 mL of room temperature water in the morning, under fasting conditions (overnight fast of at least 11 hrs) or together with a standard high-fat meal: Composition of standard high fat meal is as follows:
One buttered English muffin toasted, one fried egg (in margarine), one slice American cheese, one slice Canadian bacon, 1 cup of hash browns, 8oz (240 mL) whole milk, 8 oz (240 mL) apple juice, (total number of calories = 1011).

Reviewer's Comment: The sponsor used the modified FDA High fat diet originally developed by the Office of Generic Drugs (protein 18 %, fat 37 % and carbohydrate 45 %) and currently utilized by the Division of Bioequivalence. This is acceptable to OCPB too in that it meets the Food effect guidance recommendation of high fat ~ 50 % of total calories and high-calorie ~ 800 to 1000 calories.

PK Sampling Scheme: Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 36, 48, 72, 96, 120, 144, 168 hours post dose

Analytical Methods:LC/MS/MS. LOQ = 0.5 ng/mL

Compound	Cyclobenzaprine
Internal Standard	[redacted]
Matrix	Plasma
Accuracy (%) ***Between-Day***	[redacted]
Precision (CV %) ***Between-Day***	[redacted]
Standard curve range	0.5 to 50 ng/mL R> = 0.998 (N = 37)
Sensitivity (LOQ)	0.5 ng/ml (CV% = 1.2)
Selectivity	No interfering peaks @ retention time of tramadol
Conclusions	In study method validation acceptable

PK data Analysis: Peak plasma cyclobenzaprine concentration (Cmax), time to peak plasma cyclobenzaprine concentration (Tmax), area under the plasma cyclobenzaprine concentration versus time curve to the last measurable time point (AUC $_{0\text{-}168}$), total area under the plasma cyclobenzaprine concentration versus time curve extrapolated to infinity (AUC $_{0\text{-}inf}$), absorption lag time (Tlag) and terminal elimination half-life ($t_{1/2}$) of cyclobenzaprine were observed or calculated from the plasma data.

Statistical Analysis: A comparative analysis was performed on log-transformed values of Cmax and both AUC parameters. The ANOVA model had fixed effects for treatment, period, sequence, and subject (treatment sequence). The following statistics were produced: least-squares (LS) means for each treatment, and the corresponding 90% confidence intervals (CIs), were calculated by the ANOVA for the fed and fasting dosing. The LS means, ratios, and 90% CIs were transformed back from the log scale to the arithmetic scale. If the 90 % CI fell within 80-125 % for AUC and Cmax, then the presence of a food effect was excluded and vice versa.

Results:

SUMMARY OF PHARMACOKINETIC PARAMETERS IN HEALTHY ADULT SUBJECTS

Parameter/Statistic	30 mg Fed (N = 15) Mean ± SD [Range]	30 mg Fasted (N = 16) Mean ± SD [Range]
$AUC_{0\text{-}168}$ (ng·hr/mL)	673.6 ± 230.1	538.5 ± 174.2
	[309.4 – 980.5]	[294.6 – 907.9]
$AUC_{0\text{-}\infty}$ (ng·hr/mL)	710.3 ± 240.2	585.7 ± 183.5
	[331.4 – 1005.3]	[318.9 – 975.1]
C_{max} (ng/mL)	25.4 ± 9.9	18.2 ± 5.3
	[12.0-47.4]	[10.9-30.8]
T_{lag} (hrs)	2.1 ± 0.7	1.8 ± 0.6
	[1 – 3]	[1 – 3]
T_{max} (hrs)	7.4 ± 2.1	6.6 ± 1.5
	[5 – 12]	[5 – 10]
$t_{1/2}$ (hrs)	33.4 ± 8.6	32.42 ± 7.2
	[18.6 – 50.8]	[19.9 – 48.2]

Table: Summary of Analysis of Variance on Pharmacokinetic Parameters –

Parameter/Statistic[a]	CMR 30 mg Fed (n = 15) LS mean	CMR 30 mg Fasted (n = 15) LS Mean	Ratio[b] [90% CI] (n = 15)
AUC 0-168 (ng.hr/mL)	633.9	522.6	1.5 [1.11, **1.32**]
AUC 0-∞ (ng.hr/mL)	669.5	556.1	1.20 [1.11, **1.31**]
Cmax (ng/mL)	23.7	17.5	1.36 [1.17, **1.57**]

CI = confidence interval

[a]LS mean and 90% CI calculated from ANOVA on log-transformed parameter with subject, period, sequence, and treatment as fixed effects. All parameters are displayed on the arithmetic scale.

[b]Ratio is the LS ratio of geometric means of CMR 30 mg-Fed to CMR 30 mg-Fasted.

Study Conclusions:

There was a statistically significant increase in bioavailability when CMR 30 mg was given with food relative to the fasted state. There was a 35% increase in mean peak plasma cyclobenzaprine concentrations (Cmax) and a 20% increase in mean extent of absorption (AUC) in the presence of food. No effect was noted in absorption lag time (Tlag), which was approximately 2 hours, in both the Fed and Fasted subjects. In addition, the mean time to maximum plasma cyclobenzaprine levels (Tmax.) was about 7 hr for both treatments. The similarity of the shape of the mean plasma cyclobenzaprine concentration versus time profile and the absence of a pronounced difference between the times to peak concentration suggest there was no dose dumping of the formulation in the presence of food.

How does this increase in exposure with food impact safety? It appears that there were no notable differences in frequency of AEs between treatments suggesting that this increase in BA in the fed state may not have impacted the safety of the formulation. Pivotal clinical studies were conducted without regard to the timing of meals.

Safety: A total of 25 treatment-emergent AEs, all mild in intensity, were reported in 10 subjects (12 AEs in Fed subjects and 13 AEs in Fasted subjects). Eleven AEs (5 AEs in Fed subjects and 6 AEs in Fasted subjects) were considered related to study medication by the Investigator. Adverse events that were considered related to study medication were: insomnia, headache, limb pain, stomatitis, dizziness, and aggravated fatigue.

Study Number: 1101

Title of Study: A Pilot Study to compare the safety and Preliminary Pharmacokinetics of Cyclobenzaprine HCl Modified-Release (MR) 30 mg Once Daily and Cyclobenzaprine HCl 10 mg Three Times Daily in Healthy Male Subjects

Principal Investigator (s): Lawrence A. Galitz, MD

Study Center (s): SFBC International, Inc., Miami, FL

Objectives: To compare the safety and preliminary pharmacokinetics of cyclobenzaprine modified-release (CMR) 30 mg and cyclobenzaprine HCL 10 mg three times daily (TID) in healthy male subjects

Methodology: Randomized, two-period, crossover, single center study. There was a 14 day washout period between doses.

Study Period/Clinical Phase: 11 May 2001 to 08 June 2001/Phase 1

Study Population Demographics: 12 healthy male subjects Aged between 18-37 years old, Height (range 168-185 cm) Weight (range 59.1 to 111.4 kg) Ethnic Origin (Black 2, Caucasian 7 and Hispanic 3).

Investigational Product (s): Test product was CMR 30 mg (batch No PF267EZ001) capsules once daily and Reference product was Flexeril ® 10 mg Tablets [Cyclobenzaprine 10 mg tablets] (batch No. K5224) TID

Treatment Duration: Single Dose of 30 mg CMR and 3 doses of 10 mg TID cyclobenzaprine HCl

PK Sampling Scheme/Analytical Method/Data Analysis: Plasma samples were collected over a 168-hr period post-dose (same as study # 1107). Concentrations of cyclobenzaprine in plasma were determined by a validated LC/MS/MS method (LOQ = 0.5 ng/mL). Pharmacokinetic parameters were estimated with WinNonlin. (90 % CI for Cmax and AUC were calculated.

Results: The bioavailability of the CMR 30 mg was lower than cyclobenzaprine 10 mg TID. The adjusted mean ratio was 0.9 and the 90% CI was 79 % -100 % for AUC 0-T and 79 % -101 % for AUC0-inf. The Cmax was also lower for the 30 mg CMR compared to cyclobenzaprine 10 mg TID. The adjusted mean ratio for Cmax was 0.9

and the 90 % CI was 79 % -94 %. Tmax was faster for the CMR 30 mg (10.5 (3.32)) hrs compared with cyclobenzaprine 10 mg TID (17.7 (7.62)) hrs over the 24 hr dosing period.

Reviewer's Comments: The CMR capsules used in this study were different from the TBMF and this study was not reviewed in detail. It was only partially reviewed because the sponsor used some of the data to support their altered active control arguments. Following process optimization and analytical methods validation, both the 15 mg and 30 mg CMR capsules were manufactured and released for clinical study 1101. It was noted by the applicant, however, that these CMR capsules stored in sealed HDPE bottles at accelerated stability conditions exhibited significantly faster dissolution profiles. This resulted in the decision to stop clinical testing with this product. The ——— were then reformulated. The applicant stated that their drug release profiles for the CMR capsules manufactured with the reformulated ——— were similar to the profiles for the CMR capsules used in study 1101

Dissolution Data

TABLE 6.20: INDIVIDUAL DISSOLUTION DATA FOR PIVOTAL CLINICAL BATCH OF CMR CAPSULES, LOT NO. PF307EA002, 15 MG.

	No. of units	Time in Hours						
Testing Dates	N	1	2	4	6	8	12	16
4-29-02	1							
	2							
	3							
	4							
	5							
	6							
	7							
	8							
	9							
	10							
	11							
	12							
	Avg							
	SD							
	Max							
	Min							

TABLE 6.19: INDIVIDUAL DISSOLUTION DATA FOR PIVOTAL CLINICAL BATCH OF CMR CAPSULES, LOT NO. PF306EA001, 30 MG

	No. of units	Time in Hours						
Testing Dates	N	1	2	4	6	8	12	16
4-3-02	1							
	2							
	3							
	4							
	5							
	6							
	7							
	8							
	9							
	10							
	11							
	12							
	Avg							
	SD							
	Max							
	Min							

Review of the Response to Request for information submitted on December 29th, 2004

Sponsor's Response:

1. Standard USP dissolution methodology and acceptance parameters for Flexeril (cyclobenzaprine hydrochloride), 10 mg were used to demonstrate comparable systemic exposure of the altered and approved Flexeril 10 mg tablets.

Cyclobenzaprine hydrochloride is a freely water soluble compound and it is practically insoluble in hydrocarbons. The latter suggests that membrane permeability would be the rate limiting step in the absorption of cyclobenzaprine. Thus similar dissolution results between the two immediate release dosage forms ([illegible] dissolution in [illegible] hours, 0.1N HCl) should be predictive of comparable systemic exposure levels. To support this statement the applicant provided the following data:

Dissolution Conditions:

Apparatus: *USP 1 (basket)*
Medium: *900 mL of 0.1N HCl*
Temperature: *37 °C ± 0.5 °C*
Speed: 50 rpm
Units Tested: 12
Specifications: Q = [illegible] in [illegible] hr

The data indicate similar dissolution between the altered flexeril tablets and the approved

Cyclobenzaprine HCl Tablets (Flexeril): Lot # [illegible] 0121729 (Eurand Sample # F12507959) (n=12): 0.1N HCl Media

[redacted]	No. of units	Time in Hours
Testing Dates	N	[illegible]
3/27/02 50 rpm	1	[illegible]
	2	[illegible]
	3	[illegible]
	4	[illegible]
	5	[illegible]
	6	[illegible]
	7	[illegible]
	8	[illegible]
	9	[illegible]
	10	[illegible]
	11	[illegible]
	12	[illegible]
	Avg	9[illegible]
	SD	1.9
	RSD	2.0
	Max	[illegible]
	Min	[illegible]

flexeril tablet at the [illegible] hr sampling point. Usually a dissolution profile is preferable but since cyclobenzaprine is rapidly dissolving (> [illegible] dissolved in [illegible] minutes), the single time point is probably acceptable.

2. Stability summary sheet for altered Flexeril tablet suggests that appropriate potency mean (% label claim ranged from [illegible]) was maintained after the process of encapsulating the tablet. However, the dissolution data was very variable as shown in the table below.

3. A cross comparison pharmacokinetic analysis of subjects receiving approved Flexeril tablets, 10 mg from study 1101 and a similar group of healthy subjects receiving encapsulated Flexeril 10 mg in study 1107 was also conducted to further support the similar behavior of the two IR dosage forms. The data are discussed below:

Study 1101 was a randomized, 2-period, crossover study in which 12 healthy male subjects (aged 18-40 years old) were assigned to randomly ordered treatment sequences. The treatments were (1) CMR·30 mg capsule given as a single dose and (2) one immediate release tablet of cyclobenzaprine HCl 10 mg (Flexeril) given every 8 hours for three doses. Study 1107 was a randomized, open-label, 2-period, crossover study in which healthy adult subjects (aged 18-45 years old) and elderly subjects (aged 65-75 years old). The treatments were (1) CMR 30 mg capsule given as a single dose and (2) one immediate release tablet of cyclobenzaprine HCl 10 mg (Flexeril) ground into a capsule given every 8 hours for three doses. In both studies the IR tablet (Study 1101) or IR capsule (Study 1107) was administered three times daily for one day (at 0, 8, and 16 hours).
Methods of assessment:
Two primary methods were used (1) PK parameters obtained following 3 doses (Sampling over 0-168 hrs) (2) PK parameters obtained following one dose (0-8 hrs).

PK Assessment following three doses over 24 hours (Sampling from 0-168 hrs)

Comparison of Flexeril 10 mg PK Parameters by Study in Subjects Aged ≤ 40 years old

PK Parameter	Study 1101 (tablet) Male subjects only	Study 1107 (capsule) Male Subjects only	Study 1107 (capsule) Males and Females
	Mean ± SD [range] (N = 12)	Mean ± SD [range] (N = 8)	Mean ± SD [range] (N = 11)
AUC_{0-168} (ng·hr/mL)	504 ± 206 [214-752]	697 ± 304 [270-1192]	693 ± 265.2 [270-1192]
$AUC_{0-\infty}$ (ng·hr/mL)	534 ± 215.3 [228-817]	720 ± 305 [291-1213]	718 ± 267.5 [291-1213]
C_{max} (ng/mL)	12.4 ± 3.6 [6.3-17.8]	16.7 ± 4.8 [7.6-24.7]	16.4 ± 4.2 [7.6-24.7]
T_{max} (hrs)	17.7 ± 7.6 [4.0-24.0]	17.3 ± 5.8 [12.0-24.0]	16.7 ± 5.5 [12.0-24.0]

Reviewer's Comments: The Cmax, AUC_{0-168} and $AUC_{0-\infty}$ were increased 34.6 %, 38.3 % and 34.8 % for the ground tablet in the capsule (Study 1107) relative to the intact tablet (Study 1101). Tmax was similar for both formulations. The inclusion of the female data in Study 1107 did not change the conclusions obtained from evaluating males only. However, due to the previously observed differences in the half-life of cyclobenzaprine HCl between young and elderly subjects, this data provided may not provide a true picture of the exposure differences in a more heterogeneous population (i.e. young and elderly subjects).

PK Assessment following one dose (0-8 hrs)

Comparison of Flexeril 10 mg PK Parameters by Study in Male Subjects ≤ 40 years old

PK Parameter	Study 1101 (tablet) Males only	Study 1107 (capsule) Males only	Study 1107 (capsule) Males and females
	Mean ± SD [range] (N = 12)	Mean ± SD [range] (N = 8)	Mean ± SD [range] (N = 11)
AUC_{0-8} (ng·hr/mL)	48 ± 15 [16-66]	59 ± 25.9 [24-113]	63 ± 23 [24-113]
C_{max} (ng/mL)	9.2 ± 3.1 [3.4-13.1]	11.3 ± 4.8 [5.0-21.0]	11.8 ± 4.2 [5.0-21.0]
T_{max} (hrs)	4.6 ± 0.8 [3.0-6.0]	4.1 ± 1.1 [2.5-6.0]	4.0 ± 1.0 [2.5-6.0]

Reviewer's Comments: The Cmax, AUC_{0-168} and $AUC_{0-\infty}$ were increased about 23% for the ground tablet in the capsule (Study 1107) relative to the intact tablet (Study 1101). Tmax was still similar for both formulations. Although the 0-8 hr comparison suggested a decrease in the differences in Cmax and exposure relative to those observed when assessments were performed over 168 hour sampling period, this should be interpreted with caution. The inclusion of the female data in Study 1107 for the 0-8 hr comparison did not change the conclusions obtained from evaluating males only. One cannot really draw definite conclusions from this data in a homogenous population of subjects aged less than 40 years old. Comparison in elderly patients too is needed.

4.4. OCPB Filing form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA Number	21-777	**Brand Name**	Amrix ®
OCPB Division (I, II, III)	DPEIII	**Generic Name**	Cyclobenzaprine HCL
Medical Division	HFD-550	**Drug Class**	Muscle Relaxant
OCPB Reviewer	Abi Adebowale	**Indication(s)**	As an adjunct to rest and physical therapy for the relief of muscle spasm associated with acute, painful muscoskeletal conditions
OCPB Team Leader	Dennis Bashaw	**Dosage Form**	Modified release capsules 15 and 30 mg
		Dosing Regimen	One 15mg capsule taken once daily, up to 30 mg daily given as 2 x 15mg or 1x 30mg capsule.
Date Received	April 30th, 2004	**Route of Administration**	Oral
Estimated Due Date of OCPB Review	28th December, 2005	**Sponsor**	ECR Pharmaceuticals
PDUFA Due Date	**28th February, 2005**	**Priority Classification**	3S
Division Due Date	**28th January, 2005**	**IND Number**	62, 261

Clin. Pharm. and Biopharm. Information

Background and Introduction: This submission by ECR Pharmaceuticals is an original 505 (b) (2) NDA for AMRIX capsules. Cyclobenzaprine HCL (NDA 17-821) tablet was approved prior to January 1st, 1982 for the same indications being proposed for the modified release dosage form (i.e. relief of muscle spasms associated with acute, painful, muscoskeletal conditions). The MR capsules are manufactured in 15 and 30 mg strengths comprised of the same spherical, [redacted] intended for once daily application as opposed to the current TID administration for the immediate release tablets. Five pharmacokinetic studies and two clinical efficacy and safety studies were included in this application.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			

Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			1101, 1104 and 1107
multiple dose:	X			
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			1102
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X			1107
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference (IR):	X			1104 and 1107
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X			1103
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		5		

a.) Filability and QBR comments		
Types and #'s of studies and supplementary information (literature review) are adequate to conduct a review	"X" if yes X	**Comments**
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	No	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	**Abi Adebowale 02/15/04**	
Secondary reviewer Signature and Date	**Dennis Bashaw**	

CC: NDA 21-177 HFD-850 (P.Lee), HFD-550 (Balcer, P), HFD-880 (D. Bashaw, A. Selen)

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/s/

Abi Adebowale
2/15/05 05:41:26 PM
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Dennis Bashaw
2/22/05 10:18:25 AM
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