CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-777

MEDICAL REVIEW

FDA Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
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DEPUTY DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE: February 24, 2005

DRUG: Amrix (Cyclobenzaprine HCl 15 and 30 mg modified-release capsules)

NDA: 21-777

SPONSOR: ECR Pharmaceuticals, Inc..

INDICATION: Moderate to moderately severe pain

LETTER DATE: April 29, 2004

ECR Pharmaceuticals has submitted a 505(b)(2) application for a modified-release formulation of cyclobenzaprine HCl (CMR), with the proposed proprietary name of Amrix. Cyclobenzaprine relieves skeletal muscle spasm of local origin and not centrally mediated spasticity, although it is believed the site of action may be the central nervous system. The reference listed drug is Flexeril, an immediate-release formulation, originally approved August 26, 1977, for dosing as 5 mg three times a day, up to 10 mg three times a day. The proposed dosing for CMR is 15 mg or 30 mg once daily. The sponsor proposes the same indication as is currently described n the Flexeril package insert:

- 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, and restriction in activities of daily living.
- Cyclobenzaprine 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.
- Cyclobenzaprine has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease, or in children with cerebral palsy.

The sponsor has conducted five phase 1 studies and two double-blind, placebo-controlled, trials in support of efficacy and safety. A genotoxicity study was the only nonclinical study

submitted in support of this application. The sponsor is referencing clinical pharmacology and nonclinical findings in the Flexeril package insert.

The chemistry, manufacturing, and controls review was performed by Dr. Sue-Ching Lin. DMF ——was reviewed and found adequate to support this NDA. The drug substance was found by Dr. Lin to meet the current USP monograph for cyclobenzaprine HCl and additional testing for impurities in accordance with ICH Q3A recommendations. The modified-release mechanism is ——————————. No deficiencies were found upon review of the manufacture process, control of excipients, and specifications for the drug product. The packaging materials were found to be adequate.

The sponsor conducted three studies to assess genotoxicity which were reviewed by Dr. Hamid Amouzadeh. No evidence of genotoxicity was found by the *in vivo* mouse micronucleus assay, chromosomal aberration in Chinese hamster ovary cell assay, or Salmonella-Escherichia coli mammalian microsome reverse mutation assay.

The clinical pharmacology and biopharmaceutics review was performed by Dr. Abimbola Adebowale. One of five studies was not reviewed in detail as a different formulation was studied. In the remaining studies, the sponsor used Flexeril as the comparator. As noted by Dr. Adebowale, the sponsor used Flexeril tablets that were ground and encapsulated for blinding purposes, although it was unclear why these were used in the pharmacokinetic studies. Had this been described in the study protocols, the resulting problems might have been anticipated. In response to a request by the reviewer for data describing whether the grinding and re-encapsulation altered the pharmacokinetic behavior of Flexeril, the sponsor submitted *in vitro* dissolution data that suggests similar dissolution profiles between CMR and this ground Flexeril preparation, but an *in vivo* cross study comparison describes an exposure as much as 38% higher than the intact tablet. Thus, there are no adequate relative bioavailability studies in this application comparing unaltered Flexeril and CMR. The T_{max} for the CMR 30 mg capsule was 7.6 hours. The mean half life was 33.4 hours for the 15 mg capsule and 32 hours for the 30 mg capsule. Administration with food increased the C_{max} by 35% and $AUC_{0\text{-}inf}$ by 20%, with no evidence of dose dumping. The PK following multiple dosing demonstrated accumulation of cyclobenzaprine based on the C_{maxss} which was twice the C_{max} following single dose administration.

An evaluation of PK characteristics in the elderly (65-75 year old subjects) revealed notably greater exposure with $AUC_{0\text{-}inf}$ 40% higher than in 18-45 year old subjects and T_{max} 50% higher. Given the prolonged half life in the elderly and the two-week duration of the multiple-dose study, it is not yet known what the degree of accumulation would be in the elderly population. As noted by Dr. Adebowale, the dissolution specifications are too wide to ensure patch to batch quality. Revised dissolution specifications are recommended.

Dr. Christina Fang reviewed the clinical studies for efficacy and safety. Two identically designed, 14-day, randomized, double-blind, placebo- and active-controlled clinical trials were submitted in support of efficacy enrolling a total of 504 patients. An additional 104 patients from the phase 1 studies contributed to the safety database consisting of 608

patients. In the efficacy trials, patients were randomized to one of four treatment arms, CMR 15 mg once a day, CMR 30 mg once a day, Flexeril 10 mg TID, and placebo. Adult patients were enrolled with self-reported pain due to muscle spasms associated with acute, painful, nontraumatic, musculoskeletal conditions confirmed by the physician. Physical therapy was not permitted during the study. Rescue was permitted only to be used before the subject was discontinued due to lack of efficacy and included nonsteroidal anti-inflammatory drugs (NSAIDs), topical over-the-counter medications, and physical therapy.

Study 1105 enrolled 254 patients. Treatment groups were reasonably balanced across demographic and baseline characteristics. Only eight patients were over the age of 65. Rescue medications were used by 25% of patients in the CMR 30 mg group, 33% of patients in the CMR-15 mg group, and 27% in the placebo group. Forty-one percent of placebo patients discontinued the study early, while 30% of the CMR-15 mg patients and 34% CMR 30 mg patients discontinued early. More placebo patients discontinued early due to a sufficient response, 9.4% than the other treatments, while fewest discontinued due to insufficient response, 1.6%, from the CMR 15 mg group.

Efficacy was based on two co-primary endpoints. For the 5-point categorical Subject's Rating Of Medication Helpfulness on Day 4 subjects responded to the question, "How would you rate this study medication in improving your condition?" There was a statistically significant separation for the CMR 30 mg group from the placebo group, but not for the CMR 15 mg group. The response for the CMR 30 mg group remained better than placebo through Day 14. Statistical comparisons were not made for the Flexeril group. Given the altered PK characteristics for this treatment as noted previously, it is unclear that such a comparison would have provided useful information. For the 5-point categorical Physician's Clinical Global Assessment on Day 4, physicians based their scores on a combination of physical examination, degree of muscle spasm, reaction to palpation, limitation of range of motion, and evaluation of the patient's reported functional assessment. There were no statistically significant differences for either CMR treatment group compared to placebo. An analysis of responders defined as "very good" or "excellent" for the Subject's Rating Of Medication Helpfulness and "moderate improvement" or "marked improvement" on the Physician's Clinical Global Assessment did not reveal any statistically significant differences between treatment groups.

There were seven secondary efficacy outcomes. On the 5-point categorical Assessment Of Relief From Local Pain, the 5-point categorical Subject-rated Clinical Global Impression of Change based on a rating of change regardless of relatedness, Subject-Rated Restriction of Movement, and Summary of Subject-Rated Daytime Drowsiness, the CMR 30 mg group was statistically better than placebo at Day 4, Day 8 and Day 14, although with correcting for multiplicity, it is likely Day 14 would not remain statistically significant. The Subject-Rated Restriction in Activities of Daily Living and the Acute SF-36 Health Survey Concepts Scores: Physical Component Summary, revealed greater improvement for the CMR 30 group at Day 8 compared to Day 14. The Subject-Rated Quality of Night-Time Sleep did not reveal any notable differences across treatment groups.

Study 1106 enrolled 250 patients. Treatment groups were reasonably balanced across demographic and baseline characteristics. Only seven patients were over 65 years of age. Rescue medications were used by 15% of patients in the CMR 30 mg group, 31% in the placebo group and 24% of patients in the CMR 15 mg group. Thirty percent of placebo patients and 30% of CMR 15 mg patients discontinued the study early, while 34% of the CMR 30 mg patients discontinued early. Few patients discontinued early due to a either a sufficient or insufficient response.

For the 5-point categorical Subject's Rating Of Medication Helpfulness on Day 4 there was a statistically significant separation for the CMR 15 mg group from the placebo group, but not for the CMR 30 mg group. The response for the CMR 15 mg group remained better than placebo through Day 14. For the 5-point categorical Physician's Clinical Global Assessment on Day 4, there were no statistically significant differences for either CMR treatment group compared to placebo. An analysis of responders defined as "very good" or "excellent" for the Subject's Rating Of Medication Helpfulness and "moderate improvement" or "marked improvement" on the Physician's Clinical Global Assessment did not reveal any statistically significant differences between treatment groups. No statistical comparisons were provided from the Flexeril group.

There were seven secondary efficacy outcomes. There were no differences compared to placebo for either CMR 15 mg or CMR 30 mg treatment groups for the 5-point categorical Assessment Of Relief From Local Pain, the 5-point categorical Subject-rated Clinical Global Impression of Change, Subject-Rated Restriction in Activities of Daily Living, Subject-Rated Restriction of Movement, Subject-Rated Quality of Night-Time Sleep, and Acute SF-36 Health Survey Concepts Scores: Physical Component Summary.

There was less Subject-Rated Daytime Drowsiness, for the CMR 15 mg group compared to placebo at Day 4 and the CMR 30 mg group at Day 4, Day 8 and Day 14.

There were no deaths or serious adverse events during the studies in support of this application. Adverse events were reported in roughly a third of all single-dose patients, and all multiple-dose patients. The most frequent adverse events were somnolence, dry mouth, dizziness, headache, nausea, palpitations, and tremor and these were present in patients receiving both CMR and Flexeril.

There were only 15 elderly (>65 year old) patients in the clinical efficacy trials, and 18 elderly patients in the phase 1 studies, too few for an adequate assessment of safety in this population.

Postmarketing safety of cyclobenzaprine was reviewed by Renan A. Bonnel, Pharm.D., MPH of the Office of Drug Safety. The most common serious reports were suicide, accidental and intentional overdose, Heart Rate Increased, Coma, Convulsion, Loss of Consciousness, Cardio-Pulmonary Arrest, Agitation, Drug Toxicity, Hallucination, Drug Interaction, Medication Error, Hypotension, and Vomiting. The overdoses were, for the most part, in combination with multiple products.

The proposed [redacted]

Labeling and tradename reviews were obtained from the Division of Drug Marketing and Communication (DDMAC) and the Office of Drug Safety, Division of Medication Errors and Technical Support (DMETS). No objections were noted for the proprietary name, Amrix. There were suggested changes to the package insert. The lack of adequate comparable bioavailability to the reference listed drug and the inconsistent efficacy findings precluded labeling negotiations.

Discussion

The sponsor failed to adequately explore the relative bioavailability to the reference listed product, Flexeril. Based on cross study comparisons, there may be as much as a 38% greater bioavailability of cyclobenzaprine with CMR than with comparable dosing with Flexeril. As a 505(b)(2) application in which prior findings of safety were to be relied upon, it was incumbent on the sponsor to demonstrate comparable systemic exposure for Amrix and Flexeril under expected conditions of use.

The results of the efficacy studies do not support a finding of efficacy. There were some positive findings for the CMR 30 mg treatment group in Study 1105, but one of the prespecified coprimary endpoints, Physician's Clinical Global Assessment on Day 4, did not reveal any statistically significant differences. There was a only one positive coprimary for the CMR 15 mg treatment group and none for the CMR 30 mg treatment group in Study 1106. It is possible that Study 1106 was a failed trial as while there were no statistical comparisons for the Flexeril treatment group, the results for this group did not look appreciably different from the CMR treatment groups. The lack of consistently positive findings in either study is particularly concerning given that there appears to be greater exposure to CMR than to unaltered Flexeril. It is possible that the results would have been more positive if the study drugs had been administered in the context of use as described in the Flexeril package insert, as an adjunct to rest and physical therapy as described in the indication.

In the presence of greater bioavailability, additional safety data would be required to assure that the additional exposure would not result in any increase in inadvertent overdose or other adverse events. This is particularly important given the prolonged half life and the presence of the total daily dose in a single unit, both factors that could result in greater harm in the setting of overdose.

This product exhibited a half life of 33 hours. That results in nearly 7 days to achieve steady state. There was clear evidence of accumulation over the two-week treatment period. Given that the condition of muscle spasm due to local causes may only last a few days, it is important to understand the effects of the long half life both for efficacy, as well as for offset of effect when no longer needed. The outstanding question is whether this product is appropriate for use when cyclobenzaprine is only needed for a few days.

The pharmacokinetics in the elderly revealed a notably prolonged half life, 50 versus 33 hours. Although there was greater exposure in the elderly to the reference listed product as well, the once daily dosing with this product precludes increasing the dosing interval as one method for managing the increased exposure. It will be necessary for the sponsor to describe how to address these age-related differences to ensure safety.

Although not explored in this application, it is known that individuals with hepatic insufficiency have a nearly doubled exposure to cyclobenzaprine following use of the reference listed product. Again, given the once daily dosing for this product, consideration must be given as to how manage patients with hepatic insufficiency.

In order to address these deficiencies, it will be necessary to demonstrate efficacy in at least one adequate and well-controlled trial. At least one, in contrast to two, in acknowledgement of the effects present in Study 1105 for the CMR 30 mg dose. The sponsor should be encouraged to do the study under conditions of expected use, as an adjunct to rest and physical therapy. Substantial evidence of efficacy for the CMR 15 mg and 30 mg doses with evidence of a dose-response effect could be sufficient to register the two doses.

An evaluation of relative bioavailability to unaltered Flexeril is recommended. If exposure is still substantially greater from the modified-release formulation, an adequate evaluation of safety will be necessary to understand how the greater exposure impacts safety. This must take into account the information known from the postmarketing adverse event review for cyclobenzaprine. In particular, a single dosage unit with a full 15 or 30 mg, particularly with greater bioavailability than the immediate-release formulation, must be assessed for risk of inadvertent overdose.

More narrow dissolution specifications are necessary to ensure batch to batch quality.

Action recommended by the Division: Approvable

Sharon Hertz, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Office of Drug Evaluation V, CDER, FDA

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/s/

Sharon Hertz
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MEDICAL OFFICER

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CLINICAL REVIEW

Application Type	NDA
Submission Number	21-777
Submission Code	N000
Letter Date	August 5, 2006
Stamp Date	August 7, 2006
PDUFA Goal Date	February 7, 2007
Reviewer Name	Christina Fang, M.D.
Review Completion Date	January 24, 2007
Established Name	Cyclobenzaprine HCl
(Proposed) Trade Name	AMRIX™
Therapeutic Class	Skeletal muscle relaxant
Applicant	ECR Pharmaceuticals Inc.
Priority Designation	S
Formulation	Modified-release tablets (capsules), 15mg and 30mg
Dosing Regimen	One oral tablet once a day
Indication	Relief of muscle spasm
Intended Population	Adults with acute, painful musculoskeletal conditions

Brief Overview of Clinical Program

The original NDA in support of Amrix (cyclobenzaprine modified-release tablets) was submitted on April 29, 2004 and was found to be approvable on February 28, 2005. This complete response to the approvable action includes the Applicant's responses to the five deficiencies listed in the approvable letter. There were no new clinical (pharmacokinetic, efficacy, or safety) data submitted in the current submission. The Applicant provided clarification about the use of the intact Flexeril 10 mg tablets, rather than an altered formulation (encapsulated, crushed Flexeril tablets), in the single-day relative bioavailability study (Study 1107), which had been one of the main concerns with the relative bioavailability between the modified-release (MR) formulation and the listed reference product, Flexeril. Because the original NDA has already been reviewed in detail (refer to the review dated February 28, 2005), the content of that review will not be repeated here. The current review is focused on the reevaluation of efficacy and safety in the context of updated pharmacokinetic (PK) analyses and a review of the revised labeling.

Pharmacokinetics

Relative bioavailability

Single-day bioequivalence in Cmax, AUC, and $t_{1/2}$ between the MR formulation (Amrix) and IR formulation (intact Flexeril) was demonstrated in Study 1107.

There are several issues with the steady-state bioequivalence between the MR and IR formulations. In contrast to Study 1107 which compared Amrix and intact Flexeril, Study 1104, designed to investigate the steady-state PK, compared Amrix and crushed Flexeril over 7 days. No *in vivo* comparison between the crushed Flexeril and intact Flexeril to bridge the PK information. The only information available is the findings of similar *in vitro* dissolution between the crushed and intact Flexeril. The results of Study 1104 demonstrated that Cmin appeared to be bioequivalent between Amrix and crushed Flexeril. Cmax for Amrix was 27% higher on the 7th day than that of the crushed Flexeril. Steady-state AUC and $t_{1/2}$ could not be compared between the two formulations because of a trial conduction error; the last two doses of the crushed Flexeril were not given to the subjects during the final 24-hour sample collection for steady-state assessments. Therefore, steady-state bioequivalence between Amrix and Flexeril is questionable in this reviewer's opinion.

According to the explanation provided by the PK reviewer, Dr. Nallani, the dosing interval in the multiple-dose PK study was irregular in that the crushed Flexeril was dosed, not at every 8

hours, but in five to six hour intervals between the first and the second dose and between the second and third dose with about 12 to 13 hours between the third dose and the morning dose (dosing interval doubled during the night). Therefore, the peak levels with each additional dose of the crushed Flexeril on a given day is expected to rise to a higher level as observed in the single-dose study, in which the Cmax of Amrix was about 30% higher than Cmax of the first of the three doses of Flexeril. If the Cmax kept increasing with the second and third dose of the crushed Flexeril (which could not be shown due to the omission of the second and third doses of the crushed Flexeril on the last day) to the same extent as the initial day (by assumption), then Cmax and AUC between Amrix and crushed Flexeril at steady state, could be similar by simulation.

For the comparison between the crushed and intact Flexeril Dr. Nallani found an article in the literature about a steady-state PK study of Flexeril and stated that the steady-state peak level in that study are comparable to the peak level (corresponding to the first of the three doses mentioned above) of the crushed Flexeril. Dr. Nallani's review (which is still pending) is referred for detail.

Drug accumulation with repeated dosing

Based on cross study comparisons, drug accumulation with repeated dosing of Amrix appears to result in at least **two-fold increase in Cmax on the 7th day** (41.1 ng/mL in Study 1104) as compared to Cmax after a single dose (19.2 ng/mL in Study 1107). AUC and $t_{1/2}$ were similar when the findings of the single-dose PK study and the multiple-dose PK study were compared.

Based on the Flexeril labeling, drug accumulation with repeated dosing of Flexeril results in a four-fold increase in drug concentrations (with no specification as to whether it was AUC or Cmax) when steady-state findings were compared to that of a single-dose study (based on cross study comparisons).

In this reviewer's opinion, the available PK data in this NDA does not allow an adequate assessment of whether there were formulation-related differences in drug accumulation after repeated dosing because of the omission of the last two doses of the crushed Flexeril on the last day.

Drug accumulation in the elderly

Age-related increases in AUC and $t_{1/2}$ were reported in the single-day study (Study 1107) as summarized in the table below. Age-related prolongation of half-life was similar for the two formulations. Age-related increase in AUC after a single-day exposure on the average was 5-

6% greater in the elderly subjects receiving Amrix than those receiving the intact Flexeril (32-40% increase versus 26-35% increase, respectively).

Table 1 Single-Day PK Comparison between Elderly and Younger Patients

	Amrix 30 mg single dose			Flexeril 10 mg three doses		
Age group	AUC_{0-168} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hour)	AUC_{0-168} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hour)
18-45	715.1±264.2	751.2±271.5	32.4±8.1	805.4±330.7	837.4±340.2	30.4±7.1
65-75	945.9±255.2	1055.2±301.9	49.0±8.3	1017.4±261.3	1129.1±309.6	47.1±9.4
Elderly vs young	32% ↑	40% ↑	16.6 hour or 51% ↑	26% ↑	35% ↑	16.7 hour or 55% ↑

An age-related increase in AUC at steady-state for Flexeril was reported as 1.7 fold in the elderly compared to younger subjects based on a cross study comparison described in the Flexeril labeling. The question about whether there is a formulation difference between the Amrix and Flexeril formulations in age-related drug accumulation at steady-state can not be answered because elderly patients were not included in the 7-day PK study.

Efficacy

As summarized in the review of the original NDA, the positive findings in support of the 30 mg dose included subject's rating of medication helpfulness on Day 4 as the primary efficacy endpoint and relief of local pain and improvement of movement limitation on Day 4 and Day 8 and patient's global impression of change on Day 4, 8, and 14 as the secondary efficacy endpoints in Study 1105. The positive findings in support of the 15 mg dose included subject's rating of medication helpfulness on Day 4 as the primary efficacy endpoint and subject's rating of medication helpfulness on Day 14 as the secondary efficacy endpoint in Study 1106. Basically, there is stronger evidence to support the 30 mg dose in one study and some evidence to support the 15 mg dose in the second study in addition to the demonstration of single-dose bioequivalence between Amrix and Flexeril.

The reanalysis of the pooled data from the two studies in the resubmission is not considered necessary and will not be reviewed here.

As noted before there was an under representation of elderly in the two efficacy studies that only 17 of 504 (3.4%) patients in the two 14-day studies were older than 65 years of age and only seven of these elderly patients received treatments with Amrix.

Safety

As summarized in the review of the original NDA exposure to Amrix included any exposure in 373 subjects and 9-14 days of exposure in 203 subjects. Exposure to the 15 mg dose was reported in 143 subjects, including 9-14 day of exposure in 104 subjects (83 had a 14-day exposure). Exposure to the 30 mg dose was reported in 230 subjects, including 9-14 days of exposure in 99 patients (89 had a 14-day exposure). According to the Flexeril labeling the longest exposure to the immediate-release formulation was ≥30 days in about 300 patients.

The most common adverse events (AEs) were similar between the Amrix and Flexeril. To compare the incidence rates of the most common AEs between the two formulations, the incidence rates of somnolence/drowsiness, dry mouth, and dizziness reported in the original NDA and in the Flexeril labeling are summarized in the table below. In the Flexeril historical database the incidences of these most common AEs were more consistent for the 5 mg and 10 mg tid dosing across controlled studies and were lower in the surveillance program. In the multiple-dose studies of Amrix in the NDA database the incidence rates of these most common AEs were similar between the two formulations (Amrix and the crushed Flexeril). Higher AE incidences associated with the use of Amrix were reported in the seven-day PK study and lower incidences were reported in the 14-day efficacy studies when NDA data are compared to the historical data from the studies of Flexeril, most likely due to smaller sample sizes in the studies of Amrix.

Table 2 Relative Incidence Rates of the Most Common AEs

Original NDA	14-day, controlled, parallel, efficacy studies				7-day, crossover, PK study	
	Placebo (N = 128)	***Amrix 15mg qd (N = 127)***	***Amrix 30mg qd (N = 126)***	***Flexeril* 10mg tid (N = 123)***	***Amrix 30mg qd (N = 36)***	***Flexeril* 10mg tid (N = 34)***
Somnolence	0	1 (0.8%)	**2 (1.6%)**	**9(7.0%)**	**36 (100.0%)**	**33 (97.1%)**
Dry Mouth	2(1.6%)	7(5.5%)	**17 (13.5%)**	**17(13.8%)**	**21 (58.3%)**	**15 (44.1%)**
Dizziness	2(1.6%)	4(3.1%)	**8 (6.3%)**	**7(5.7%)**	**7 (19.4%)**	**4 (11.8%)**
Historical data	7-day, controlled, parallel, efficacy studies				Controlled studies	Surveillance
	Placebo (N = 469)	***Flexeril 5mg tid (N = 464)***	***Flexeril 10mg tid (N = 249)***		***Flexeril 10mg tid (N = 473)***	***Flexeril 10mg tid (N = 7607)***
Drowsiness	10%	29%	38%		39%	16%
Dry Mouth	7%	21%	32%		27%	7%
Dizziness					11%	3%

Summary

The efficacy of Amrix, the cyclobenzaprine MR-formulation, 15 mg and 30 mg were supported by the results of one of the two 14-day trials and the demonstration of single-dose bioequivalence between Amrix and Flexeril. The Amrix and the crushed Flexeril appeared to have similar safety profiles in terms of the type and the incidence rates of the most common adverse events in the three multiple-dose studies, two 14-day efficacy studies and one 7-day PK study, submitted in the original NDA. Although the steady-state comparison between Amrix and crushed Flexeril was handicapped by the omission of the last two doses of the crushed Flexeril and the lack of *in vivo* comparison, the approximately constant ratio for Cmax of Amrix versus Cmax of Flexeril after the morning dose between the first day and the 7th day (by cross study comparison) and the additional PK information reported in the literature did help to bridge the PK information between Amrix and Flexeril.

The efficacy data of two weeks in duration do not support the use of the MR formulation for more than two weeks.

The drug should not be used in elderly because the lowest strength of Amrix available is 15 mg, which does not allow for a similar drug titration as what is recommended for Flexeril. Elderly patients (age ≥65 years) are expected to be at much higher risk for drug-related CNS AEs due to age-related drug accumulation and have not been adequately represented in the multiple-dose studies of Amrix. The proposed

Recommendation and regulatory action

Amrix (Cyclobenzaprine HCl modified-release) is recommended for approval as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions for up to two weeks, to improve muscle spasm and its associated signs and symptoms, namely, pain, tenderness, and limitation of motion. Restriction in the activities of daily living should not be included in the indication section because there were no significant treatment differences shown for this endpoint in either of the two studies.

The recommended adult dosage for non elderly patients is 15 mg once a day and up to 30 mg once a day as needed, for no longer than two weeks. Amrix should not be used in the elderly and patients with impaired hepatic function due to the lack of sufficient data to support the safe use of this extended release dosage form in these populations.

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/s/

Christina Fang
1/25/2007 09:44:43 AM
MEDICAL OFFICER

Sharon Hertz
1/25/2007 10:03:54 AM
MEDICAL OFFICER
I concur that there is adequate evidence of safety and efficacy for approval of Amrix. See Dep. Director memo for discussion about adequacy of pharmacokinetic information.

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CLINICAL REVIEW

Application Type	NDA
Submission Number	21-777
Submission Code	N000
Letter Date	4-29-04, 8-30-04, 12-10-04, 12-23-04, 1-22-05
Stamp Date	4-30-04, 9-3-04, 12-14-04, 12-29-04, 1-27-05
PDUFA Goal Date	February 28, 2005
Reviewer Name	Christina Fang, M.D.
Review Completion Date	February 28, 2005
Established Name	Cyclobenzaprine HCl
(Proposed) Trade Name	AMRIX™
Therapeutic Class	Skeletal muscle relaxant
Applicant	ECR Pharmaceuticals Inc.
Priority Designation	S
Formulation	Modified-release tablets (capsules), 15mg and 30mg
Dosing Regimen	One oral tablet once a day
Indication	Relief of muscle spasm
Intended Population	Adults with acute, painful musculoskeletal conditions

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

More clinical studies are required to support the efficacious and safe use of cyclobenzaprine HCl modified-release (MR) at the recommended dosage in the target population to obtain the market approval of the product.

Because substantial evidence of efficacy has not been demonstrated the Sponsor is required to provide positive results to show statistically significant and clinically meaningful treatment differences in support of treatment effects on muscle spasm and its major symptoms and signs and functional impairment through the entire treatment period for both 15mg and 30mg levels.

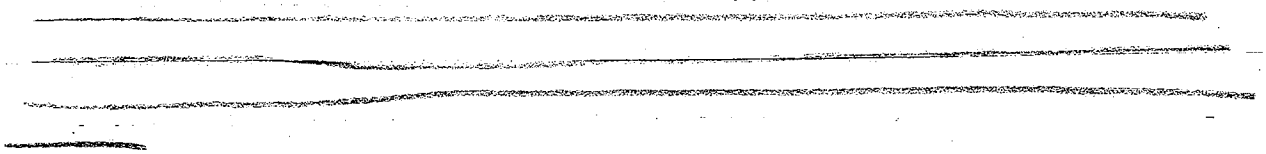
In order to address safety concerns associated with the predicted further increase in peak concentration upon repeated dosing with MR as a result of drug accumulation, the Sponsor is required to either demonstrate bioequivalence to Flexeril® during the initial day of dosing and at steady state, or provide safety data of sufficient size and duration from the studies of the target population.

Pharmacokinetic (PK) and safety data are required to address safety concerns about the impact of modified-release on the vulnerable subpopulations and to support the proposed dosing regimen for the safe use of the product in the elderly and patients with hepatic insufficiency.

1.2 Recommendation on Postmarketing Actions

Recommendation on postmarketing actions is pending on the amount of data available at the time of drug approval.

1.2.1 Risk Management Activity



1.2.2 Required Phase 4 Commitments

Required phase 4 commitments will depend on future study results.

1.2.3 Other Phase 4 Requests

Phase 4 requests will depend on future study results

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Cyclobenzaprine HCl modified-release oral tablet is a skeletal muscle relaxant indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. The current NDA submission contains two pivotal efficacy/safety trials that enrolled 504 patients (254 in study 1105 and 250 in study 1106) with acute painful muscle spasm of local origin (cervical or lumbar), associated with local pain, tenderness, limitation of motion, and restrictions in the activities of daily living. The safety database consisted of a total of 608 subjects enrolled in six clinical trials: 68 in the single-day pharmacokinetic (PK) studies, 36 in the 7-day PK study, and 504 in the two 14-day studies. The exposure to at least one dose of study medication included exposure to placebo in 128 subjects, cyclobenzaprine 15mg modified release (MR) in 143 subjects, 30mg MR in 230 subjects, and 10mg immediate release (IR) three times daily dosing (TID) in 195 subjects. The longest exposure was 9 to 14 days of repeated dosing at 30mg MR in 99 patients, with 83 completers of 14-day treatment, and at 15mg MR in 104 patients, with 89 completers of 14-day treatment. Post-marketing experience with Flexeril was also used to help to identify potential risks for adverse events with serious outcomes in the general population.

1.3.2 Efficacy

The two trials had an identical design: randomized, double blind, active- and placebo-controlled, parallel, multiple-dose (14-day), multiple-center (31 sites) U.S. studies, in which 61 to 64 patients per treatment arm received one of the following treatments: cyclobenzaprine 15mg MR once a day (QD), 30mg MR QD, 10mg IR TID, and placebo.

There were two primary efficacy endpoints, the subject's rating of medication helpfulness on day 4 and the physician's global assessment on day 4 based on the evaluation of muscle spasm, local pain, limitation of motion, and restriction in the activities of daily living, using a five-point categorical scale. The secondary endpoints included the change from baseline in subject's rating of each of the following: relief from local pain, global impression of change, health status survey (SF-36, QOL), restriction in activities of daily living, limitation of movement, quality of night-time sleep, and daytime drowsiness (this should be a measure of adverse events rather than efficacy). Patients were instructed to record all efficacy assessments daily using five-point categorical scales. The statistical analysis of the efficacy parameters was provided only for day 4, 8, and 14.

In addition to the statistical analysis on the treatment difference in the physician's global, it would be valuable to conduct statistical analysis on the physician's evaluation of the presence and severity of muscle spasm as an effort to search for study methodology, criteria, and measurement tools for evaluating the muscle relaxing effects. Statistical analysis should also be conducted on the treatment differences based on subject's daily assessment of the important secondary endpoints that measure major symptoms and signs of muscle spasm and associated functional impairment: pain, limitations of motion, and restrictions in daily living activities to obtain useful information on the onset and duration of short-term multiple-dose effects.

The active control used in the study was an altered IR formulation obtained by grounding Flexeril tablets into powder and repackaging the powder into capsules. The relative bioavailability between the altered, encapsulated formulation and the intact Flexeril tablets could not be determined because of the lack of a valid comparison. Therefore, the response of active control could not be used in the determination of assay sensitivity in these studies.

The sample study population was selected based on the proposed indication, but did not have an adequate representation of elderly patients that only 17 of 504 (3.4%) patients were older than 65 years.

The duration of the study was 14 days, which is not considered long enough to support the proposed duration of use for 2 or 3 weeks.

The major positive findings were the significant treatment differences from placebo in favor of 30mg MR in subject's rating of medication helpfulness on day 4, in local pain relief and restriction of movement on day 4 and 8, in patient's global on day 4, 8, and 12 in study 1105 and in favor of 15mg MR in subject's rating of medication helpfulness on day 4 and 14.

Based on the overall findings from the two studies there was hardly any evidence to support efficacy of 15mg MR. The supporting evidence for efficacy of 30mg MR-was not strong because of the lack of treatment differences in physician's global in both studies, in any efficacy parameters in study 1106, and in subject's rating of medication helpfulness, local pain, and restriction of movement on day 14 (to support the proposed duration of use) in study 1105. Therefore, the efficacy had not been established for the modified-release formulation of cyclobenzaprine HCl at 15mg or 30mg dose levels giving once a day for 14 days.

1.3.3 Safety

The safety database consisted of a total of 608 subjects enrolled in the six clinical trials: 68 in the single-day pharmacokinetic (PK) studies, 36 in the 7-day PK study, and 504 in the two 14-day studies. The exposure to at least one dose of study medication included to placebo in 128 subjects, cyclobenzaprine 15mg modified release (MR) in 143 subjects, 30mg MR in 230 subjects, and 10mg immediate release (IR) three times daily dosing (TID) in 195 subjects. The longest exposure was 9 to 14 days of repeated dosing at 30mg MR in 99 patients and at 15mg MR in 104 patients, with 83 patients on 15mg MR and 89 on 30mg MR completing all 14 days of treatments.

The safety data based on the findings in the sample populations consisted of mostly non elderly patients, suggested that the use of cyclobenzaprine is associated with dose-related CNS and GI symptoms, especially, somnolence/daytime drowsiness, dizziness, and dry mouth. The post marketing experience with Flexeril suggested that suicide, drug overdose, drug-drug interactions, serious adverse events of central nervous system and cardiovascular system, and drug-induced hepatic injuries are of potential safety concerns in the general population. The safety of using the MR product at the recommended dosage in the target population could not be adequately assessed due to the deficiency in demonstrating bioequivalence between the MR formulation and the approved IR formulation, insufficient safety database (small samples with minimum elderly enrollment), lack of longer-term exposure data (to address safety concerns about the clinical impact of formulation-dependent drug accumulation), and omission of the special population studies. In addition, there were no assessments of QTc prolongation, abuse potential, and drug-drug interactions, or an adequate risk management plan.

The treatment by the modified-release formulation did not appear to offer a favorable **benefit risk ratio** in the medical reviewer's opinion for the following reasons. As suggested by data there is questionable usefulness of the MR formulation (longer time to reach steady state and more concerns with drug accumulation) in treating an acute medical condition, which has a high rate of spontaneous recovery upon rest and physical therapy.

There were findings of significant treatment differences from placebo in day time drowsiness across dose levels in both studies where efficacy could not be demonstrated for 15mg MR, and findings of dose-related toxicities in the same studies. There was the uncertainty about bioequivalence between the to-be-marketed MR formulation and approved IR formulation and the uncertainty about the extent of accumulation in peak concentration at steady state and their impact on the elderly and hepatic impaired. There were safety concerns with the increasing trend in intentional and unintentional overdose with serious outcomes from postmarketing experience with Flexeril®. The formulation allowed much lesser flexibility in terms of starting dose (15mg instead of 5mg) and upward dose titration (15mg increment instead of 5mg increment).

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen of cyclobenzaprine HCl at 15mg and 30mg a day had not been demonstrated as efficacious and dose response in efficacy could not be determined. Dose-related toxicities had been shown in dropout rates due to adverse events and in the most commonly reported adverse events such as somnolence/drowsiness, dizziness, and dry mouth.

1.3.5 Drug-Drug Interactions

Drug-drug interactions based on the enzymatic pathways of drug metabolism had not been studied using the MR formulation and the information is not available on Flexeril either. Drugs known to either induce or inhibit subtypes of P450 enzyme: 3A4, 1A2, or 2D6 should be examined for if they change the concentrations of cyclobenzaprine HCl and the clinical significance of such changes. The potential inhibition or induction effect of cyclobenzaprine HCl on P450 subenzymes should also be explored to determine the need for studying metabolic enzyme-dependent drug-drug interactions.

1.3.6 Special Populations

The effect of the modified-release formulation-dependent further increase in drug accumulation upon repeated dosing in the elderly, who already had the age-related prolonged (from 32 to 49 hours in half life) and increased level of exposure (from 750 to 1055ng·hr/mL in total concentration from the one-day study), had not been evaluated (one subject in the age group of 55 to 65 years and none in the age group above 65 years were enrolled in the seven-day pharmacokinetic study). Elderly had a greater reporting frequency of central nervous system adverse events with serious outcomes than younger patients based on the post-marketing experience with Flexeril even though [redacted]. Nevertheless, elderly was under represented in the clinical trials that only 7 of the 253 patients (2.8%) who received

modified-release treatments at 15mg and 30mg level in the 14-day trials were elderly patients. The limited choice of dosage of 15mg or 30mg once a day for MR formulation makes it impossible to start at a very low dose level and titrate slowly upward and thus, making the formulation less favorable for the elderly.

Patients with mild hepatic impairment were reported to have doubling of the maximum and total concentrations with Flexeril. The effect of formulation-dependent further increase in drug accumulation should be studied in this subpopulation which was already at much higher risks for drug induced toxicities.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The established name of the product is cyclobenzaprine hydrochloride (HCl) and the proposed name is Amrix™. It is a new formulation featured by cyclobenzaprine HCl containing [redacted] packaged in capsules. It is a skeletal muscle relaxant with the proposed mechanism of action at brain stem level affecting both gamma and alpha motor systems to reduce tonic somatic motor activities.

The proposed indication is short-term (up to 2 or 3 weeks) use of the product as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions to improve muscle spasm and its associated signs and symptoms, namely, pain, tenderness, limitation of motion, and restriction in the activities of daily living. The recommended adult dosage for most patients is 15mg once a day and up to 30mg once a day as needed to be taken at about same time each day for no longer than 2 or 3 weeks. [redacted]

2.2 Currently Available Treatment for Indications

The currently available treatment for the indication is cyclobenzaprine HCl the immediate-release tablets.

2.3 Availability of Proposed Active Ingredient in the United States

Cyclobenzaprine HCl was originally approved for the U.S. market as Flexeril® in 1977. The contraindications against the use of the product include hypersensitivity to any of its components, concomitant use or 14 days after the discontinuation of monoamine oxidase (MAO) inhibitors, cardiac conditions such acute recovery from myocardial infarction, arrhythmias, heart block or conduction disturbances, and congestive heart failure, and hyperthyroidism. Cyclobenzaprine HCl carries the warnings for serious central nervous system (CNS) reactions and for concomitant use with alcohol, barbiturates, and other CNS depressants. There are precautions about use in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, in patients taking anticholinergic medication, and in patients with impaired hepatic function and in elderly.

2.4 Important Issues With Pharmacologically Related Products

Cyclobenzaprine has similar pharmacological effects as those of the structurally related tricyclic antidepressants (TCAs), including reserpine antagonism, norepinephrine

potentiation, potent peripheral and central anticholinergic effects, and sedation, based on the findings in the animals. Some of the contraindications, warnings, and precautions in the Flexeril® labeling refer to those associated with the use of TCAs, such as hyperpyretic crisis, seizures, and deaths as a consequence of concomitant use with MAO inhibitor drugs; arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke; blocking the antihypertensive action of guanethidine and similarly acting compounds; increasing seizure risk in patients taking tramadol. Although death is reported less frequently in cases of overdose with cyclobenzaprine than with the tricyclic antidepressants, (refer to review by the Division of Drug Risk Evaluation dated November 1, 1999), increasing trends in drug overdose and associated fatal outcomes are of top safety concerns for both cyclobenzaprine and TCAs.

2.5 Presubmission Regulatory Activity

The discussions about study design, eligibility criteria, efficacy endpoints, and analysis plan were the main focuses of the prior communications between the Division and the Sponsor from October 2001 to April 2003. The protocols for the phase III efficacy studies were reviewed as Specially Protocol Assessment dated October 3, 2002. The Division expressed safety concerns with the new dosage at 30mg once daily, especially in the elderly, and recommended assessment of dependence, withdrawal and abuse potential of the new formulation as recorded in the meeting minutes dated October 3, 2001. The Sponsor was commented on having a well represented sample study population with volunteers above 45 years of age in the multiple-dose PK study 1104 and a [redacted] with some specific recommendations provided according to the meeting minutes dated April 29, 2003. However, there was minimal elderly enrollment in the multiple-dose PK study and efficacy studies, no assessment of dependence, withdrawal and abuse potential, or [redacted] in the NDA submission. [redacted]

2.6 Other Relevant Background Information

The modified-release formulation of cyclobenzaprine HCl has not been marketed in any country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC information on drug substance and drug product was considered adequate according to the chemistry review. Stability data support the proposed 24-month expiration period for the drug product stored at controlled room temperature. Based on pharmacokinetic reviewer's recommendation the dissolution acceptance criteria for the 4-hour and 8-hour assessment of drug release test should be narrowed to ensure batch to batch quality.

3.2 Animal Pharmacology/Toxicology

According to pharmacology/toxicology review the updated information on non clinical pharmacology and pharmacokinetics was considered acceptable. The results of the three genotoxicity studies indicated that cyclobenzaprine HCl was not mutagenic by *in vitro* bacterial reverse mutation assay, *in vitro* chromosomal aberration assay in CHO cells, and *in vivo* rat micronucleus assay.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical review was based on efficacy finding in each of the two 14-day controlled studies, PK data from three single-dose PK studies and one 7-day PK study, and safety data pooled with respect to the proposed duration of exposure for the six clinical studies. The additional safety data sources were the three reviews of postmarketing safety of Flexeril® based on surveillance and literature reports by the consulting division, the Division of Drug Risk Evaluation, dated July 14, 1999, November 1, 1999, and January 14, 2005, respectively. Safety data for one PK study were reviewed separately because a discontinued formulation of 30mg MR was used in the study.

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4.2 Tables of Clinical Studies

Study number/ type/investigator	*Study design*	*Treatment dosage/duration*	*# of subjects per treatment*	*Data relevance*
Pharmacokinetic trials				
1101 Relative bioavailability Galitz (USA)	Randomized, two-period, crossover	30 mg MR (different formulation) single am dose or 10mg MR TID for 1 day in each dose period	12 (6/sequence)	Safety reviewed separately in section 7.2.2.1
1102 Dose proportionality Gutierrez (USA)	Randomized, double-blind, two-period crossover	15mg MR or 30mg MR as a single am dose in each dose period	16 (8/sequence)	Data used for PK and safety review
1103 Food effect Gutierrez (USA)	Randomized, open-label, two-period crossover with or without food	30mg MR given fasted or fed in each dose period	16 (8/sequence)	Data used for PK and safety review
1107 One-day relative bioavailability Gutierrez (USA)	Randomized, open-label, two-period crossover	30mg MR single am dose or 10mg IR TID for 1 day in each dose period	36 (18/sequence)	Data used for PK and safety review
1104 7-day relative bioavailability Gutierrez (USA)	Randomized, double-blind, multiple-dose, two-period crossover	30mg MR or 10mg IR TID for 7 days in each dose period	36 (18/sequence)	Data used for PK and safety review
Efficacy trials for muscle spasm				
1105 Efficacy study 31 centers (USA)	Randomized, double-blind, placebo and active-controlled, 4-arm parallel, 14-day multiple-dose	15mg MR 30mg MR 10mg IR TID Placebo for 14 days	64 64 62 64	Data used for efficacy and safety review
1106 Efficacy study 35 centers (USA)	Randomized, double-blind, placebo and active-controlled, 4-arm parallel, 14-day multiple-dose	15mg MR 30mg MR 10mg IR TID Placebo for 14 days	63 62 61 64	Data used for efficacy and safety review

Refer to Table 2.1-1 in Volume 60 of the NDA submission.

4.3 Review Strategy

Efficacy findings from each of the two 14-day controlled studies were considered equally important for providing evidence to support efficacy. Because this was a 505(b)(2) application, PK data from comparing relative bioavailability between the MR-formulation and Flexeril®, safety data from clinical studies of the MR formulation, and postmarketing experience with Flexeril® were all considered important components in the review of safety.

4.4 Data Quality and Integrity

Site audit will be postponed due to the lack of sufficient evidence to support efficacy.

4.5 Compliance with Good Clinical Practices

The protocols and the informed consent forms were reviewed and approved by the Institutional Review Boards (IRBs). The Informed Consent contained information explaining the purpose, nature and procedures of the study, the potential risks and benefits involved, and the opportunity for voluntary withdrawal, alternative treatment, and compensation for injury. Protocol violation cases involved mainly positive urine drug tests (21 of 26 cases in study 1105 and 17 of 20 cases in study 1106). The Sponsor claimed that the studies were conducted in accordance with the criteria defined in the Declaration of Helsinki, ICH, and CFR.

4.6 Financial Disclosures

The financial disclosure form signed by the Sponsor certified that no financial arrangements had been made, where outcomes affects compensation, with any principle investigator or sub-investigators involved in the clinical studies, and that these investigators had no proprietary, significant equity interest, or any significant payments of other sorts as defined in 21 CFR 54.2(f).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

There were 5 pharmacokinetic studies. To-be-marketed modified-release (MR) formulation was studied in 4 of them: 1102 (dose proportionality), 1103 (food effect), 1107 (relative bioavailability after a single day of drug administration), and 1104 (relative bioavailability after one week of multiple dosing). The immediate-release (IR) formulation used in the two bioequivalence PK studies (1007 and 1004), as well as in the two efficacy studies, was

altered by encapsulating crushed Flexeril® tablets for the blinding purpose. A discontinued MR formulation and the intact Flexeril® 10mg tablets were studied in the single-dose bioequivalence study 1101.

The **single-dose PK profile** of cyclobenzaprine 30mg MR was characterized by C_{max} of about 19ng/mL, T_{max} of about 7 hours, $AUC_{0-\infty}$ of about 750ng·hr/mL, and $t_{1/2}$ of about 32 hours in the younger (age 18-45) healthy volunteers. In the **elderly** (age ≥65 years, who accounted for 18 of the 36 subjects enrolled in study 1107) there was a 40% increase in $AUC_{0-\infty}$ (1055ng·hr/mL), about 50% prolongation in $t_{1/2}$ (49 hours), and about 1 to 2 hour delay in T_{max} (8.5 hours) in comparison to those of the younger age group. C_{max} was about equal in the two age groups. In the study of **dose proportionality** the exposure to 30mg MR was slightly more than twice in comparison to 15mg MR in terms of the dose-unadjusted bioavailability. The 10 to 20% increases in dose-adjusted ratios of the arithmetic means of AUC and C_{max} were suspected of resulting from inter-subject variation. **Food** increased the peak exposure (C_{max}) by 35% and total exposure (AUC) by 20% and had no effect on T_{max}, lag time (Tlag), or the shape of the time-concentration curve, suggesting that dose dumping did not occur.

The **PK parameters** of cyclobenzaprine 30mg MR obtained from the **one-week multiple-dose** study were very similar to those obtained from the single-dose PK studies in terms of AUC, T_{max}, and $t_{1/2}$. However, C_{max} was about 40ng/mL, about twice as high as C_{max} from a single-dose exposure, suggesting dose accumulation in peak exposure after one week of repeated dosing. The minimum concentration (C_{min}) was about 20ng/mL, average concentration (C_{ave}) was about 30ng/mL, and CL/F was about 44L/hr. As noted the trial did not include any elderly subject (only 4 of 36 enrolled were 45 to 55 years old and 1 subject was in the age group of 55 to 65 years) and might not be long enough for the MR formulation to reach the **steady state** because of the long half life (mean $t_{1/2}$ of 32 hours in adults age <45 years and 49 hours in the elderly after a single dose) associated with the drug metabolism of MR.

In the study of relative bioavailability between 30mg MR and 10mg IR TID (the encapsulated formulation), the **initial day bioequivalence** was shown in C_{max} and AUC. T_{max} was 7.6 hours for 30mg MR and 4.7 hours for 10mg IR to reach a C_{max} of 12.6ng/mL after the initial dose and 18.5 hours to reach a C_{max} of 18.3ng/mL after 3 doses, suggesting dose accumulation with repeated dosing of 10mg IR.

The comparison of **relative bioavailability** of the two formulations at the **steady state** was compromised by a major protocol deviation that the last two doses were not given to the subjects in the 10mg IR treatment group during the last 24 hours while the blood samples were collected for analysis of steady-state PK parameters, and thus, made the study

inconclusive. The estimation by simulation was complicated by unpredictable errors and thus, not considered acceptable in the medical reviewer's opinion. One reasonable conclusion from this study was that the minimum exposure to the two formulations was bioequivalent after one week of multiple dosing since the sample collection for Cmin (before the dose actually given) was not affected by the omission of the last 2 doses.

The unaltered Flexeril® tablet was only studied in 1101. In response to the Division's question about the **relative bioavailability** between 30mg MR and **Flexeril® 10mg TID**, the Sponsor selected younger (age <40 years) males from study 1107 (consisted of male and female healthy volunteers age 18-45 and 65-75) to match the population in study 1101 for the purpose of comparing PK profiles of the two IR formulations. There was a much higher exposure to the encapsulated tablet (study 1107) than to the intact tablet (study 1101), a 34.6%, 38.3% and 34.8% increase in C_{max}, AUC_{0-168} and $AUC_{0-\infty}$, respectively, after administration of all 3 doses. The Sponsor's attempt of limiting data analysis to the initial of the 3 doses was not considered acceptable because of the drug accumulation with increasingly higher C_{max} upon repeated dosing in the first 24 hours.

The pharmacokinetic issues of potential safety concerns included the much higher total concentration and longer half life in the elderly, dose accumulation in peak concentration upon repeated dosing for a week in a younger population and uncertainty about how high would C_{max} reach with a longer (more than one week) exposure and how much would it affect elderly. Bioequivalence between the to-be-marketed MR formulation and the approved IR formulation had not been demonstrated for the initial day dosing and data from the indirect comparison suggested higher exposure to the MR formulation. Steady state bioequivalence between the two formulations had not been demonstrated either due to the deficiency in trial design (wrong comparator and insufficient duration of exposure) and conduct (under enrollment of elderly and omission of last 2 doses of 10mg IR in the period of blood sample collection).

5.2 Pharmacodynamics

There were no pharmacodynamic studies.

5.3 Exposure-Response Relationships

The dose selection for clinical studies was based on the total daily dose recommended for Flexeril®. There was no combined PD/PK study to evaluate exposure-response relationship. Dose response in efficacy and safety will be discussed in section 6 and 7, respectively.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for the cyclobenzaprine MR formulation is identical to the approved indication for the cyclobenzaprine IR formulation, Flexeril®, as the following:

Cyclobenzaprine 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, and restriction in the activities of daily living.

Cyclobenzaprine 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.

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

6.1.1 Methods

There were two controlled efficacy studies 1105 and 1106 of the identical design. Results of individual studies are used in the evaluation of the strength of evidence in support of efficacy claim.

6.1.2 General Discussion of Endpoints

The **primary endpoints** were:
1) Subject's rating of medication helpfulness on day 4;

2) Physician's global assessment based on the day 4 evaluation of the presence of muscle spasm, local pain, limitation of motion, and restriction in activities of daily living.

The **secondary endpoints** included the change from baseline in subject's rating of each of the following
1) Relief from local pain
2) Global impression of change

3) Health status survey (SF-36, QOL)
4) Restriction in activities of daily living
5) Limitation of movement
6) Daytime drowsiness
7) Quality of night-time sleep

Additional supportive measures were:
1) Response to treatment defined by the percentage of responders with a rating of "very good" or "excellent" on the subject's rating of medication helpfulness and a rating of either "moderate improvement" or "marked improvement" on the physician's global assessment
2) Time to improvement in terms of the days to reach "fair" to "excellent" rating on the subject's rating of medication helpfulness

The **measurement** of muscle spasm and the impact of muscle spasm had not been well studied in the past. There had been no commonly recognized study methodology, established criteria, or validated measurement tools. There are **limitations** with regard to the evaluation of the presence and severity of muscle spasm since patient's self reporting of muscle spasm has not been shown to be accurate. The assessment of muscle spasm by evaluator's palpation has also unpredictable intra-evaluator and inter-evaluator variations and thus, may not be that reliable.

The set of the primary and secondary endpoints had been discussed and agreed upon between the Division (Dr. Villalba was the reviewer, who provided the Special Protocol Assessment) and the Sponsor in 2002. The **selection** of the subject's rating of medication helpfulness and physician's global assessment on day 4 as the **primary endpoints** was based on the consideration of the limitations inherited in the measurement of muscle spasm and the attempt of being consistent with the endpoints described in the clinical trial section of the original Flexeril® labeling.

In this **reviewer's opinion**, the major symptoms and signs of muscle spasm and its functional impairment, the pain, the limitation of motion, and the restriction in activities of daily living should all be considered the key parameters in measuring the effects of muscle relaxant during the course of treatment. Patient's assessment of medication's helpfulness on day 4 alone has limited usefulness because it did not cover information about pain, limited motion and restriction in daily activity and thus, would not accurately reflect the major treatment effect. It is analogous to the use of the patient's global as the primary endpoint in evaluating analgesic efficacy in a short-term multiple-dose study.

6.1.3 Study Design

The two studies had an identical design. They were randomized, double blind, active- and placebo-controlled, parallel, multiple-dose (14-day) studies of cyclobenzaprine 15mg MR and 30mg MR daily dosing, which were conducted at 31 centers in the U.S.

The choice of the **active control**, cyclobenzaprine 10mg IR given three times a day, appeared to be reasonable at the first glance since it had the daily dose level equivalent to the test drug of interest, the 30mg MR. However, the active control used in the study was an altered formulation obtained by grounding Flexeril® tablets into powder and repackaging the powder into capsules. Because of the lack of evidence for bioequivalence between the altered, encapsulated formulation and the intact Flexeril® tablets the treatment difference between the active control and placebo could not be used in the determination of assay sensitivity in this case.

In addition to the use of centralized random assignment and capsules of identical appearance to double blind the investigator and the research subjects for minimizing **bias and confounding** factors, other efforts included the restriction of any concomitant treatments that had a potential for treating muscle spasm such as analgesics, CNS depressants, other prescription, OTC and herbal products or physical therapy.

The choice of the **study population** in terms of patient's medical condition, was consistent to the proposed indication and considered a representative sample of the target population. The study population consisted of subjects with acute painful muscle spasm of local origin (cervical or lumbar), associated with local pain, tenderness, limitation of motion, and restrictions in the activities of daily living. The presence of muscle spasm and tenderness was confirmed by the physician. Subjects were required to have a moderate to severe degree of local pain and the duration of the muscle spasm prior to the study entry was restricted to no more than 7 days. Subjects with muscular pain secondary to acute trauma or fractures based on medical history, X-ray, or physical examination were excluded from the study.

The choice of **dose levels** 15mg and 30mg was considered adequate since they were equivalent to the recommended daily dosing level of the immediate-release formulation.

The 14-day **treatment duration** would provide efficacy data to support the short use of the product for at most 2 weeks, but not 3 weeks as proposed in the indication section.

6.1.4 Efficacy Findings

The results of the treatment comparison between cyclobenzaprine 15mg MR and placebo and between cyclobenzaprine 30mg MR and placebo are summarized for the two studies as shown in the tables below.

Table 6.1.4.1 Efficacy summary for study 1105

Study 1105	***Statistically significant better performance over placebo***					
Dose	***Cyclobenzaprine 15 mg MR N=64***			***Cyclobenzaprine 30 mg MR N=64***		
Evaluation day	Day 4	Day 8	Day 14	Day 4	Day 8	Day 14
Primary (day 4 only)						
Subject's rating of medication helpfulness	p>0.05	p>0.05	p>0.05	**p=0.007**	p=0.027	p=0.042
Physician's global assessment	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Secondary						
Subject-rated relief of local pain	p>0.05	p>0.05	p>0.05	**p=0.004**	**p=0.01**	p=0.03
Subject-rated global impression of change	p>0.05	p>0.05	p>0.05	**p=0.008**	**p=0.003**	**p=0.025**
Subject health status survey (SF-36, QOL) physical mental		p>0.05 p>0.05	p>0.05 p>0.05		**p=0.012** p>0.05	p>0.05 p>0.05
Restriction in activities of daily living	p>0.05	p>0.05	p>0.05	p>0.05	p=0.035	p>0.05
Limitation of movement	p>0.05	p>0.05	p>0.05	**p=0.002**	**p=0.016**	p=0.032
Daytime drowsiness	p=0.027	p=0.033	**p=0.010**	**p=0.004**	**p=0.016**	p>0.05
Quality of night-time sleep	p=0.029	p>0.05	p>0.05	p=0.045	p>0.05	p>0.05
Supportive						
Response to treatment	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	P=0.048
Time to improvement	p>0.05			p>0.05		

Refer to Table 12 to 22 in Volume 28 of the NDA submission.

In terms of the predefined primary efficacy parameters in **study 1105** cyclobenzaprine 30mg MR performed statistically better than placebo in the subject's rating of medication helpfulness on day 4 but not in the physician's global on day 4. For the secondary efficacy parameters 30mg MR performed statistically better than placebo in patient's global on day 4, 8, and 12, in local pain relief and limitation of movement on day 4, and 8, but not in subject's rating of medication helpfulness or physician's global on day 8 and 12, restriction of activities of daily living or quality of night-time sleep on any of the three days. Cyclobenzaprine 15mg did not have statistically significant ($p<0.025$) treatment differences from placebo in any of the primary and secondary efficacy parameters, of which day time drowsiness (not considered a measure of efficacy) was the only exception.

Table 6.1.4.2 Efficacy summary for study 1106

Study 1106	***Statistically significant better performance over placebo***					
Dose	***Cyclobenzaprine 15 mg MR N=63***			***Cyclobenzaprine 30 mg MR N=62***		
Evaluation day	Day 4	Day 8	Day 14	Day 4	Day 8	Day 14
Primary (day 4 only)						
Subject's rating of medication helpfulness	**p=0.018**	p=0.045	**p=0.024**	p>0.05	p>0.05	p>0.05
Physician's global assessment	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Secondary						
Subject-rated relief of local pain	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Subject-rated global impression of change	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Subject health status survey (SF-36, QOL) physical mental		p>0.05 p>0.05	p>0.05 p>0.05		p>0.05 p>0.05	p>0.05 p>0.05
Restriction in activities of daily living	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Limitation of movement	p=0.045	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Daytime drowsiness	**p=0.01**	p>0.05	p>0.05	**p=0.013**	**p=0.001**	**p=0.004**
Quality of night-time sleep	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
Supportive						
Response to treatment	p>0.05	p>0.05	P=0.04	p>0.05	p>0.05	p>0.05
Time to improvement	P=0.012			P=0.004		

Refer to Table 12 to 21 in Volume 44 of the NDA submission.

In **study 1106** cyclobenzaprine 30mg MR was not shown to have statistically significant ($p<0.025$) treatment difference from placebo in any of the primary and secondary efficacy parameters except day time drowsiness, which was considered a sign for adverse effect rather than efficacy. The isolated finding that 15mg MR had statistically significant ($p<0.025$) separation from placebo in subject's rating of medication helpfulness on day 4 and 14, was not supported by the performance of 30mg MR with respect to the same parameters or by the performance of either 30mg MR and 15mg MR with respect to the rest of the primary and secondary efficacy parameters.

Based on the **overall findings** from the two studies there was hardly any evidence to support efficacy of MR at 15mg dose level. Although some finding in study 1105 pointed to the direction that 30mg MR might have some effects, the evidence was not strong because of the lack of treatment difference in terms of the physician's global (which was

required for demonstration of efficacy by previous commitment) on any day in either studies, the lack of significant findings in any of the efficacy parameters to support 30mg dose in study 1106, and the lack of significant treatment differences in subject's rating of medication helpfulness, local pain, restriction of movement, and restriction of activities of daily living on day 14 to support the proposed duration of use of the product.

There could be many explanations as to why the efficacy results were not satisfactory. Demographic and other characterization at baseline did not appear to a major source of bias in that regard. The treatment groups were approximately balanced with regard to **baseline demographic characteristics** such as age, gender, ethnic origin, height, weight, location of muscle spasm, and baseline pain intensity in both studies. There were 61 to 64 patients per treatment arm. More than 95% of the study population were between age 18 to 65 with the mean age close to 40 years. Most treatment groups had slightly more females than males. Caucasians counted for more than 80% of the study population in study 1105 and more than 70% in study 1106. On the average there were about 2/3 of patients with low back muscle spasm and 1/3 with neck muscle spasm. Majority of patients had either moderate or moderately severe pain at baseline.

There appeared to be a relatively high **placebo response** in this disease population. The placebo response was 33% on day 8 and 48% on day 14 in the combined categories of good, very good and excellent rating of medication helpfulness, 45% on day 8 and 58% on day 14 in the combined categories of complete relief, a lot of relief, and some relief of local pain, 50% on day 8 and 66% on day 14 in the combined categories of complete relief, a lot of relief, and some relief of restriction of motion. It could be explained by the natural course of disease with spontaneous improvement of the condition over time or by a strong and longer lasting response to continuous placebo treatment.

Cyclobenzaprine is expected to be used as an adjunct to rest and physical therapy. If physical therapy was allowed in these efficacy studies, the anticipated placebo response on top of the physical therapy would be even much higher and leave no more space for improvement with the muscle relaxant. Using a medication with a long half life and known drug accumulation to treat an acute medical condition, which has a high rate of spontaneous recovery upon rest and physical therapy, does not appear to be a reasonable choice.

The results were not analyzed for the subpopulations because of the limited sample size.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Based on the findings from the two efficacy studies there were no replicable positive results to provide sufficient evidence to support the efficacious use of cyclobenzaprine extended-release formulation at either 30mg or 15mg dose level for 14 days. A treatment difference in physician's global needs to be demonstrated and supported by patient's improvement in pain, limitation of movement, and restriction of activities of daily living throughout the evaluation period with the positive results replicated in different studies. In addition, the onset of the treatment differences should also be analyzed based on patient's daily assessments.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There was no reported case of death from any of the clinical studies of the cyclobenzaprine modified-release formulation.

7.1.2 Other Serious Adverse Events

There were 2 reports of serious events in study 1106 (14-day study), and no serious AE reported from the other clinical studies. The first case was a 69-year-old male patient in the placebo group, who experienced atrial fibrillation 2 days after his last dose of the 14-day treatment. The event resolved upon hospitalization and treatment. The second case was a 21-year-old female patient in the 30mg MR treatment group, who was bitten by her gerbil and developed cellulitis of her right index finger subsequently, 3 days after her last dose of the 14-day treatment. She was hospitalized and recovered after treatment. Neither event was considered treatment related.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In the three single-dose PK studies (study 1102, 1103, and 1107) six of 68 subjects had early discontinuation, all due to withdrawal of consent. In the one-week multiple-dose PK study (1104) two of 36 subjects dropped out from the study, due to withdrawal of consent in the first case and lost to follow-up in the second case. The most common reason for early

dropout in both studies was protocol violation, mostly due to positive urine drug tests (21 of 26 protocol deviation cases in study 1105 and 17 of 20 in study 1106). The trends in dropouts due to AE were similar in the 2 studies, i.e., there were noticeably more dropouts in the 10mg IR group than 30mg MR group (14.5% vs. 4.7% in study 1105 and 8.2% vs. 4.8% in study 1106), and more dropouts in the 30mg MR group than 15mg MR group (4.7% vs. 1.6% in study 1105 and 4.8% vs. 1.6% in study 1106). The rates of dropout due to other reasons varied without a clear pattern with respects to the treatment group, when the dropout profiles of the 2 studies were compared.

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Table 7.1.3.1 Overall dropout summary

Study	*1102, 1103, 1107*	*1104*	*1105 and 1106*			
	Number of Subjects (%)					
Number of subject	*N = 68*	*N = 36*	*Placebo (N = 128)*	*15mg MR (N = 127)*	*30mg MR (N = 126)*	*10 mg IR TID (N = 123)*
Randomized	68 (100.0%)	36 (100.0%)	128 (100.0%)	127 (100.0%)	126 (100.0%)	123 (100.0%)
Randomized but Never Returned Study Drug			9 (7.0%)	5 (3.9%)	2 (1.6%)	4 (3.3%)
Completed Study	62 (91.2%)	34 (94.4%)	83 (64.8%)	89 (70.1%)	83 (65.9%)	75 (61.0%)
Discontinued Study	6 (8.8%)	2 (5.6%)	45 (35.2%)	38 (29.9%)	43 (34.1%)	48 (39.0%)
Reasons for dropout						
Adverse event			3 (2.3%)	2 (1.6%)	6 (4.8%)	14 (11.4%)
Sufficient response			7 (5.5%)	3 (2.4%)	4 (3.2%)	3 (2.4%)
Insufficient response			5 (3.9%)	2 (1.6%)	2 (1.6%)	7 (5.7%)
Lost to follow-up		1 (50.0%)	8 (6.3%)	6 (4.7%)	4 (3.2%)	3 (2.4%)
Consent withdrawal	6 (100.0%)	1 (50.0%)	4 (3.1%)	3 (2.4%)	2 (1.6%)	4 (3.3%)
Protocol violation			12 (9.4%)	10 (7.9%)	17 (13.5%)	7 (5.7%)
Administrative			0	5 (3.9%)	2 (1.6%)	4 (3.3%)
Other			5 (3.9%)	7 (5.5%)	6 (4.8%)	6 (4.9%)
Missing			1 (0.8%)	0	0	0

Refer to Table 4.1-1 and 5.1-1 in Volume 60 of the NDA submission.

7.1.3.2 Adverse events associated with dropouts

The adverse events (number and percentage of subjects) leading to dropouts of more than one patient in the three active treatment arms in the two 14-day studies are summarized below. Somnolence (10 patients on active treatments versus none on placebo), dizziness (5 on active treatments versus none on placebo), and dry mouth (4 on active treatments versus none on placebo), were the leading AEs associated with dropouts. Other AEs associated with dropouts of more than one patient on active treatments and none on placebo were nausea, fatigue, confusion, tinnitus, constipation, disorientation, and orthostatic hypotension. The database was not adequate for analysis of dose-response or time dependency of dropout, dropout-related drug-demographic, drug-disease, and drug-drug interactions because of the small sample size (123 to 128 patients per treatment arm for the pooled data from the 2 phase III studies) and the relatively short duration of exposure.

Table 7.1.3.2 AEs Leading to Dropouts - ITT Population

Study 1105 and 1106	*Number of Subjects (%)*			
Preferred term	*Placebo (N = 128)*	*15mg MR (N = 127)*	*30mg MR (N = 126)*	*10mg IR TID (N = 123)*
Somnolence	0	0	**2(1.6%)**	**8(6.5%)**
Dizziness	0	0	**1(0.8%)**	**4(3.3%)**
Dry mouth	0	0	**1(0.8%)**	**3(2.4%)**
Nausea	0	1(0.8%)	0	1(0.8%)
Fatigue	0	1(0.8%)	0	1(0.8%)
Confusion	0	0	1(0.8%)	1(0.8%)
Headache NOS	2(1.6%)	0	0	3(2.4%)
Tinnitus	0	0	0	2(1.6%)
Constipation	0	0	0	2(1.6%)
Disorientation	0	0	0	2(1.6%)
Orthostatic hypotension	0	0	0	2(1.6%)

Refer to Table 5.5-6 in Volume 60 of the NDA submission

7.1.3.3 Other significant adverse events

The treatment difference in daytime drowsiness was statistically significant on day 4 and 8 in study 1105 and on day 4, 8, and 12 in study 1106. Based on the pooled data from the 2 studies the proportion of patients in the category of a lot to extreme drowsiness peaked on day 4 and retuned to baseline level on day 8 and 14 for the 15mg MR group, and peaked on day 4 and gradually decreased on day 8 and 14 for the 30mg MR and 10mg IR TID group.

In the 7-day PK study in healthy volunteers the proportion of subjects in the category of a lot to extreme drowsiness peaked around day 2 and day 3 and again on day 8 after the last dose of treatment with 30mg MR and 10mg IR TID group, and returned to baseline after the completion of treatment.

7.1.4 Other Search Strategies

Due to the limitation of the safety database (small sample size and short-term duration of exposure) no major safety signal could be identified.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were monitored and recorded during the studies and followed for 3 weeks after the completion of the multiple-dose studies (1104, 1105, and 1106). In the two 14-day studies adverse events were assessed at each clinic visit scheduled on day 4, 8, and 14 and then at 3 weeks after treatment, by a follow up phone call. In the multiple-dose PK study the subjects were instructed to call the study site if they had any AE during the 3 weeks after the treatments.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The assignment of AE using preferred terms and categorization of AE into system organ class by MedDRA are considered appropriate.

7.1.5.3 Incidence of common adverse events

Based on the data presented in the summary tables of the most common adverse events in the 14-day phase III studies, the 7-day, 2-period crossover study, and the three single-dose studies the common AEs were basically those of CNS and GI systems, and general symptoms. The most common AEs reported from the active treatment groups that appeared to be clearly different from those of the placebo group were dry mouth, dizziness, nausea, constipation, dyspepsia, and somnolence in the 14-day studies. Somnolence, dry mouth, dizziness, and nausea were also on the top of the list of the most common AEs in the 7-day study. Somnolence and dizziness were the most commonly reported AEs associated with the single-dose treatment as well.

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7.1.5.4 Common adverse event tables

Table 7.1.5.4.1 Summary of common AEs in the 14-day studies

Study 1105 and 1106	***Number of Subjects (%)***			
Preferred term	***Placebo (N = 128)***	***15mg MR (N = 127)***	***30mg MR (N = 126)***	***10mg IR TID (N = 123)***
Subjects with at least 1 AE	36(28.1%)	49 (38.6%)	50 (39.7%)	60 (48.8%)
Dry Mouth	2(1.6%)	7(5.5%)	**17 (13.5%)**	**17(13.8%)**
Dizziness	2(1.6%)	4(3.1%)	**8 (6.3%)**	**7(5.7%)**
Dyspepsia	1 (0.8%)	0	5 (4.0%)	3(2.4%)
Nausea	1 (0.8%)	4(3.1%)	4(3.2%)	3(2.4%)
Fatigue	3(2.3%)	4(3.1%)	4(3.2%)	4(3.3%)
Constipation	0	1 (0.8%)	4(3.2%)	7(5.7%)
Somnolence	0	1 (0.8%)	**2 (1.6%)**	**9(7.0%)**
Paraesthesia	0	3(2.4%)	1 (0.8%)	1 (0.8%)
Headache NOS	9(7.0%)	7(5.5%)	1 (0.8%)	6(4.9%)
Diarrhea NOS	3(2.3%)	1 (0.8%)	0	4(3.3%)

Refer to Table 5.5-3 in Volume 60 and Table 26 in Volume 62 of the NDA submission.

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Table 7.1.5.4.2 Summary of common AEs in the 7-day crossover PK study

Study 1104	*Number of Subjects (%)*	
Preferred Term	*30mg MR (N = 36)*	*10mg IR TID (N = 34)*
Somnolence	**36 (100.0%)**	**33 (97.1%)**
Dry mouth	**21 (58.3%)**	**15 (44.1%)**
Dizziness	**7 (19.4%)**	**4 (11.8%)**
Headache NOS	6(16.7%)	9(26.5%)
Nausea	3(8.3%)	2(5.9%)
Dry throat	3(8.3%)	1 (2.9%)
Dysgeusia	2(5.6%)	2(5.9%)
Palpitations	2(5.6%)	2(5.9%)
Tremor	2(5.6%)	2(5.9%)
Acne NOS	2(5.6%)	0
Disturbance in	2(5.6%)	0
Vision blurred	1 (2.8%)	4(11.8%)
Insomnia	0	2(5.9%)

Refer to Table 4.5-4 in Volume 60 of the NDA submission.

Table 7.1.5.4.3 Summary of common AEs in the in the single-dose PK studies

Study 1102, 1103, and 1107	*Number of Subjects (%)*	
Preferred Term	*All CMR (N = 67)*	*10mg IR TID (N = 35)*
Somnolence	**6(9.0%)**	**3(8.6%)**
Headache NOS	5(7.5%)	1(2.9%)
Dizziness	**4(6.0%)**	**1(2.9%)**
Insomnia	2(3.0%)	0(0.0%)
Musculoskeletal pain	2(3.0%)	0(0.0%)
Pain in limb	2(3.0%)	0(0.0%)

Refer to Table 4.5-3 in Volume 60 of the NDA submission.

7.1.5.5 Identifying common and drug-related adverse events

The common and drug-related adverse events reported from the two 14-day studies are summarized below:

Table 7.1.5.5 Summary of common drug-related AEs in the 14-day studies

Study 1105 and 1106	*Number of Subjects (%)*			
Preferred term	*Placebo (N = 128)*	*15mg MR (N = 127)*	*30mg MR (N = 126)*	*10mg IR TID (N = 123)*
Subjects with at least one AE	19 (14.8)	26(20.5%)	41(32.5%)	50(40.7%)
Dry Mouth	**2(1.6%)**	**7(5.5%)**	**17 (13.5%)**	**17(13.8%)**
Dizziness	**1 (0.8%)**	**3(2.4%)**	**8(6.3%)**	**7(5.7%)**
Somnolence	**1 (0.8%)**	**0**	**5 (4.0%)**	**9(7.3%)**
Fatigue	3(2.3%)	4(3.1%)	4(3.2%)	4(3.3%)
Nausea	1(0.8%)	4(3.1%)	4(3.2%)	3(2.4%)
Constipation	0	1(0.8%)	4(3.2%)	7(5.7%)
Headache NOS	7(5.5%)	2(1.6%)	1(0.8%)	4(3.3%)

Refer to Table 5.5-4 in Volume 60 of the NDA submission.

The list is very similar to the common AEs identified and discussed above. The reviewer does not include fatigue and headache in the previous discussion because the placebo group had similar or higher incidence of these AEs in comparison to the active treatment groups.

The common and drug-related adverse events for the 7-day study include somnolence, glossodynia, dizziness, pain in limb, and insomnia.

7.1.5.6 Additional analyses and explorations

Based on the data in the summary table of the common AEs reported in the two 14-day studies there appeared to be a dose response in dry mouth, dizziness, constipation, dyspepsia, and somnolence. Of these dose-related and most common AEs, patients on 10mg IR TID had higher incidence of somnolence and constipation than patients on 30mg MR once a day.

In terms of the AE adaptation patients appeared to adapt to daytime drowsiness after a week of continuous daily treatment at 15mg dose level. However, at the higher daily dose level, 30mg MR once a day or 10mg IR TID, there was not a clear and consistent pattern to suggest adaptation to daytime drowsiness during the 2-week treatment period. The daytime drowsiness was reversible after cessation of treatment as suggested by data in the 7-day PK study, in which daytime drowsiness was evaluated for three more days after the last dose of treatment.

The database was not sufficient for analysis of drug-demographic, drug-disease, and drug-drug interactions because of the small sample size (123 to 128 patients per treatment arm for the pooled data from the 2 phase III studies) and relatively short duration of exposure.

7.1.6 Less Common Adverse Events

The database is too small to identify rare events.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine hematology, blood chemistry, and urinalysis were tested at the screening and the termination of treatment.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Only the two 14-day studies were placebo-controlled and had the longest duration of exposure and thus, were selected for drug-control comparisons of laboratory values.

7.1.7.3 Standard analyses and explorations of laboratory data

The number and percentage of patients with abnormal values and the individual findings against predefined criteria were presented in ISS and individual study reports.

7.1.7.3.1 Analyses focused on measures of central tendency

Group means were not provided since very few patients in each treatment group had abnormal laboratory findings with respect to the individual tests. Majority of the abnormal findings were just borderline deviations from the normal range. By comparing the findings among treatment groups they did not suggest a strong association between the active treatments and laboratory test abnormalities or a dose response relationship.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

As shown in the tables below in comparing all the treatment arms with regard to the difference between placebo and active treatments, between different daily dose levels, and between different dosing regimen at the same total daily dose, there was not a clear pattern to suggest a dose response or drug relationship in any of the shifts from normal to abnormal laboratory values. As discussed above an analysis of central tendency and outliers was not feasible because of the limitation by the size of database and duration of exposure.

Table 7.1.7.3.2.1 Hematology test value shifts from normal to abnormal

Study 1105 and 1106	*Number of Subjects (%)*			
Laboratory Parameter (Units)/Shift	***Placebo (N = 128)***	***15mg MR (N = 127)***	***30mg MR (N = 126)***	***10mg IR TID (N = 123)***
Hematocrit (%)				
From Normal to Low	4 (3.1%)	1 (0.8%)	3 (2.4%)	2 (1.6%)
Hemoglobin (g/dL)				
From Normal to Low	4 (3.1%)	1 (0.8%)	4 (3.2%)	0
From Normal to High	0	0	1 (0.8%)	1 (0.8%)
Monocytes (%)				
From Normal to Low	1 (0.8%)	0	0	1 (0.8%)
From Normal to High	1 (0.8%)	0	1 (0.8%)	0
Total neutrophils (%)				
From Normal to Low	0	0	0	0
From Normal to High	0	0	0	1 (0.8%)
Platelet count (103/mm3)				
From Normal to Low	1 (0.8%)	1 (0.8%)	1 (0.8%)	0
From Normal to High	1 (0.8%)	3 (2.4%)	5 (4.0%)	4 (3.3%)
Red blood cells (106/mm3)				
From Normal to Low	8 (6.3%)	1 (0.8%)	6 (4.8%)	2 (1.6%)
From Normal to High	0	0	1 (0.8%)	2 (1.6%)
White blood cells (103/mm3)				
From Normal to Low	1 (0.8%)	0	0	1 (0.8%)
From Normal to High	4 (3.1%)	4 (3.1%)	2 (1.6%)	3 (2.4%)

Refer to Table 5.7-3 in Volume 60 of the NDA submission.

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Table 7.1.7.3.2.2 Chemistry test value shifts from normal to abnormal

Study 1105 and 1106	*Number of Subjects (%)*			
Laboratory Parameter (Units)/Shift	*Placebo (N = 128)*	*15mg MR (N = 127)*	*30mg MR (N = 126)*	*10mg IR TID (N = 123)*
Alanine aminotransferase (SGPT/ALT) (U/L)				
From Normal to High	2 (1.6%)	4 (3.1%)	5 (4.0%)	3 (2.4%)
Alkaline phosphatase (IU/L)				
From Normal to High	1 (0.8%)	0	2 (1.6%)	1 (0.8%)
Aspartate aminotransferase (SGOT/AST) (U/L)				
From Normal to High	1 (0.8%)	3 (2.4%)	3 (2.4%)	2 (1.6%)
Blood urea nitrogen (BUN) (mg/dL)				
From Normal to Low	0	0	1 (0.8%)	1 (0.8%)
From Normal to High	0	1 (0.8%)	0	0
Calcium (mg/dL)				
From Normal to Low	1 (0.8%)	0	3 (2.4%)	1 (0.8%)
From Normal to High	0	0	1 (0.8%)	0
Chloride (mEq/L)				
From Normal to Low	1 (0.8%)	5 (3.9%)	8 (6.3%)	3 (2.4%)
From Normal to High	0	0	0	1 (0.8%)
Creatine phosphokinase (IU/L)				
From Normal to Low	0	0	1 (0.8%)	1 (0.8%)
From Normal to High	7 (5.5%)	8 (6.3%)	12 (9.5%)	8 (6.5%)
Creatinine (mg/dL)				
From Normal to Low	1 (0.8%)	0	0	1 (0.8%)
From Normal to High	0	1 (0.8%)	1 (0.8%)	0
Glucose (mg/dL)				
From Normal to Low	1 (0.8%)	4 (3.1%)	5 (4.0%)	6 (4.9%)
From Normal to High	8 (6.3%)	5 (3.9%)	9 (7.1%)	4 (3.3%)
Lactic dehydrogenase (U/L)				
From Normal to High	6 (4.7%)	2 (1.6%)	6 (4.8%)	0
Potassium (mEq/L)				
From Normal to Low	0	2 (1.6%)	4 (3.2%)	1 (0.8%)
From Normal to High	1 (0.8%)	0	1 (0.8%)	0
Sodium (mEq/L)				
From Normal to Low	3 (2.3%)	4 (3.1%)	7 (5.6%)	4 (3.3%)
Total bilirubin (mg/dL)				
From Normal to High	1 (0.8%)	0	1 (0.8%)	1 (0.8%)
Uric acid (mg/dL)				
From Normal to Low	0	0	2 (1.6%)	1 (0.8%)
From Normal to High	2 (1.6%)	1 (0.8%)	6 (4.8%)	2 (1.6%)

Refer to Table 5.7-6 in Volume 60 of the NDA submission.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

There were 2 cases of marked increase in liver enzyme at study termination: increase in SGOT from 60 to 263 and SGPT from 90 to 300 in a placebo patient and increase in SGOT from 13 to 124 and SGPT from 18 to 112 in a patient on 15mg MR. The abnormal laboratory findings reported as AEs were all classified as mild in study 1105 and as moderate in 3 cases and severe in one case in study 1106. Only one abnormal laboratory findings, the increased blood creatine phosphokinase appeared on the list of reasons for early termination from the study.

7.1.7.4 Additional analyses and explorations

Again the database was not sufficient for analysis of dose-response or time dependency, drug-demographic, drug-disease, and drug-drug interactions.

7.1.7.5 Special assessments

Not suggested by data provided.

7.1.8 Vital Signs

Vital signs, including standing and sitting measurements of blood pressure and pulse rates were recorded at baseline, day 4, 8, and 14 in the two 14-day, placebo-controlled studies. Based on the group means there was not a clear pattern to suggest a dose response in terms of the proportion of patients with changes in blood pressure measurements. The increased standing and sitting pulse rates were recorded in more patients at the study termination than on day 4 and 8 cross the study groups and more in the active treatment groups than in the placebo group on day 4, 8, and 14. Tachycardia was listed as an AE leading to early termination in one patient on 10mg IR TID. Orthostatic hypotension was associated with 2 cases of dropouts from the 10mg IR group. Hypotension was reported as AE in one dropout case for the 15mg MR group.

7.1.8.1 Overview of vital signs testing in the development program

Refer to section 7.1.8.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Refer to section 7.1.8.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Refer to section 7.1.8.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Refer to section 7.1.8.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Refer to section 7.1.8.

7.1.8.4 Additional analyses and explorations

Refer to section 7.1.8.

7.1.9 Electrocardiograms (ECGs)

About one quarter of patients in each treatment group in the two 14-day, placebo-controlled studies had abnormal EKG. The incidence of shifts from normal at screening to abnormal at termination occurred in 7% of patients in the placebo group, 3% in the 15mg MR group, 8% in the 30mg MR group, and 3% in the 10mg IR TID group. Most were considered non-clinically significant EKG changes in the investigator's opinion, but the type of these EKG abnormalities were not described in the submission. The clinically significant EKG changes are listed below:

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Table 7.1.9 Clinically significant EKG findings

	Placebo (N = 128)	*15mg MR (N = 127)*	*30mg MR (N = 126)*	*10 mg IR TID (N = 123)*
Study 1105	One case of sinus tachycardia			
	One case of nonspecific T-wave changes			
Study 1106	One case of new onset atrial fibrillation at termination	One case of left ventricular hypertrophy at screening that returned to normal at termination	One case of sinus tachycardia, supraventricular extra systoles, and abnormal inferior and lateral ST-T changes at termination.	

In the PK studies the shifts from normal EKG at screening to abnormal ones at termination occurred in three (4.4%) subjects in the single-dose study and in two (5.6%) subjects in the 7-day study. Also, four (11%) subjects had abnormal EKG at screening that remained abnormal at termination in the 7-day study. None of the cases were considered clinically significant based on the investigator's evaluation.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Refer to section 7.1.9.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Refer to section 7.1.9.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Refer to section 7.1.9.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Refer to section 7.1.9.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Refer to section 7.1.9.

7.1.9.4 Additional analyses and explorations

Refer to section 7.1.9.

7.1.10 Immunogenicity

No data were available.

7.1.11 Human Carcinogenicity

There were no long-term exposure data for evaluation of human carcinogenicity. (Non clinical carcinogenicity studies were not required for the MR formulation.)

7.1.12 Special Safety Studies

There were no special safety studies of the modified-release formulation.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Potential for drug abuse and dependence/withdrawal was not evaluated in the current NDA. It has been described in the Flexeril labeling, "Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when FLEXERIL 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." Based on the postmarketing experience with Flexeril complete suicide and intentional drug overdose were the most frequently reported AEs (refer to section 7.2.2.2)

7.1.14 Human Reproduction and Pregnancy Data

There were 2 reports of pregnancies in study 1106. The first case was a 22-year-old Hispanic female on **placebo**, who had negative urine pregnancy test at screening, was on Yasmin oral contraceptive pill during the study, and was found pregnant by the termination urine pregnancy test after 13 days of treatment. The second case was a 27-year-old African American female on **10mg IR TID**, who had negative urine pregnancy tests at screening and termination visits, was using condoms with spermicide as the method of contraception during the study, and was detected pregnant 2 weeks after the completion of the study. The conception probably occurred about a few days after the start of treatment based on the calculation of the date of last menstrual period. Both patients delivered full-term healthy babies according to the 120-day safety update reports.

Cyclobenzaprine HCl was not genotoxic based on the findings from 3 genotoxicity studies discussed in the pharmacology/toxicology review.

7.1.15 Assessment of Effect on Growth

There were no pediatric studies.

7.1.16 Overdose Experience

There were no reports of overdose in the NDA studies.

7.1.17 Postmarketing Experience

The extended-release formulation has not been approved for marketing in the U.S. or abroad.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Six of the seven studies conducted (1102, 1103, 1107, 1104, 1105, and 1106) were used as primary clinical data source for the evaluation of drug exposure and safety. Study 1101 was not included as primary data source because a discontinued formulation of 30mg MR was studied in 12 healthy volunteers (refer to section 7.2.2.1).

7.2.1.1 Study type and design/patient enumeration

There were 4 phase I pharmacokinetic (PK) studies, all of which were of 2-period crossover design. Three PK studies were single-dose trials investigating dose proportionality between the 15mg MR and 30mg MR doses, food effect tested at 30mg MR, and relative bioavailability between 30mg MR QD and 10mg IR TID. One PK study was one-week multiple-dose trial investigating relative bioavailability between 30mg MR QD and 10mg IR TID. There were 2 phase III efficacy studies of identical design: randomized, double-blind, placebo and active-controlled, 4-arm, parallel, 14-day multiple-dose studies of dose response between the 15mg MR and 30mg MR doses.

As shown in the summary table below a total of 608 subjects had been included in the safety database, 68 in the single-dose (or first day dosing) PK trials, 36 in the 7-day PK study, and 504 in the two 14-day studies. There were 128 patients exposed to at least one dose of placebo, 143 exposed to at least one dose of 15mg MR, 230 exposed to at least one dose of

30mg MR, and 195 exposed to at least one dose of 10mg IR (the total should exceed 604 because subjects received more than one treatments in the PK studies of crossover design). More details about the duration of exposure will be discussed in section 7.2.1.3.

Table 7.2.1.1 Overview of study type and design and patient enumeration

Study number/ type/investigator	***Study design***	***Study population by eligibility***	***Treatment dosage/duration***	***# of subjects per treatment***
1102 Dose proportionality Gutierrez (USA)	Randomized, double-blind, two-period crossover	Healthy male and female volunteers ages 18 to 40	15mg MR or 30mg MR as a single am dose in each dose period	16 (8/sequence)
1103 Food effect PK study Gutierrez (USA)	Randomized, open-label, two-period crossover with or without food	Healthy male and female volunteers ages 18 to 40	30mg MR given fasted or fed in each dose period	16 (8/sequence)
1107 One-day Relative bioavailability Gutierrez (USA)	Randomized, open-label, two-period crossover	Healthy male and female volunteers ages 18-45 and 65-75	30mg MR single am dose or 10mg IR TID for 1 day in each dose period	36 (18/sequence)
1104 7-day relative bioavailability Gutierrez (USA)	Randomized, double-blind, multiple-dose, two-period crossover	Healthy male and female volunteers ages 18 to 75	30mg MR or 10mg IR TID for 7 days in each dose period	36 (18/sequence)
1105 Efficacy study 31 centers (USA)	Randomized, double-blind, placebo and active-controlled, 4-arm parallel, 14-day multiple-dose	Patients with moderate to severe pain due to muscle spasms secondary to acute, painful musculoskeletal conditions	15mg MR 30mg MR 10mg IR TID Placebo for 14 days	64 64 62 64
1106 Efficacy study 35 centers (USA)	Randomized, double-blind, placebo and active-controlled, 4-arm parallel, 14-day multiple-dose	Patients with moderate to severe pain due to muscle spasms secondary to acute, painful musculoskeletal conditions	15mg MR 30mg MR 10mg IR TID Placebo for 14 days	63 62 61 64

Refer to Table 2.1-1 in Volume 60 of the NDA submission.

7.2.1.2 Demographics

The mean age of the study population across studies was close to 40 years and was mostly below 65 years. Elderly was only enrolled in one single-day study 1107 (18 subjects or 50% study population) and accounted for <5% of the efficacy trial population. There were

more females than males in general. More than 90% of the PK study population and about 80% efficacy study population were Caucasian.

Table 7.2.1.2 Overall demographics

Study	*1-day studies 1102, 1103, 1107*	*7-day study 1104*	*14-day studies 1105 and 1106*			
Number of subject	*N = 68*	*N = 36*	*Placebo (N = 128)*	*15mg MR (N = 127)*	*30mg MR (N = 126)*	*10 mg IR TID (N = 123)*
Age (years)						
Mean ± SD	41.4 ±18.12	37.3 ±10.33	41.6 ±12.96	38.6 ±12.77	39.9 ±13.33	40.7 ±12.69
Min, Max	18, 73	19, 59	19, 73	18, 70	18, 74	18, 74
Age group--N (%)						
18 – 64	50 (73.5%)	36 (100.0%)	123 (96.1%)	124 (97.6%)	122 (96.8%)	118 (95.9%)
≥65	18 (26.5%)	0	5 (3.9%)	3 (2.4%)	4 (3.2%)	5 (4.1%)
Gender--N (%)						
Female	41 (60.3%)	23 (63.9%)	69 (53.9%)	75 (59.1%)	60 (47.6%)	69 (56.1%)
Male	27 (39.7%)	13 (36.1%)	59 (46.1%)	52 (40.9%)	66 (52.4%)	54 (43.9%)
Ethnic origin--N (%)						
Caucasian	62 (91.2%)	36 (100.0%)	104 (81.3%)	98 (77.2%)	101 (80.2%)	99 (80.5%)
Black	6 (8.8%)	0	10 (7.8%)	13 (10.2%)	16 (12.7%)	16 (13.0%)
Hispanic	0	0	13 (10.2%)	12 (9.4%)	6 (4.8%)	5 (4.1%)
Asian	0	0	0	4 (3.1%)	2 (1.6%)	3 (2.4%)
Other	0	0	1 (<1%)	0	1 (<1%)	0
Weight (kg)						
Mean ± SD	70.0 ±10.62	68.7 ±9.35	87.0± 24.55	84.1 ±22.27	85.9 ±22.45	81.6 ±20.02
Height (cm)						
Mean ± SD	165.3 ±10.27	163.6 ±7.37	171.6 ±11.59	169.4 ±10.14	171.6 ±11.05	170.3 ±9.40

Refer to Table 4.2-1 and 5.2-1 in Volume 60 of the NDA submission.

7.2.1.3 Extent of exposure (dose/duration)

As shown in the table below the mean duration of exposure was about 7 days in the 7-day PK study and was about 12 days cross study groups in the two 14-day studies. The maximum exposure to 30mg MR was at least a single dose in 230 patients and 9-14 days of

dosing in 99 patients (83 of 99 were completers of the 14 day study). The maximum exposure to 15mg MR was at least a single dose in 143 patients and 9-14 days of dosing in 104 patients (89 of 104 were completers of the 14 day study) (refer to section 7.1.3.1).

Table 7.2.1.3 Extent of multiple-dose exposure (dose/duration)

Study	*1104 (7-day study)*		*1105 sand 1106 (14-day studies)*			
Study group (#subjects)	*30mg MR (N = 36)*	*10 mg IR TID (N = 34)*	*Placebo (N = 128)*	*15mg MR (N = 127)*	*30mg MR (N = 126)*	*10 mg IR TID (N = 123)*
Duration of Exposure (days)						
Mean ± SD	6.9 ±0.33	7.0 ±0.00	11.6 ±4.64	12.4 ±3.80	11.8 ±4.52	11.4 ±4.50
Range (days)						
1 – 4	0	0	21 (16.4%)	10 (7.9%)	16 (12.7%)	18 (14.6%)
>4 – 8	36 (100.0%)	34 (100.0%)	6 (4.7%)	9 (7.1%)	11 (8.7%)	12 (9.8%)
>8	0	0	98 (76.6%)	104 (81.9%)	99 (78.6%)	91 (74.0%)

Refer to Table 4.4-1 and 5.4-1 in Volume 60 of the NDA submission.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

In the single-day PK trial 1101, where a discontinued MR formulation was used for comparison with Flexeril, 12 subjects were exposed to a single dose of 30mg MR and 3 doses Flexeril 10mg, in a crossover fashion. There were no reports of AEs or AEs associated with laboratory test changes. None of the abnormal laboratory test results were considered clinically significant findings. One subject had a normal to abnormal shift in EKG (abnormal left axis deviation), which was not considered clinically significant.

7.2.2.2 Postmarketing experience

The Division of Drug Risk Evaluation provided two reviews of serious adverse events associated with the use of the immediate-release formulation of cyclobenzaprine, a 1999 review and a 2005 update, respectively. The 1999 postmarketing safety review identified 72 unduplicated fatal cases, mostly confounded by underlying disease (28) and/or concomitant medication (12), or due to intentional drug overdose (25), especially, the overdose with multiple drugs. The serious AE reported in the literature were primarily CNS-related, which included drug-induced central hyperthermic syndrome similar to the neuroleptic malignant syndrome and psychotic symptoms (delirium, depersonalization, derealization, disorientation, illusions, and hallucinations). There was also a literature case report of QTc interval prolongation and one case of cognitive and neurological impairment,

both were suspected of secondary to drug-drug interactions. The most frequently reported AEs with serious outcomes in the AERS system were non-accidental overdose (39), hallucinations (38), confusion (35), suicide attempt (25), tachycardia (24), overdose NOS (22), and sedation (22). Both accidental overdose and deliberate overdose were among the most frequently reported serious AEs. Elderly had greater reporting frequency of serious CNS AEs than younger patients, e.g., 83% dementia, 53% delirium, 50% hallucinations, 38% hepatitis, 37% confusion, 30% dizziness, 28% urinary retention, and 25% agitation cases with serious outcomes were reported in the elderly.

The 2005 postmarketing safety update reviewed 235 reports of fatal cases (duplicated cases were not excluded), of which 230 involved drug overdose, mostly of multiple drug overdose. Four of the remaining 5 cases were confounded by serious underlying disease and/or concomitant medication. The fifth case had very limited information. The causal relationship of cyclobenzaprine in all these cases was inconclusive. The serious AE reported in the literature were cases related to psychosis, hallucination, and cyclobenzaprine-alcohol drug interaction. The most frequently reported AEs with serious outcomes in the AERS system were completed suicide (81), multiple drug overdose (57), intentional drug overdose (46), coma (44), overdose (42), accidental overdose (38), cardio-pulmonary arrest (26), drug toxicity (26), drug interaction (22), hypotension (21), cardiac arrest (20), toxicology test abnormal (20), heart rate increased (19), drug screen positive (18), convulsion (17), loss of consciousness (17), agitation (16), hallucination (16), medication error (16), and vomiting (16). Suicide and drug overdose, both intentional and accidental, were on the top of the list of the most frequently reported serious AEs.

7.2.2.3 Literature

According to the literature review by the Division of Drug Risk Evaluation 16 of 45 references retrieved had discussions about AEs in the 1999 review and 3 of 18 references retrieved had discussions about AEs in the 2005 review update. The findings have been briefly described in the section above (refer to section 7.2.2.2).

7.2.3 Adequacy of Overall Clinical Experience

The data in the submission were not considered adequate to address safety concerns with the use of the modified-relief product from both a pharmacokinetic and a clinical perspective. The Sponsor had not provided adequate information on steady state characterization of 30mg MR in a representative sample population, including elderly. There was not an adequate comparison of relative bioavailability between 30mg MR and Flexeril 10mg TID for the initial dosing day and at steady state in the representative population (refer to section 5). Because cyclobenzaprine 30mg MR had not been shown to

be bioequivalent to the approved product Flexeril during the initial 24 hours of drug administration or at steady state, safety information on Flexeril could not be used as supportive evidence to meet the exposure requirements for the MR formulation. The safety information based on the limited exposure of only about 100 subjects exposed to the 30mg MR for 9 to 14 days was not considered sufficient to address safety concerns with repeated dosing at 30mg MR. The under representation of elderly in the multiple-dose PK study (1 of 36 subjects enrolled in the age group of 55-65 and none in the age group >65) and clinical studies (7 of 253 patients received 15mg and 30mg MR for 14 days) raised additional safety concerns about the use of the MR product in this target subpopulation particularly vulnerable to drug-related toxicities.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Non-clinical studies were considered adequate according to pharmacology/toxicology review.

7.2.5 Adequacy of Routine Clinical Testing

It is considered acceptable to have routine clinical testing at screening and study termination and AE monitoring during the study and followed for three weeks after the termination of the study in these short-term clinical studies.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

There were no studies of drug metabolism or interactions in the current submission. The Sponsor described drug metabolism and elimination by referencing to the literature reports and Flexeril® labeling. The enzymatic pathways responsible for the clearance of Flexeril® have been described in the labeling. However, there were no statements about the effects on Flexeril concentrations by other drugs that inhibit or induce P450 subenzymes involved in the Flexeril metabolism. It has not been studied whether Flexeril will induce or inhibit P450 subenzymes and change the rate of metabolism of other drugs.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

There are **formulation-related safety concerns** with prolonged half life and higher level of drug accumulation associated with repeated dosing of the MR product in comparison to the IR product. Two-week exposure was too short to investigate the clinical impact of the MR based PK characteristics.

The impact of the MR formulation-related AE was not adequately studied in the **elderly**, who were already at a much higher risk for CNS AEs starting even at just 5mg IR as reported from postmarketing experience.

The effect of cyclobenzaprine HCl on **QTc interval** had not been adequately studied. There had been literature case report on QTc prolongation associated with the concomitant use of Flexeril and fluoxetine. In the current submission most of the individual data about the treatment emergent EKG abnormalities, other than those identified as clinically significant by the Sponsor, were not available for review.

Intentional drug overdose was one of the most frequently reported AE associated with the use of Flexeril based on post-marketing experience. However, the Sponsor had not made the effort to study **abuse potential** of cyclobenzaprine HCl.

The clinical impact of the predicted higher levels of drug accumulation due to the modified release feature should be evaluated in a sufficiently large and representative population that includes adequate number of elderly patients. The study should have adequate control and sufficient duration to allow assessment of time dependency of the adverse events. The effect of cyclobenzaprine HCl on QTc interval and its potential for drug abuse should all be evaluated.

7.2.8 Assessment of Quality and Completeness of Data

There were no descriptions of the treatment emergent EKG abnormalities for the cases not judged as clinically significant.

7.2.9 Additional Submissions, Including Safety Update

The 120-day safety update was focused on comparing the incidence of the most common AEs, especially, somnolence/drowsiness, dry mouth, and dizziness, reported by patients on MR treatment in the current NDA, to those associated with the use of Flexeril as reported in the literature. The Sponsor cited 3 references as the database for comparison: a systematic review of the comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions by Chou et al (J Pain Symptom Manage 2004;28:140-75), a meta-analysis of cyclobenzaprine for back pain by Browning et al (Arch Intern Med 2001;161:1613-20), and a report of two placebo-controlled studies not covered in the other 2 references.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The most commonly AEs reported by noticeable more patients on active treatments than placebo were mostly CNS and GI symptoms such as somnolence, dizziness, dry mouth, nausea, constipation, and dyspepsia. Somnolence, dizziness, and dry mouth were the leading cause of AE-related dropouts. There appeared to be a dose response in the incidence of somnolence, dry mouth, dizziness, dyspepsia, and constipation and in the dropout rates due to AE in general.

The database was limited by short duration of exposure and small sample size (9 to 14-day exposure in about 100 patients on each dose level), and under representation of elderly patients (<5% of the study population).

Because of these important data limitations and the lack of evidence for single-day or steady state bioequivalence the relative safety of using the MR product at the recommended dosage in the target population could not be determined.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The safety data were pooled from the two studies of identical design and almost identical sample size because of the small study populations and low frequency of AE reports.

7.4.1.2 Combining data

The numerator events and the denominator risk population were just simply combined for the reasons mentioned above (refer to section 7.4.1.1).

7.4.2 Explorations for Predictive Factors

Time dependency of AE, drug-demographic, drug-disease, and drug-drug interactions could not be explored adequately because of the short-term exposure in a very small and basically non elderly study population.

7.4.2.1 Explorations for dose dependency for adverse findings

Refer to section 7.3.

7.4.2.2 Explorations for time dependency for adverse findings

Refer to section 7.3.

7.4.2.3 Explorations for drug-demographic interactions

Refer to section 7.3.

7.4.2.4 Explorations for drug-disease interactions

Refer to section 7.3.

7.4.2.5 Explorations for drug-drug interactions

Refer to section 7.3.

7.4.3 Causality Determination

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen of cyclobenzaprine HCl at 15mg and 30mg a day had not been demonstrated as efficacious. Dose-related toxicities had been shown in rates of dropouts due to AEs and in most commonly reported adverse events such as somnolence/drowsiness, dizziness, and dry mouth.

When there is sufficient evidence to support efficacy at these dose levels, the minimum effective dose should be recommended and the daily dose should be taken at bed time to minimize dose-related toxicities and daytime drowsiness.

The actual use pattern of Flexeril, in terms of how often and how long patients are actually taking the medication, should be investigated to determine the extent of off-label use and to _____ Elderly patients who have more problems with drug accumulation and are already at higher risks for CNS toxicities and their complications,

should be studied to determine the effective and safe doing regimen for the vulnerable population.

8.2 Drug-Drug Interactions

Drug-drug interactions should be studied based on the information known about the enzymatic pathways of drug metabolism for Flexeril. Drugs known to either induce or inhibit subtypes of P450 enzyme: 3A4, 1A2, or 2D6 should be examined for if they change the concentration of cyclobenzaprine HCl and the clinical impact of such changes. The potential inhibition or induction effect of cyclobenzaprine HCl on P450 subenzymes should also be explored to determine the need for studying metabolic enzyme-dependent drug-drug interactions.

8.3 Special Populations

The effect of the modified-release formulation-dependent further increase in drug accumulation upon repeated dosing in the elderly, who already had the age-related prolonged (from 32 to 49 hours in half life) and increased level of exposure (from 750 to 1055ng·hr/mL in total concentration from the one-day study), had not been evaluated (one subject in the age group of 55 to 65 years and none in the age group above 65 years in the seven-day pharmacokinetic study). Elderly had a greater reporting frequency of central nervous system adverse events with serious outcomes than younger patients based on the post-marketing experience with Flexeril even though [redacted] Nevertheless, elderly was under represented in the clinical trials that only 7 of the 253 patients (2.8%) who received modified-release treatments at 15mg and 30mg level in the 14-day trials were elderly patients. The limited choice of dosage of 15mg or 30mg once a day for MR formulation makes it impossible to start at a very low dose level and titrate slowly upward and thus, making the formulation less favorable for the elderly.

Patients with mild hepatic impairment were reported to have doubling of the maximum and total concentrations with Flexeril. The effect of formulation-dependent further increase in drug accumulation should be studied in this subpopulation which was already at much higher risks for drug induced toxicities.

8.4 Pediatrics

The Sponsor requested for a waiver of pediatric studies for the reasons that there is no intended use of the product in the pediatric patients and the modified-release dosage form offers no enhanced benefits to the pediatric population (refer to the submission dated January 22, 2005).

8.5 Advisory Committee Meeting

An Advisory Committee meeting to discuss issues associated with the use of MR product has not been planned. There was a joint Advisory Committee meeting between the Nonprescription Drug Advisory Committee and the Arthritis Advisory Committee held on July 20, 1999 for the discussion of issues associated with the proposed OTC switch of Flexeril 5mg dose.

8.6 Literature Review

Refer to sections 7.2.2.2, 7.2.2.3, and 7.2.9 for discussions.

8.7 Postmarketing Risk Management Plan

[redacted]

8.8 Other Relevant Materials

The use of the proprietary name, Amrix™ was considered acceptable according to the recommendations by Division of Medication Errors and Technical Support.

9 OVERALL ASSESSMENT

9.1 Conclusions

Bioequivalence between cyclobenzaprine HCl modified release and Flexeril had not been demonstrated during the initial 24-hour exposure or at steady state. Steady-state Pharmacokinetic profile of the cyclobenzaprine HCl MR formulation had not been fully characterized (refer to section 5 for detail). The extent of the formulation-related prolongation in half life and the extent of increase in drug accumulation after repeated dosing had not been studied in the special population such as elderly or patients with hepatic impairment (refer to section 5 and 8.3). Pharmacokinetic interactions between cyclobenzaprine and other drugs with respect to their role as a substrate, inducer, or inhibitor of P450 subenzymes had not been studied (refer to section 7.2.6 and 8.2).

None of the proposed dosing regimen, 15mg MR or 30mg MR to be given once a day, had been demonstrated as efficacious based on the findings from each of the two clinical studies (refer to section 6 for detail).

The safety data based on the findings in the sample populations consisted of mostly non elderly patients, suggested the use of cyclobenzaprine is associated with dose-related CNS and GI symptoms, especially, somnolence/daytime drowsiness, dizziness, and dry mouth. The post marketing experience with Flexeril suggested that suicide, drug overdose, drug-drug interactions, serious adverse events of central nervous system and cardiovascular system, and drug-induced hepatic injuries are of potential safety concerns in the general population. The safety of using the MR product at the recommended dosage in the target population could not be adequately assessed due to the deficiency in demonstrating bioequivalence between the MR formulation and the approved IR formulation, insufficient safety database (small samples with minimum elderly enrollment), lack of longer-term exposure data (to address safety concerns about the clinical impact of formulation-dependent drug accumulation), and omission of the special population studies. In addition, there were no assessments of QTc prolongation, abuse potential, and drug-drug interactions, and not an adequate risk management plan (refer to sections 7.2, 8.2, 8.3, and 8.7).

The efficacy and safety data in the current NDA were not sufficient to support the market approval of the cyclobenzaprine HCl modified-release product.

As suggested by data there is questionable usefulness of the MR formulation (longer time to reach steady state and more concerns with drug accumulation) in treating an acute medical condition, which has a high rate of spontaneous recovery upon rest and physical therapy. There were findings of significant treatment differences from placebo in day time drowsiness across dose levels in both studies where efficacy could not be demonstrated for 15mg MR, and findings of dose-related toxicities in the same studies. There was the uncertainty about bioequivalence between the to-be-marketed MR formulation and approved IR formulation and the uncertainty about the extent of accumulation in peak concentration at steady state and their impact on the elderly and hepatic impaired. There were safety concerns with the increasing trend in intentional and unintentional overdose with serious outcomes from postmarketing experience with Flexeril®. The formulation allowed much lesser flexibility in terms of starting dose (15mg instead of 5mg) and upward dose titration (15mg increment instead of 5mg increment). Taking all these into consideration the treatment did not appear to have a favorable benefit risk ratio in the medical reviewer's opinion.

9.2 Recommendation on Regulatory Action

The Sponsor needs to conduct further studies to support the efficacious and safe use of cyclobenzaprine HCl modified-release at the recommended dosage in the target population to obtain the market approval of the product.

9.3 Recommendation on Postmarketing Actions

Recommendation on postmarketing actions is pending on the amount of data available at the time of drug approval.

9.3.1 Risk Management Activity

[redacted]

9.3.2 Required Phase 4 Commitments

Required phase 4 commitments will depend on future study results.

9.3.3 Other Phase 4 Requests

Phase 4 requests will depend on future study results

9.4 Labeling Review

Labeling Review will be postponed until there are sufficient data to support efficacy and safety with the use of the MR product.

9.5 Comments to Applicant

1. Because substantial evidence of efficacy has not been demonstrated you are required to provide positive results to show statistically significant and clinically meaningful treatment differences in support of treatment effects on muscle spasm and its major symptoms and signs and functional impairment through the entire treatment period for both 15mg and 30mg levels.

2. In order to address safety concerns associated with the predicted further increase in peak concentration upon repeated dosing with MR as a result of drug accumulation, you are required to either demonstrate bioequivalence to Flexeril® during the initial day of dosing and at steady state, or provide safety data of sufficient size and duration from the studies of the target population.

3. Pharmacokinetic (PK) and safety data are required to address safety concerns about the impact of modified-release on the vulnerable subpopulations and to support the proposed dosing regimen for the safe use of the product in the elderly and patients with hepatic insufficiency.

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10 APPENDICES

10.1 Review of Individual Study Reports

The original protocols of the two clinical studies were reviewed in detail as Special Protocol Assessment dated October 3, 2002. The Sponsor submitted one protocol amendment dated November 26, 2002, to address comments by the Division. The important components of the protocol are summarized in section 6.1.2 and 6.1.3 of this review. The results of the studies have been discussed in detail in terms of disposition in section 7.1.3.1, demographics in section 7.2.1.2, baseline characteristics and efficacy findings in section 6.1.4, and safety findings in section 7.1.

10.2 Line-by-Line Labeling Review

Labeling Review will be postponed until there are sufficient data to support efficacy and safety with the use of the MR product.

REFERENCES

The reviews and meeting minutes were all available in the electronic system of FDA.

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/s/

Christina Fang
2/28/05 05:20:38 AM
MEDICAL OFFICER

Sharon Hertz
2/28/05 10:46:33 AM
MEDICAL OFFICER
I concur with the findings and conclusions in this review.

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