

NONPRESCRIPTION DRUGS
ADVISORY COMMITTEE AND
ARTHRITIS ADVISORY
COMMITTEE

JULY 20, 1999

NDA 21070 FLEXERIL OTC
SWITCH

MEDICAL OFFICER REVIEW
HFD-550

**Flexeril MR Tablets
(cyclobenzaprine hydrochloride)**

DRAFT

NDA 21-070

Medical Officer Review

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Drug Name: Flexeril®MR

Generic Name: cyclobenzaprine hydrochloride

Applicant: Merck & Co., Inc.
West Point, PA 19486

Pharmacologic category: muscle relaxant

Proposed Indication: OTC management of acute painful muscle spasms
of the back and neck

Dosage forms and route: Oral capsule, 5 mg

Submission type: Original NDA

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(James Witter, M.D., Ph.D. Medical Officer)

Flexeril MR (Flex 5)

NDA 21-070

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Flexeril MR (Flex 5) Executive Summary

Significant Issues

- Three doses of cyclobenzaprine (2.5, 5.0 and 10.0 mg TID; referred to as Flex 2.5, Flex 5 and Flex 10, respectively) were studied in this NDA.
- If approved, Flex 5 would be the first over-the-counter use of cyclobenzaprine worldwide
- Results of efficacy endpoints, though statistically significant, were clinically modest. The placebo-controlled trials employed a "flare" design which should maximize any treatment effect.
- Since only single-use trials were conducted, it is unknown if repeat use of Flex 5 results in continued efficacy.

Highlights

- The placebo-controlled trials (006, 008) appear to support the conclusion that Flex 5 is efficacious. The degree of symptom improvement appears to be clinically modest but durable to the end of the trial. Higher doses of Flex do not seem to result in any substantial clinical (or statistical) improvement in efficacy. However, higher doses of Flex do increase the frequency of adverse events (all types).
- The pattern-of-use trial (009) does not appear to support the conclusion that Flex 5 is effective. Effectiveness, in this particular trial, was not shown because of lack of physician confirmation of patient self-diagnosis of muscle spasm and follow-up, lack of placebo control, and allowing the use of concomitant analgesics.
- It would appear useful, in any future effectiveness trials, to address the issue of "dose creep" by determining if there is continued efficacy with continued use of Flex 5. This has implications for the consideration of the safety of OTC use of Flex 5.

BACKGROUND AND OVERVIEW:

Muscle relaxants consist of a diverse group of drugs that have historically been used to treat low back pain (LBP); pharmacologic classes include benzodiazepines, sedative-hypnotics, antihistamines or antidepressant derivatives. The therapeutic objective of these drugs is to improve symptoms by relieving muscle spasms, however, the exact mechanism of action of these drugs is unknown. To date, all the muscle relaxants note in the **INDICATIONS** section of their labels wording to the effect that "X is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions."

Most of the drugs that fall into this group are fairly old products, having been approved in the 1960s and found to be effective under the DESI review. In the 1980s, several sponsors had contacted the FDA about the possibility of switching their products to the over-the-counter (OTC) market. At that time, the review division responsible for these products (Division of Neuropharmacological Drug Products; DNDP, HFD-120) issued a letter describing what would be required of sponsors having products that might be switched. These requirements consisted of the following trials:

- cognitive impairment,
- cognitive impairment and sedation in the elderly,
- large usage trial to mimic the actual OTC conditions, and
- pharmacologic (PK) trials conducted in
 - healthy volunteers
 - elderly patients with renal failure
 - cirrhotic patients.

Efficacy per se did not need to be proved if the drug was actually switched (same dose), since it was assumed that efficacy had been proven when the product was originally approved as a prescription product. However, **efficacy did need to be proven if a lower dose was being considered.** It was felt that the major obstacle to a switch was safety. Since that time, a number of sponsors have conducted trials and several products have been discussed during closed or open sessions of the advisory committee. The most recent discussion was a joint meeting of the Arthritis Advisory Committee (AAC) and the Non Prescription Drug Advisory Committee (NPDAC) on March 28, 1995.

Cyclobenzaprine, known chemically as 3-(5H -dibenzo[a,d]cyclohepten-5-ylidene)- N,N -dimethyl-1-propanamine hydrochloride, is structurally related to the tricyclic antidepressants. Because of its structural similarity to other tricyclic compounds used in treating depression, the drug was originally evaluated as an antidepressant. However, results of initial clinical trials performed during the 1960s and early 1970s failed to show any significant efficacy for the treatment of depression. Experimental studies performed later showed that cyclobenzaprine did, however, seem to possess skeletal muscle-relaxant activity. Controlled clinical investigations suggested that cyclobenzaprine 10 mg t.i.d.

significantly improved the signs and symptoms of skeletal muscle spasm as compared with placebo. The most frequent side effect of cyclobenzaprine was sedation which occurred in about 39% of patients receiving 10 mg t.i.d. in these clinical trials. Cyclobenzaprine appeared to produce clinical improvement, whether or not sedation occurred.

Although experimental studies have defined the possible mode of action of cyclobenzaprine in animals, the mechanism responsible for its muscle-relaxant activity in humans remains unknown. Cyclobenzaprine has no activity at the neuromuscular junction and no direct effect on skeletal muscle. It has been hypothesized that cyclobenzaprine provides relief by interrupting a self-reinforcing pathway of muscle spasm and local pain. When injury to a muscle occurs, stimulation of pain endings in the muscle and adjacent tissues may result, giving rise to afferent impulses to the brain and spinal cord. When such impulses, mediated by alpha motor neurons, reach the cerebral cortex, the perceived pain may lead to reflex contraction or voluntary muscle splinting. In addition, the tightening of muscle spindles by the unconscious activation of gamma efferents results in increased muscle tone. The prolonged tonic contraction produced by the continued augmentation of muscle tone by the gamma efferents in response to persistent pain serves to further aggravate pain by producing local ischemia and may perpetuate the spasm leading to more pain which may help establish a pain-spasm cycle. A centrally acting muscle relaxant such as cyclobenzaprine may break the cycle and hasten resolution of the condition.

The original application provided comprehensive preclinical safety data from a standard battery of animal studies. Because of the extensive clinical experience with the prescription dose, and the existing data from the original NDA, no further animal studies were conducted to support this application for nonprescription use; this was discussed at the pre-NDA meeting held on April 8, 1998.

The New Drug Application for prescription-strength FLEXERIL™ (cyclobenzaprine), NDA 17-821, was submitted on December 29, 1975 and subsequently approved by the FDA on August 26, 1977. It was approved "*as an adjunct to rest and physical therapy for the relief of muscle spasm, associated with acute, painful musculoskeletal conditions.*" The usual dosage of Flexeril is 10 mg TID with a range of 20 to 40 mg a day in divided doses. Merck is now seeking marketing authorization for a 5-mg nonprescription or OTC dose. This NDA application is intended to document the safety and efficacy of nonprescription strength cyclobenzaprine hydrochloride in patients with painful muscle spasm or strain of the back or neck.

The studies provided in NDA 21-070 to support this OTC switch application are noted in Table 1.

Table 1 : Flexeril OTC Clinical Studies¹

Protocol Number	Short Study Description
Clinical Pharmacology – Pharmacokinetic	
005	Open-label crossover study of single- and multiple-dose pharmacokinetics and dose proportionality of cyclobenzaprine in young healthy volunteers
007	Open-label multiple-dose parallel study of pharmacokinetics of cyclobenzaprine in hepatically impaired patients and healthy subjects
010	Open-label multiple-dose study of pharmacokinetics of cyclobenzaprine in elderly subjects
011	Open-label crossover bioequivalence/bioavailability study of cyclobenzaprine tablets made by 2 different processes
Psychomotor	
001	Double-blind, single-dose, crossover psychomotor study of cyclobenzaprine, diphenhydramine, and placebo in young subjects
002	Double-blind, multiple-dose, crossover psychomotor study of cyclobenzaprine in young subjects
003	Double-blind, multiple-dose, crossover psychomotor study of cyclobenzaprine, diphenhydramine, and placebo in elderly subjects
012	Double-blind, multiple-dose, crossover psychomotor study of cyclobenzaprine, diphenhydramine, clemastine, and placebo in young subjects
014	Double-blind, multiple-dose crossover study to compare effects of cyclobenzaprine, diphenhydramine, and amitriptyline on driving-related psychomotor skills in elderly subjects
015	Double-blind, multiple-dose crossover study to compare effects of cyclobenzaprine, diphenhydramine, and amitriptyline on driving-related psychomotor skills in young subjects
Phase 3	
006	Double-blind, multiple-dose, parallel-group efficacy and safety study in patients with acute skeletal muscle spasm
008	Double-blind, multiple-dose, parallel-group dose-confirmation-study in patients with acute skeletal muscle spasm
009	Open-label, multiple-dose, pattern-of-use study in patients with self-diagnosed muscle spasm

1. Three of the studies (001, 002, 003) were conducted in the United Kingdom; the other 10 were conducted in the United States. Each of the studies included orally administered cyclobenzaprine 5 mg.

Efficacy/Effectiveness Trials:

Reviewer's comment: This NDA review will focus on the phase 3 trials, 006 and 008, for efficacy. Study 009 will be primarily reviewed by OTC (Dr. Rosemarie Neuner), however, its efficacy components will be addressed in this review. Dr. Neuner's review will focus on the safety aspects of use of Flexeril MR, especially as they apply to the setting of OTC. The trails that addressed the sedative properties of cyclobenzaprine, studies 001, 002, 003, 012, 014 and 015, will reviewed by the Division of Neuropharmacological Drug Products (DNBP, HFD-120; Dr. Paul Andreason).

Summary of Protocols/Procedures:

The clinical study program for Flexeril MR was based on the hypothesis that Flex 5* for 7 days is more efficacious than placebo in treating patients with acute musculoskeletal spasm. This was based on their purported prior experience with a reduced dosage of Flexeril (i.e. 5 mg twice daily) where in two of three studies (May 1984-October 1985), Flexeril was superior to placebo by the physician's assessment of global improvement. However, the evaluations of the muscle spasm and local pain showed inconsistent results compared to placebo. It was, therefore, expected that a total daily dose of 15 mg of Flexeril (i.e. Flex 5) would be required to obtain clinically relevant efficacy.

**Reviewer's comment: In this review, Flex 2.5, 5 or 10 refers to Flexeril 2.5 mg, 5.0 mg or 10. 0 mg three times daily (t.i.d.), respectively.*

Since the basic design of trials 006 and 008 are similar, they will be described together with any important differences noted in the review. The three phase 3 studies are entitled as follows:

Protocol 006

"A Double-Blind, Placebo-Controlled, Dose Confirmation Study of the Safety and Efficacy of Two Dosage Regimens of FLEXERIL ® in Outpatients with Acute Skeletal Muscle Spasm."

Protocol 008

"A Multicenter, Double-Blind, Placebo-Controlled Replicative Pivotal Safety and Efficacy Study of Two Dosage Regimens of FLEXERIL™ in Outpatients with Acute Skeletal Muscle Spasm."

Protocol 009

"An Open-Label Study to Evaluate the Safety and Pattern of Use of FLEXERIL MR™ in Patients with Painful Muscle Spasm."

Although protocols 006 and 008 are placebo-controlled, randomized, double-blinded studies each with Flex 5 as one of the test treatments, there are some important differences as listed in Table 2.

Table 2: Differences in Design of Protocol 006 and 008¹

	Protocol 006	Protocol 008
FLEXERIL doses (mg)	5, 10	2.5, 5
Timing of Visit 2	Study Day 3 or 4 (within 72 hrs of 1st Dose)	Study Day 3 (within 48 hrs of 1st dose)
Duration of spasm pre-study	≤ 14 days	≤ 7 days
Stratification by pre-study duration of spasm	≤ 7, >7 days	≤ 3, >3 days
Number of sites enrolling patients	20	19

1. Both protocols, including 009, were conducted in the United States.

Since the sponsor felt that the results of these studies (006, 008) confirmed that the Flex 5 mg was safe and efficacious when used by patients with acute musculoskeletal spasm over 1 week of treatment, further development for OTC use was investigated. They felt it was necessary to evaluate how consumers would use the OTC product for self-diagnosed muscle spasm of the neck or back when provided with clear and easy-to-understand instructions. This "usage" trial (**protocol 009**) was, therefore, designed to test the hypotheses that consumers would use Flex 5 tablets according to appropriate dosing instructions, and that the OTC product would be generally well tolerated when taken according to the product label.

In contrast to protocols 006 and 008 where a 7-day regimen was used, dosing instructions were less directive in protocol 009, stating: "Take 1 tablet every 6 to 8 hours. Do not exceed 3 tablets in 24 hours. Do not take continuously for more than 7 days". The intent was to observe the typical duration of dosing followed by the patients. Accordingly, a 10-day supply of tablets was provided. Protocol 009 was, therefore, an open-label study designed to evaluate the safety and pattern of use of Flex 5 in subjects treating themselves for self-diagnosed painful muscle spasm.

In all these phase 3 trials, there were originally 56 principle investigators (PIs) involved; this was later reduced to 54 with the lose of two PIs (Fiddes from 008, Schwartz from 006). Some of the same PIs were involved in both protocol 006 and 008; all PIs in 009 were unique. Therefore, 14 of the PIs were the same in protocols 006 and 008 (or 6/20 PIs in 006 and 5/19 PIs in 008 were unique to these studies). However, two unique PIs from protocol 006 (see Table 8, below) were later discontinued.

Reviewer's comment: Discussion of protocol 009 will be added where deemed appropriate in this review.

Patient Selection:

Protocols 006 and 008:

These randomized, double-blind, parallel-group, placebo-controlled outpatient studies evaluated the safety, tolerability, and efficacy of 3 doses of cyclobenzaprine as noted in Table 2. Patients needed to have a physician-rating of moderate to moderately severe painful muscle spasm of the lumbar and/or cervical spine of ≤ 7 or 14 days duration (see Table 2).

As noted later in Table 3, patients had three study visits: Visit 1 (Baseline/Study Day 1), Visit 2 (Study Day 3, within 48 or 72 hours of first dose; see also Table 2), and Visit 3 (End of Treatment/Study Day 8). An effort was made to schedule each patient's visits at the same time of day and with the same physician at all visits. Prospective patients were instructed to discontinue acetaminophen use for 8 hours prior to presentation to the clinic, and any other analgesic, NSAIDs and muscle relaxants for 24 hours prior to presentation to the clinic for evaluation of inclusion and exclusion criteria.

Criteria for Inclusion in Protocols 006 and 008

- 1) Men and women ≥ 18 years of age.
- 2) Ability to cooperate, be reliable, and be of adequate intelligence to complete the diary.
- 3) Acute (≤ 7 days, P-008; ≤ 14 days, P-006), physician-rated moderate or moderately severe painful muscle spasm of the lumbar and/or cervical region.
- 4) Otherwise normal neurologic examination.
- 5) Ability to discontinue all analgesics and NSAID medications for the duration of the study.
- 6) Willingness to participate and provide written informed consent.

Criteria for Exclusion in Protocols 006 and 008

- 1) Duration of current episode of painful muscle spasm >7 days (P-008) or > 14 days (P-006).
- 2) Inability to discontinue analgesics, NSAIDs, and muscle relaxants for 24 hours prior to, and acetaminophen for at least 8 hours prior to, presentation to the clinic.
- 3) Participation in prior dose confirmation study of Flexeril or participation in any drug study within the preceding 30 days.
- 4) Vertebral body or spinous process percussive tenderness.
- 5) Unexplained constipation, diarrhea, or urinary retention.
- 6) Contraindication to the use of cyclobenzaprine (e.g., angle-closure glaucoma, hyperthyroidism, hypersensitivity to the drug, congestive heart failure, history of arrhythmias).
- 7) Current evidence of depression, psychosis, or alcohol or drug abuse.
- 8) Pending or likely workman's compensation case or other litigation related to the cause of the cervical or lumbar spasm.
- 9) Pregnant or nursing women.
- 10) Sustained systolic blood pressure >160 mm Hg or diastolic blood pressure >105 mm Hg at baseline.
- 11) Myocardial infarction within 1 year prior to the study.
- 12) Any situation or condition that in the investigator's opinion may interfere with optimal participation in the study.

Patients who met all study entry criteria were randomized to study medication. Eligible patients were assigned to the treatment groups according to a randomized allocation schedule. Allocation to study group was stratified based on duration of spasm at study entry (see Table 2). Randomized patients were "Patient Diary" cards and a bottle of drug. The bottle was labeled with instructions stating, "Take 1 tablet upon awakening, at approximately 2 PM and at bedtime." The bottle for each treatment group contained cyclobenzaprine 10, 5, or 2.5-mg tablets or a matching placebo.

As noted above, study medication was taken each day upon awakening, at approximately 2 PM and at bedtime with at least 6 hours between doses. The first dose was taken on Study Day 1, at the first dosing time after the patient was randomized. On Study Days 2 through 7, study medication was taken t.i.d. as prescribed. Study Day 8 was the final day of treatment; the morning dose was taken and, if the patient's clinic visit was after 2 PM, the 2 PM dose was also taken.

Prohibited medications/therapies:

All analgesics including NSAIDs, all psychotropic agents (e.g., antidepressants, antipsychotics), any prescription or OTC product known to produce sedation and any muscle relaxants were prohibited throughout both these studies. Nonpharmacologic therapies, except local application of heat, e.g., physical therapy, manipulation, ultrasound, external ointments, were also prohibited.

Protocol 009

Patient selection for this study, as noted by the sponsor, was consistent with all the warnings, precautions, and contraindications associated with the use of FLEXERIL MR™, as indicated in the product label. In addition, every effort was made to recruit patients from a variety of environments, targeting a broad base of consumers with acute muscle spasm. The inclusion and exclusion criteria for protocol 009 were as follows:

Criteria for *Inclusion* in Protocol 009

- 1) **Men and nonpregnant women, ≥18 years of age (or legal age of consent).**
- 2) **Women of childbearing potential who were practicing an acceptable method of birth control.**
- 3) **Patients must have been cooperative, reliable, and of adequate intelligence to complete the diary.**
- 4) **Patients must have believed they were experiencing painful muscle spasm, tightness, or soreness, due to strain, overexertion, and minor injuries to the back or neck.**
- 5) **Patients must have been in general good health.**
- 6) **Patients must have demonstrated a willingness to participate in the study as evidenced by written informed consent.**
- 7) **Only those patients who, in the opinion of the study coordinator or investigator, were motivated to participate were enrolled into the study.**

Criteria for Exclusion in Protocol 009

- 1) Participation in a previous FLEXERIL® study within the past 2 years or participation in any drug study within the past year.
- 2) Any contraindication to the use of FLEXERIL®. Patients should not have been taking any sedative, antidepressant, or tranquilizer while in the study. Patients refrained from alcoholic beverage consumption while in the study.
- 3) History of heart disease or thyroid problems.
- 4) Pending or likely workman's compensation case or other litigation related to the cause of the cervical or lumbar spasm.
- 5) Pregnant or nursing women.
- 6) Recent history of substance abuse (drug or alcohol), psychosis, or other condition that would have made the patient unlikely to comply with the protocol.

Study Design:

Protocols 006 and 008

The general schedule of clinical observations and clinical safety measurements for these protocols is outlined in Table 3.

Reviewer's comment: It is important to note that there were no laboratory measurements taken during these studies.

Table 3: Schedule of Clinical Observation in Protocol 006, 008¹

Observation	Clinic visit 1	Clinic visit 2	Clinic visit 3
	Baseline /Study day 1	Study day 3	End Treatment /Study Day 8
Evaluation of inclusion/exclusion criteria	X	-	-
Physical/neurologic exam	X	-	X
Vital signs	X	-	X
Patient (Pt) severity rating of backache	X	-	-
Physician severity rating of backache	X	-	-
Physician rating of spasm	X	X	X
Pt-rated clinical global impression of change ²	X	X	X
Pt rating of medication helpfulness ²	X	X	X
Pt diary (relief from starting backache) ^{2,3,6}	X	X	X
Adverse experiences ⁴	X	X	X
Study medication administration ⁵	X	X	X
Tablet counts	X	X	X

1. Clinic visit 1 was predose; clinic visit 2 was different as described in prior table; clinic visit 3 was day 8.
2. Primary efficacy endpoints
3. Evaluated after initiation of double-blind therapy, Study Days 1 through 7.
4. Began after study drug administration.
5. Doses (> 6 hours apart) taken upon awakening, at approximately 2 PM, and at bedtime.
6. The evaluation for efficacy occurred on study Day 3 (48-56 hours after the first dose) or Day 7 (prior to final physician assessments on day 8).

Protocol 009

This open-label, multicenter study evaluated patients' patterns of use when taking Flex 5 for self-diagnosed painful muscle spasm for up to 7 days. According to the sponsor, "In order to create a clinical study environment that reflected expected "actual use" of FLEXERIL MR™ in the OTC consumer population, patients were considered for enrollment if, by their own assessment, they felt they were experiencing painful muscle spasm, tightness, or soreness of the neck or back".

A total of 468 patients were enrolled in 15 U.S. investigative sites. All study sites were advised to use a variety of advertising media in their recruitment efforts, to reach a broad base of consumers. Advertising methods may have differed somewhat among sites, depending on the populations most accessible to an individual site's recruitment area (such as college health center notices, fitness center flyers, radio ads, newspapers, word-of-mouth, etc.). The method by which patients learned of the study, was collected at the baseline visit for all 468 patients enrolled. Individuals who responded to recruitment advertising believing they were experiencing painful muscle spasm, or tightness or soreness of the neck or back were asked to present to the clinic where patient history, inclusion/exclusion criteria, and informed consent were reviewed. If no contraindications to cyclobenzaprine use were identified at screening, patients were provided with study drug and a diary card that included the proposed OTC product label.

Reviewer's comment: The "chief complaint" of patients in this protocol were not included. Patients did not present, to this reviewer's knowledge, with the complaint that their back ache/tightness/soreness was due to a muscle spasm in the area of interest.

The protocol targeted a study enrollment of 440 patients. However, at the end of the enrollment period, 28 additional patients (across the 15 sites) were already scheduled for the first clinic visit and were permitted to complete the study.

In order to assess patient compliance, patients were asked to count the number of tablets dispensed to them at study start, and again upon the return of unused drug, in the presence of study personnel. For drug accountability purposes, this was documented on the patient's case report form. The label was not read or explained to the patients. Study staff instructed patients on the completion of the diary card for the purposes of recording drug use and adverse experiences. Professional intervention was otherwise kept to a minimum (i.e., **no physical examinations were performed to confirm the presence of muscle spasm**). There were **no restrictions imposed on study participants regarding prior or concomitant medication use**, diet or activities, other than those noted in the WARNINGS section of the product label which was:

WARNINGS:

Do not take FLEXERIL MR™ if:

- you are taking antidepressant medication.
- you have a history of heart attack or heart disease.
- you have a history of thyroid problems.

FLEXERIL MR™ may cause marked drowsiness.
Do not drink alcoholic beverages while taking this product.
Do not take this product if you are taking other medications that may cause drowsiness.
Avoid driving a motor vehicle or operating machinery while taking this product.

Staff were available by telephone throughout the study to answer any patients' questions regarding adverse events or concomitant drug use. If patients were unable to return to the clinic for the follow-up visit, study staff were permitted to make telephone contact and obtain follow-up information. While the study was in progress, additional questions were added to some case report forms to collect patients' occupations, activity impairment and avoidance of driving and/or operating machinery. This information was collected on approximately 225 of the 468 total study participants. These parameters were added to better characterize the impact of muscle pain and/or potential drug side effects on patients' normal daily activities.

Reviewer's comment: It is important to note that subjects in protocol 009 did not have their self diagnosis of muscle spasm as the potential source of their backache confirmed by a qualified physician. As noted above, there were no restrictions on the use of concomitant medications. Also, this was an open-label study.

Patients had two study visits: Visit 1 (Baseline/Day 1), at which time eligibility was assessed, informed written consent was obtained, and participants were instructed on the completion of a diary card and provided with the product label and a supply of study drug; and Visit 2 (Follow-up/Day 8 to 10), when patients returned unused study drug and the completed diary card. **In addition, at Visit 2 patients were asked to respond to an efficacy question regarding clinical global impression of change.**

Table 4 gives the schedule of clinical observations during protocol 009. Again, because this study was intended to evaluate actual use of the OTC product (where the consumer, not physician, would assess muscle pain/spasm and self-administer treatment), there was minimal intervention by health-care intermediaries. **Other than the review of eligibility criteria and the assessment of reported, nonsolicited adverse experiences, there were no clinical observations or laboratory measurements done.**

Table 4: Schedule of Clinical Observation in Protocol 009¹

Observation	Clinic visit 1	Clinic visit 2
	Baseline/Study day 1	Follow-up-Study day 8-10
Review of inclusion/exclusion criteria with Pt	X	-
Review of Pt medical history	X	-
Obtain informed written consent from Pt	X	-
Provide drug & diary card (including product label)	X	-
Review of diary card information with Pt	-	X
Review of adverse events with Pt	-	X
Tablet counts	-	X
Pt-rated global impression of change	-	X

1. Professional staff intervention regarding instructions on taking study drug were minimized. From Table 1, protocol 009 (page 8).

Patient Characteristics for Protocols 006, 008, 009

Demographics of the study population:

Table 5 presents some of the baseline characteristics of the patients/subjects enrolled in the three phase 3 trials (006, 008, and 009); the patients (N=233) in the Clinical Pharmacology portion of the NDA are not included here.

In general, the populations were similar, with some important exceptions. The population in the phase 3 trials tended to be white females in their early forties while subjects in the Clinical Pharmacology portion (Table C-23, Worldwide Clinical Summary) tended to be male (i.e. 53%). The location of the "muscle spasm" was usually only in the lumbar region except for study 009 which had a higher tendency to involve both the cervical and lumbar regions. The duration of the spasm prior to entry into the studies was different, being shortest in trial 008 (mean 3.5 days) and longest in trial 009 (mean 14 days). The patient rating of severity tended to be more toward the severe end of the scale for both trials 006 and 008 vs. trial 009 which tended to be milder disease. The physician rating of muscle spasm was in general agreement with that of the patient (i.e. moderate) in trials 006 and 008; there was no physician input in this regard in trial 009.

Table 5: Baseline Demographics in Protocols 006, 008, 009¹

	Protocol 006 (N=737)	Protocol 008 (N=668)	Protocol 009 (N=468)
	n (%)	n (%)	n (%)
Gender			
Female	422 (57)	381 (57)	253 (54)
Male	315 (43)	287 (43)	215 (46)
Age (years)			
Mean ± SD	42.0 ± 13.2	42.6 ± 13.2	40 ± 12.7
Median	40.0	41.0	40
Range	18-85	18-81	18-76
Racial Origin			
Caucasian	638 (87)	593 (89)	427 (91)
Black	70 (9)	60 (9)	22 (5)
Other	29 (4)	15 (2)	19 (4)
Duration of Primary Diagnosis Prior to Entry (Days)²			
Mean ± SD	6.1 ± 3.8	3.5 ± 1.8	14
Median	5.1	3.4	7
Range	0.04-23	0.04-7.0	1-99
Location of Muscle Spasm³			
Cervical	245 (33)	226 (34)	127 (27)
Lumbar	475 (64)	405 (61)	227 (49)
Both	16 (2)	37 (6)	63 (14)
Physician Rating of Muscle Spasm⁵			
Moderate	533 (72)	427 (64)	ND ⁴
Moderately Severe	204 (28)	239 (36)	ND
Severe	0	2 (<1)	ND
Patient Pain Severity Rating⁵			
Mild	30 (4)	28 (4)	70 (15)
Moderate	380 (52)	316 (47)	224 (48)
Marked	252 (34)	238 (36)	135 (29)
Severe	75 (10)	86 (13)	39 (8)

1. For trials 006 and 008, all groups (i.e. placebo and Flexeril) are combined; any differences are as noted in the footnotes.
2. The median time in the placebo patients in protocol 006 was 5.8 days; this was not statistically significantly ($p > 0.05$) than the treatment groups (from Table 5, page 1669 in protocol 006).
3. In protocol 009, the location of pain in the subjects not noted above includes-neck and other (22 subjects=5%), neck, back and other (9 subjects = 2%), back and other (16 subjects = 3%), other (2 subjects = <1%).
4. ND = not done.
5. More information regarding this parameter can be found in the next table and efficacy discussion below

Table 6 presents a more detailed look at some of the baseline characteristics of the secondary endpoints (see efficacy section below) in protocols 006 and 008. There appears to be a consistency in the characterizations of these endpoints of spasm, backache or overall musculoskeletal condition both within each protocol as well as between the protocols. Once again, the physician rating of muscle spasm reveals that most patients (especially those in protocol 006) fell into the "moderate" category; none were rated as severe. While there seems to be more of a tendency for patients in protocol 008 to have "moderately severe" muscle spasm as rated by the physician, there were no significant differences when compared within the protocols themselves.

The physician and patient severity rating suggests that patients in both studies generally rated themselves with more severe or involved symptoms as compared to the physician assessments. Nonetheless, the bulk of the severity rating by either physician or patient fell into the "moderate" or "marked" category, rather than "severe" category which roughly correlates with the physician rating of muscle spasm.

Reviewer's comment: It is important to note that all these demographic comparisons are based on mean scores, not correlations within individuals.

Table 6: Demographics of Secondary Endpoints in Protocols (P) 006, 008¹

Parameter	Flex 10	Flex 5		Flex 2.5	Placebo	
	N=249 (P-006)	242 (P-006)	222 (P-008)	223 (P-008)	246 (P-006)	223 (P-008)
MD Rating of Muscle Spasm 2=moderate 3=moderately severe 4=severe	177 (71%) 72 (29%) 0	169 (70%) 73 (30%) 0	145 (65%) 77 (35%) 0	137 (61%) 86 (39%) 0	187 (76%) 59 (24%) 0	145 (65%) 76 (34%) 0
Mean ±SD	2.29±0.45	2.30±0.46	2.35±0.48	2.39±0.49	2.24±0.43	2.36±0.50
MD Severity Rating 0=mild 1=moderate 2=marked 3=severe	0 170 (68%) 75 (30%) 4 (2%)	1 (<1%) 168 (69%) 65 (27%) 8 (3%)	8 (4%) 138 (62%) 61 (28%) 15 (7%)	4 (2%) 144 (65%) 69 (31%) 6 (3%)	1 (<1%) 182 (74%) 56 (23%) 7 (3%)	7 (3%) 136 (61%) 73 (33%) 7 (3%)
Mean ±SD	1.33±0.51	1.33±0.54	1.37±0.67	1.35±0.56	1.28±0.52	1.36±0.60
Pt Severity Rating 0=mild 1=moderate 2=marked 3=severe	7 (3%) 134 (54%) 79 (32%) 29 (12%)	10 (4%) 123 (51%) 84 (35%) 25 (10%)	11 (5%) 95 (43%) 84 (38%) 32 (14%)	10 (5%) 109 (49%) 73 (33%) 31 (14%)	13 (5%) 123 (50%) 89 (36%) 21 (9%)	7 (3%) 112 (50%) 81 (36%) 23 (10%)
Mean ±SD	1.52±0.74	1.51±0.74	1.62±0.74	1.56±0.79	1.48±0.7	1.54±0.72

1. There were no significant treatment-group differences observed ($p>0.05$) in either protocol.

Table 7 lists the primary diagnosis for the patients entered into protocol 008; musculoskeletal strain is the dominant diagnosis in all treatment groups. There were few patients noted to have their backache following trauma or other causes including pain associated with radicular symptoms. This suggests that the major cause of spasm and contributor to the severity rating noted by both the patients and physicians in Table 6 is from such musculoskeletal strain although a similar listing for protocol 006 was not found in the NDA.

Table 7: Primary Diagnosis-Protocol 008¹

	Flex 5 (N=222)	Flex 2.5 (N=223)	Placebo (N=223)	Total (N=668)
	n (%)	n (%)	n (%)	n (%)
Musculoskeletal strain	199 (90)	195 (87)	196 (88)	590 (88)
Posttraumatic	9 (4)	12 (5)	8 (4)	29 (4)
Other	11 (5)	15 (7)	16 (7)	42 (6)
Radiculopathy	2 (1)	0 (0)	2 (1)	4 (1)
Unknown	1 (0)	1 (0)	1 (0)	3 (0)

1. From Table 5, Protocol 008.

Concomitant medications/therapies:

Medications and noninvasive, nonpharmacologic therapies used both before entry into the trials and during the study in each treatment group were listed for each protocol 006 (Tables 8-11 of NDA) and 008 (Tables 8-10 of NDA).

At least 70% of the patients in all treatment groups were on some sort of drug therapy at enrollment. The most common prior drug therapies in each treatment group were ibuprofen and acetaminophen (range: 14-26%). While there were some instances where significantly more patients took certain medications (mostly before the trial i.e. atenolol and other cardiovascular drugs), **none appeared to be capable of significantly influencing treatment outcomes.** A few patients (two in protocol 008, seven in protocol 006) had taken Flexeril prior to the study, but this was more than 24 hours prior; these patients were, therefore, not excluded. It should be recalled that all analgesics and NSAIDs, psychotropic agents, and any prescription or OTC product known to produce sedation and any muscle relaxants were prohibited in protocols 006 and 008.

Regarding prior and concomitant noninvasive, nonpharmacological treatments, **the most common therapy before the study was heat therapy** (e.g., heating pads and hot showers-approximately 14-18% of patients in each group); this was the only therapy used during the study (approximately 27-38% in each group). Few patients used any other noninvasive therapy (i.e. cold therapy, hydromassage, massage, TENS unit, physical therapy, chiropractic therapy, etc.). With one exception (i.e. prior use of cold compresses in protocol 006), there were no significant differences prior to, or during the studies, with respect to these treatments.

Number of Patients/Subjects in Phase 3 trials:

Table 8 describes the number of patients "treated" in these three trials. As can be seen in study 006, there were 14 patients that may or may not have been included in various sections of the NDA that were enrolled with either Drs. Bevers or Pinson (see Table footnote); the numbers were similar between the treatment groups. In protocol 008, the patients with Dr. Fiddes were not included in the NDA except in only a few locations; similarly they are not discussed in this review except here. As can be seen, most patients/subjects were in the Flex 5 group.

Table 8: Number of Patients/Subjects in Phase 3 Protocols

Study	Treatment ³				Total
	Flex 2.5	Flex 5	Flex 10	Placebo	
006 ¹ with discontinued investigators (without discontinued investigators)	-	242 (238)	249 (244)	246 (241)	737 (723)
008 ²	223	222	-	223	668
009		468			468
Total	223	932 (928)	249 (244)	469 (464)	1873 (1859)

1. Investigators Bevers and Pinson were discontinued from protocol 006. Dr. Bevers had 4 patients in each group (total of 12), while Dr. Pinson had 1 patient in the Flex 10 and placebo groups (2 total).
2. Dr. Fiddes was disqualified after indictment by the FDA. His 40 patients are only noted in the NDA in a few tables (mostly as footnotes) in protocol 008.
3. Flex = 2.5 mg TID; Flex 5 = 5 mg TID; Flex 10 = 10 mg TID.

Primary Efficacy Endpoints

The same three primary efficacy parameters were used to assess the effectiveness of Flex 5 versus placebo in both of these controlled trials. **As noted by the Sponsor, in order to conclude better efficacy for Flex 5 over placebo (using a significance level of 0.030), at least two out of the three primary parameters needed to have statistical significance at either primary time point.** Three primary parameters, discussed below, were assessed by the patient at two primary time points:

- Patient-Rated clinical global impression of change at Clinic Visits 2 and 3
- Patient rating of medication helpfulness at Clinic Visits 2 and 3
- Relief from starting backache Diary on Study Days 3 and 7

Patient-Rated Clinical Global Impression of Change: (5-point categorical scale)

For this efficacy variable, patients were asked: "Compared to how you felt prior to starting study medication, and regardless of whether you think the change was due to medicine, please indicate if you have experienced:

- marked improvement = 4
- moderate improvement = 3
- mild improvement = 2
- no change = 1
- worsening = 0

Patient Rating of Medication Helpfulness: (5-point categorical scale)

For this efficacy variable, patients were asked the following question: "How would you rate this study medication in improving your condition?"

- Excellent = 4
- Very good = 3
- Good = 2
- Fair = 1
- Poor = 0

**Diary Card: Relief From Starting Backache:
(5-point categorical scale)**

For this efficacy variable, patients recorded on their Diary Card, at the end of each study day, prior to the bedtime dose of medication, their response to the following: "I have obtained:

- 4 = complete relief
- 3 = a lot of relief
- 2 = some relief
- 1 = a little relief
- 0 = no relief

from the backache I had just before I took my first dose of medication (on study Day 1)." This endpoint was evaluated as a primary endpoint on **Study Days 3 and 7** and as a secondary endpoint (see below) during the rest of the study days.

Statistical Issues Relating to Primary Endpoints:

Mean scores were calculated by treatment group for each parameter and time point. A multiplicity adjustment was defined a priori. As noted by the Sponsor, statistical significance in favor of Flex 5 was required for at least two of the three parameters for at least one of the two time points in order to conclude superior efficacy for Flex 5 over placebo. Each of the six individual comparisons was made at the 0.030 level. Requiring at least two out of three parameters to achieve significance at the 0.030 level assured a nominal type I error rate <0.025 at each time point. A nominal type I error rate <0.025 at each time point assures an overall type I error rate ≤ 0.050 across the two time points based on Bonferroni's inequality. The term "significant" refers to a statistically significant difference of $p \leq 0.030$ when applied to primary endpoints.

A post-hoc responder's analysis was conducted for each of the primary parameters. For this analysis, the definition of a responder was established for each parameter. The treatment groups were then compared with respect to the proportion of responders. For this analysis, statistical significance was defined as $p \leq 0.050$.

Secondary Efficacy Endpoints:

The following parameters in both studies were considered secondary:

- Relief from starting backache by Diary on Study Days 1, 2, 4-6
- Physician rating of spasm at Clinic Visits 1, 2 and 3. For this secondary efficacy parameter, the physician rated the muscle spasm according to a five-point scale of:
 - 0 = none, no hardness of muscles detected by palpation
 - 1 = mild, muscles somewhat harder than usual

- 2 = moderate, muscles harder and borders of increased consistency can be determined
 - 3 = moderately severe, muscles very hard and borders are sharply defined
 - 4 = severe, board-like hardness of muscles
- Patient diary ratings of discomfort on motion were also assessed in study 008
 - Physician severity rating of the overall condition of the patient with regard to current musculoskeletal condition **at Visit 1 only**. This was rated on a four-point scale of mild, moderate, marked, or severe.
 - Patient severity rating of backache in which the patient rated his/her backache (**at Visit 1 only**) according to the same four-point scale of mild, moderate, marked, or severe.

Statistical Issues Relating to Secondary Endpoints:

Mean scores were calculated by treatment group for each parameter and time point. In addition, a post-hoc responder's analysis was conducted for each of the secondary parameters. For this analysis, the definition of a responder was established for each parameter. The treatment groups were then compared with respect to the proportion of responders.

Pairwise treatment comparisons were made at the 0.050 level for all secondary parameters and secondary time points. In this document the word "significant" refers to a statistically significant difference of $p \leq 0.050$ when applied to analyses of secondary endpoints.

Results:

Patient/subject disposition:

Table 9 shows the disposition of the patients/subjects in the three phase 3 trials for Flexeril MR. As can be seen, the bulk of the exposure was to Flex 5. The discontinuation rates ranged from 7-14% with the highest percentage of patients discontinuing from the Flex 10 group in protocol 006; **the discontinuation rate for clinical adverse events (AEs) was significantly different for the Flex 10 group than the other groups in this trial.** In fact, in both trials 008 and 006, discontinuations in the Flex 5 and 10 groups were mostly due to clinical AEs while those in the Flex 2.5 mg and placebo groups tended to result from ineffective therapy. In fact, the difference in withdrawal due to ineffective therapy was significantly different between the Flex 5 vs. the Flex 2.5 and placebo groups in protocol 008. These results are not inconsistent with an interpretation that the Flex 2.5 and placebo are ineffective or sub-therapeutic treatments.

Seven hundred thirty-seven patients were randomly assigned to one of the three treatment groups. One patient (AN 474, Study Site 006-022, Flex 10 group) did not report taking any study medication, but was included in the analysis of safety. Dr. Pinson (Study Site 006-023) and Dr. Bevers (Study Site 006-003) were discontinued from the

trial after recruiting only two and 12 patients, respectively. These 14 patients were combined into "one investigator" for analysis purposes.

Table 9: Patient/Subject disposition in Phase 3 trials

Study		Treatment (%)				Total
		Flex 2.5	Flex 5	Flex 10	Placebo	
006						
Entered:	Total	-	242	249	246	737
male			105 (43)	108 (43)	102 (41)	315
female			137 (57)	141 (57)	144 (59)	422
Completed			220 (91)	215 (86)	225 (91)	660
Discontinued:	Total	-	22 (9)	34 (14)	21 (9)	77
clinical AE			12 (5)	20 (8) ³	6 (2)	38
therapy ineffective			5 (2)	5 (2)	9 (4)	19
other ¹			5 (2)	9 (4)	6 (2)	20
008						
Entered:	Total	223	222	-	223	668
male		90 (40)	99 (45)		98 (44)	287
female		133 (60)	123 (55)		125 (56)	381
Completed		203 (91)	207 (93)		202 (91)	612
Discontinued:	Total	20 (9)	15 (7)	-	21 (9)	56
clinical AE ²		5 (2)	9 (4)		4 (2)	18
therapy ineffective ⁴		10 (5)	2 (1)		10 (5)	22
other ¹		5 (2)	4 (2)		7 (3)	16
009						
Entered:	Total	-	468	-	-	468
male			215 (46)			215
female			253 (54)			253
Completed			410 (88)			410
Discontinued:	Total	-	58 (12)	-	-	58
clinical AE			25 (5)			25
therapy ineffective			11 (2)			11
other			22 (5)			22
Total		223	932	249	469	1873

1. Other includes; lost to follow-up, protocol deviation, never took therapy, patient uncooperative, patient withdrew consent.
2. Not included in protocol 008 are 3 patients (one/treatment) from disqualified site 021 (Dr. Fiddes). One patient, AN 2489 (Flex 5 group) had a serious adverse experience, discontinued the study and died.
3. Significantly different than the placebo groups $p=0.05$.
4. Significantly greater incidence in the Flex 2.5 and placebo groups (vs. Flex 5), $p=0.036$.

Flex 5-Efficacy:

Prior to testing for significant treatment differences, interaction tests between treatment and investigator and between treatment and duration of muscle spasm (prior to entering the study) were performed. Although some significant interactions were noted (i.e. patient-rated global impression of change, treatment-by-investigator interaction was significant at Visits 2 and 3 in protocol 008-Table 22), these significant interactions were examined further to determine if they were quantitative or qualitative. As noted by the Sponsor, a qualitative interaction would imply that the difference in mean response between treatment groups varies in direction while a quantitative interaction (usually of lesser concern) would imply that the difference in mean response between treatment groups varies in magnitude. All differences were noted to be quantitative in nature.

Because there were no significant qualitative interactions for any of the three primary parameters at either primary time point, the model used to test for treatment differences included terms for treatment, duration of muscle spasm, investigator, and treatment-by-investigator interaction. This model was also used to test for significant treatment differences for all secondary parameters.

All-Patients-Treated Approach:

In protocol 006, seven hundred thirty-six (736) patients took at least one dose of study medication and were eligible for the efficacy analysis. However, 6 (3 in the Flex 10 group, 2 in Flex 5 group, 1 in placebo group) of the 736 patients did not have any efficacy data (they did not return for the clinic evaluations and did not record any diary data). Thus, 730 patients were included in the efficacy analysis. There were an additional 5 patients (3 in Flex 10 group, 2 in Flex 5 group) who did not have any diary data, but did return for Clinic Visits 2 and 3. This accounts for the 725 patients who were analyzed for the relief from starting backache parameter.

There were 3 patients (1 patient in each of the three treatment groups) who returned their diary data, but did not return for Clinic Visits 2 and 3. Another patient (placebo group) did return for Clinic Visits 2 and 3, but only completed the global impression of change evaluation. This explains why there was one less patient with evaluations for medication helpfulness than for global impression of change.

Finally, there were 10 patients who returned their diary data and returned for Visit 3, but were not included in the analysis of the Visit 2 data. Seven of these patients did not return at all for Visit 2, and the other 3 patients returned on Study Day 6. By convention, the relative day ranges placed evaluations occurring on Study Day 6 in the Visit 3 evaluation.

In protocol 008, six hundred and sixty-eight patients (668) were eligible for the efficacy analysis. The 40 patients from the disqualified site were not eligible. In addition,

9 patients (2 in the Flex 5 group, 2 in the Flex 2.5 group, 5 in the placebo group) did not return for the clinic evaluations and did not record any diary data (i.e., they had no efficacy data). The remaining 659 patients returned their diary cards and were included in the analysis of the diary rating of relief from starting backache parameter. There were 6 patients (3 in the Flex 5 group, 2 in the Flex 2.5 group, 1 in the placebo group) who returned their diary data, but did not return for Clinic Visit 2 or 3. There were also 5 patients (2 in the Flex 5 group and 3 in the Flex 2.5 group) who did not return for Clinic Visit 2 but did return with their diary card for Clinic Visit 3.

Table 10: Accounting for Patients in Efficacy Analysis-Phase 3 trials

Study	Treatment				Total
	Flex 2.5	Flex 5	Flex 10	Placebo	
006					
Patients Entered into the Study	-	242	249	246	737
Patients Who Took Study Medication	-	242	248	246	736
Patients Contributing Any Efficacy Data	-	240	245	245	730
Included in All-Patients-Treated Approach					
Clinical Global Impression of Change					
Visit 2	-	238	238	241	717
Visit 3	-	239	244	244	727
Medication Helpfulness					
Visit 2	-	238	238	240	716
Visit 3	-	239	244	243	726
Diary-Relief from Starting Backache					
Study Day 3	-	238	242	245	725
Study Day 7	-	238	242	245	725
008					
Patients Entered into the Study	223	222	-	223	668
Patients Who Took Study Medication	-	-	-	-	-
Patients Contributing Any Efficacy Data	221	220	-	218	659
Included in All-Patients-Treated Approach					
Clinical Global Impression of Change					
Visit 2	216	215	-	217	648
Visit 3	219	217	-	217	653
Medication Helpfulness					
Visit 2	216	215	-	218	648
Visit 3	219	217	-	218	653
Diary-Relief from Starting Backache					
Study Day 3	221	220	-	245	659
Study Day 7	221	220	-	245	659

Results-Primary Endpoints:

The overall efficacy results for the primary efficacy parameters employed in protocols 006 and 008 are summarized in Table 11. Pairwise comparisons of the FLEX 5 and placebo groups in both studies demonstrated statistically significant differences for all three primary parameters at Visit 3 and/or Day 7 of treatment. In Protocol 006, FLEX 5 was significantly better than placebo in all three primary parameters at the earlier time point as well. As noted by the Sponsor, these findings exceeded the predefined criteria that two of the three parameters for at least 1 of the 2 time points be significant at the 0.030 level. Protocol 006 also suggested that FLEX 10 was significantly better than placebo in the three primary parameters at both primary time points. On the other hand, protocol 008 showed that FLEX 2.5 was significantly better than placebo in only one of three parameters at the first primary time point but none at the second primary time point.

Table 11: Summary of Primary Efficacy Parameters vs. Placebo^{1,2}

	Visit/Day	Protocol 006		Protocol 008 ³	
		Flex 10	Flex 5	Flex 5	Flex 2.5
Pt rated global impression of change	Visit 2	**	**	0.242	0.528
	Visit 3	**	**	0.004	0.074
Pt rating of medication helpfulness	Visit 2	**	**	0.145	0.845
	Visit 3	**	**	0.009	0.147
Relief from starting backache	Day 3	**	**	0.051	0.004
	Day 7	**	**	0.002	0.081

1. ** P ≤ 0.001;
2. From Table C-8, (Worldwide Clinical Summary) and Table 15 (Protocol 008)
3. Actual p values vs. placebo noted.

A more detailed analysis of these primary efficacy results, based on an intent-to-treat (ITT) analysis is found in Table 12 (protocol 006) and Table 13 (protocol 008) below. These tables help to further understand the onset and magnitude of effect as well as examine any dose-response relationships.

The three primary efficacy endpoints for protocol 006 are noted in Table 12. As can be seen, both Flex 10 and Flex 5 had a significantly higher mean "Patient rated global impression of change" than placebo at Visit 2 (48 or 72 hours after the first dose) and Visit 3. Patients in both the Flex 10 and Flex 5 treatment groups also rated their medication to be significantly more helpful than patients in the placebo group at Clinic Visit 2 (48 or 72 hours after the first dose) and Clinic Visit 3. Additionally, the Flex 10 and Flex 5 treatment groups had a significantly higher mean response in the "relief from starting backache" than the placebo group at both time points. However, there were no significant differences between Flex 10 and Flex 5.

Table 12: Primary Efficacy Parameters (ITT)-Protocol 006 ¹

Parameter	When				
		Flex 10	Flex 5	Placebo	
		N: Entered Study	249	242	246
		N: Took Medication	248	242	246
		N: Any Efficacy Data	245	240	245
Pt rated global impression of change ² (Scale 0 to 4)	Visit 2	N: Mean: S.D.:	238 2.30 0.94	238 2.29 0.90	241 1.91 0.97
	Visit 3	N: Mean: S.D.:	244 2.82 1.13	239 2.88 1.06	244 2.47 1.16
Pt rating of medication helpfulness ² (Scale 0 to 4)	Visit 2	N: Mean: S.D.:	238 1.62 1.13	238 1.62 1.10	240 1.24 1.14
	Visit 3	N: Mean: S.D.:	244 2.13 1.32	239 2.09 1.27	243 1.65 1.33
Relief from starting backache ^{2,3} (Scale 0 to 4)	Day 3	N: Mean: S.D.:	242 1.83 1.03	238 1.74 1.01	245 1.41 1.12
	Day 7	N: Mean: S.D.:	242 2.38 1.18	238 2.37 1.21	245 2.00 1.34

1. There were no significant differences ($p > 0.030$) between Flex 10 and Flex 5.
2. For all three primary efficacy parameters at both time points, Flex 10 and Flex 5 were significantly ($p < 0.001$) than placebo.
3. The time points for evaluation of this endpoint are at days 3 and 7 (vs. clinic visits).

Similarly, the three primary efficacy endpoints for protocol 008 are noted in Table 13. As can be seen, the Flex 5 group had significantly higher mean responses for all three endpoints than the placebo group, at Clinic Visit 3 only. The Flex 2.5 group had a significantly higher mean response than the placebo group only at the Day 3 evaluation for "relief from starting backache" endpoint. There were no significant differences between Flex 5 and Flex 2.5 mg.

Table 13: Primary Efficacy Parameters (ITT)-Protocol 008

Parameter	When				
		Flex 5	Flex 2.5	Placebo	
		N: Entered Study	222	223	223
		N: Any Efficacy Data	220	221	218
Pt rated global impression of change ² (Scale 0 to 4)	Visit 2	N:	215	216	217
		Mean:	2.19	2.05	1.97
		S.D.:	0.88	0.96	0.98
	Visit 3	N:	217 ¹	219	217
		Mean:	2.82	2.63	2.41
		S.D.:	1.07	1.19	1.19
Pt rating of medication helpfulness ² (Scale 0 to 4)	Visit 2	N:	215	216	217
		Mean:	1.49	1.25	1.20
		S.D.:	1.07	1.05	1.11
	Visit 3	N:	217 ¹	219	217
		Mean:	2.00	1.72	1.50
		S.D.:	1.28	1.35	1.30
Relief from starting backache ² (Scale 0 to 4)	Day 3	N:	220	221 ¹	218
		Mean:	1.62	1.63	1.29
		S.D.:	1.02	1.10	1.03
	Day 7	N:	220 ¹	221	218
		Mean:	2.24	2.03	1.72
		S.D.:	1.26	1.30	1.28

1. For these three parameters, the Flex 5 group had a significantly ($p \leq 0.030$) higher mean response than placebo; p values (based on multiplicity adjustments) were 0.004, 0.009, and 0.002 for the Pt-rated global impression of change, Pt rating of medication helpfulness and Relief from starting backache, respectively. For Flex 2.5, this was significant ($p = 0.004$) only on day 3 of the relief from starting backache. There were no significant differences ($p > 0.030$) between Flex 2.5 and Flex 5.
2. Clinic visit 2 occurred on study Day 3 (48 hours after first dose); Clinic visit 3 occurred on Study day 8; Study Day 3 occurred 48-56 hours after the first dose while Study Day 7 occurred prior to the physician assessment.

Table 14 presents the proportion of patients classified as **responders** (marked, moderate, mild improvement) and **nonresponders** (no change, worsening) and shows p-values for the comparisons between treatments. As can be seen in this post-hoc analysis, the difference in responder rates between the Flex 5 and placebo groups varied from 11 to 20 percentage points for all these efficacy parameters at the two time points; as noted these response rates were significantly different vs. placebo. These per patient results are in general agreement with the results of the mean analysis for the placebo-controlled trials (i.e. see Table 11) but differ in that they suggest Flex 5 is also effective at the earlier time points. This responder analysis tends to reinforce the efficacy of Flex 5 with these same endpoints. While statistical comparisons were not done in protocol 009, the percentage of responders (i.e. 88%) was comparable to the responder rate noted in the placebo-controlled trials (006 and 008).

Table 14: Responder (ITT) Analysis-Primary Efficacy Endpoints-Protocols 006 /8/9

		Visit 2		Visit 3	
Patient-Rated Global Impression of Change ¹					
		N	% (p vs. plc)	N	% (p vs. plc)
P-006					
Flex 10		238	81 (<0.001)	244	86 (=0.02)
Flex 5		238	83 (<0.001)	239	90 (<0.001)
Placebo		241	66	244	77
P-008					
Flex 5		215	78 (=0.007)	217	88 (<0.001)
Flex 2.5		216	72 (=0.253)	219	81 (=0.166)
Placebo		217	66	217	75
P-009					
Flex 5		-	-	452	88 ⁴
Patient Rating of Medication Helpfulness ²					
P-006					
Flex 10		238	53 (<0.001)	244	65 (=0.006)
Flex 5		238	54 (<0.001)	239	64 (=0.013)
Placebo		240	37	243	53
P-008					
Flex 5		215	50 (=0.006)	217	64 (<0.001)
Flex 2.5		216	38 (=0.766)	219	50 (=0.214)
Placebo		217	36	217	44
Patient Diary Rating of Relief from Starting Backache ³					
		Study Day 3		Study Day 7	
P-006					
Flex 10		242	62 (<0.001)	242	76 (<0.001)
Flex 5		238	59 (=0.002)	238	75 (=0.003)
Placebo		245	44	245	62
P-008					
Flex 5		220	57 (=0.002)	220	69 (=0.013)
Flex 2.5		221	54 (=0.013)	221	66 (=0.05)
Placebo		218	42	218	57

1. Categorized as responders (marked, moderate, mild improvement) and nonresponders (no change, worsening).
2. Categorized as responders (excellent, very good, good) and nonresponders (fair, poor).
3. Categorized as responders (complete, a lot, some relief) and nonresponders (a little, no relief).
4. From Table 25 of protocol 009. Subjects were asked the degree of improvement since taking study medication either by phone or by visit at the end of the study. Note 88% = 397/452.

In order to place the results from protocol 009 in some perspective, Table 15 presents, in more detail, the results of the patient-rated global impression of change at the last visit for all three phase 3 protocols. As can be seen, the results suggest that the type and magnitude of responses in this parameter are similar between the placebo-controlled trials and the "use" trial. However, as noted earlier (Table 5), people in the use trial tended to be less symptomatic with their back pain at baseline. Few patients actually worsened or had no change as compared to their baseline scores. Of interest, the type and magnitude of responses seem similar regardless of the dose of Flex studied in any of the trials suggesting there is not much in the way of a dose-response with this efficacy parameter.

Reviewer's comment: Without a placebo group in trial 009, it is difficult to interpret the results with Flex 5.

Table 15: Patient-Rated Global Impression of Change (Last Visit)-Protocols 006/8/9

Category	Protocol 006 ¹					
	Flex 10 (N=244)		Flex 5 (N=239)		Placebo (N=244)	
	n	%	n	%	n	%
Marked Improvement (4)	91	37	90	38	54	22
Moderate Improvement (3)	58	24	59	25	74	30
Mild Improvement (2)	60	25	66	28	60	25
No Change (1)	30	12	20	8	45	18
Worsening (0)	5	2	4	2	11	5
Category	Protocol 008 ¹					
	Flex 2.5 (N=219)		Flex 5 (N=217)		Placebo (N=217)	
	n	%	n	%	n	%
Marked Improvement (4)	73	33	75	35	53	24
Moderate Improvement (3)	42	19	59	27	46	21
Mild Improvement (2)	62	28	57	26	64	30
No Change (1)	35	16	22	10	44	20
Worsening (0)	7	3	4	2	10	5
Category	Protocol 009 ²					
	Flex 5 (N=452)					
	n	%				
Marked Improvement (4)	172	38				
Moderate Improvement (3)	162	36				
Mild Improvement (2)	63	14				
No Change (1)	53	12				
Worsening (0)	2	<1				

1. From Tables 17, protocols 006 and 008 (visit 3); all patients treated.
2. From Table 25, protocol 009.

A post hoc evaluation of "effect size" was performed for the two double-blind efficacy trials. The effect sizes (calculated by dividing the difference in means by the pooled standard deviation-also included in the table) for Flex 10, Flex 5, and Flex 2.5 vs. placebo in protocols 006 and 008 are presented in Table 16. It is argued that since this measure has no units, it and can be used to compare magnitude of effect across different endpoints. As noted by the Sponsor, arbitrary criteria for interpreting effect size suggested an effect size of 0.20 is small, 0.50 is moderate, and 0.80 or greater is large. Both of the efficacy trials in this submission were designed with sufficient power to detect an effect size of approximately 0.32 (i.e. small-to-moderate effect).

As can be seen in Table 16, for Flex 10 and 5, all effect sizes fell between 0.20 and 0.50. The exceptions were relief from starting backache at Day 1 (006 and 008) and physician rating of muscle spasm at Visit 2 (008), both of which fell below 0.20 for the Flex 5 group. In contrast, the effect sizes for the Flex 2.5 comparison all fell below 0.32 with 8 of the 13 falling below 0.20. As noted by the Sponsor, these effect sizes for Flex 5 and Flex 10 are comparable to those for of OTC famotidine (i.e. 0.21-0.31 vs. placebo for 10 mg) a nonprescription medication which also relies on subjective self-assessment of symptoms.

Table 16 : Effect Sizes-Efficacy Parameters, Protocol 006/008

Parameter	Time Point	Study 006 ¹		Study 008 ¹	
		Flex 10	Flex 5	Flex 5	Flex 2.5
Pt-Rated Global Impression of Change	Clinic Visit 2	0.408 (0.96)	0.406 (0.94)	0.236 (0.93)	0.082 (0.97)
	Clinic Visit 3	0.306 (1.15)	0.369 (1.11)	0.362 (1.13)	0.185 (1.19)
Pt Rating of Medication Helpfulness	Clinic Visit 2	0.335 (1.14)	0.339 (1.12)	0.266 (1.09)	0.046 (1.08)
	Clinic Visit 3	0.362 (1.32)	0.338 (1.30)	0.388 (1.29)	0.166 (1.33)
Pt Diary Rating of Relief from Starting Backache	Study Day 1	0.374(1.02)	0.074 (0.94)	0.135 (0.97)	0.144 (0.97)
	Study Day 2	0.464(1.04)	0.315 (1.01)	0.245 (1.02)	0.154 (1.04)
	Study Day 3	0.390(1.08)	0.309 (1.07)	0.322 (1.02)	0.319 (1.07)
	Study Day 4	0.339(1.12)	0.245 (1.14)	0.370 (1.08)	0.256 (1.10)
	Study Day 5	0.296 (1.15)	0.308 (1.17)	0.376 (1.17)	0.249 (1.17)
	Study Day 6	0.245 (1.23)	0.284 (1.23)	0.389 (1.26)	0.252 (1.27)
	Study Day 7	0.301 (1.26)	0.290 (1.28)	0.409 (1.27)	0.240 (1.29)
Physician Rating of Muscle Spasm	Clinic Visit 2	0.244 (0.78)	0.247 (0.77)	0.121 (0.75)	0.079 (0.75)
	Clinic Visit 3	0.235 (0.90)	0.265 (0.90)	0.284 (0.92)	0.138 (0.95)

1. Results are expressed as Flex dose vs. placebo with effect size (pooled standard deviation-SD)

Results-Secondary Endpoints:

Descriptive statistics and pairwise treatment comparisons of mean relief from starting backache on Study Days 1 through 7 for each treatment group in Protocols 006 and 008 are presented in Table 17. It should be recalled that study Days 3 and 7 were considered primary time points for the analysis of mean scores. As can be seen, the Flex 5 group appears significantly better ($p \leq 0.030$) than placebo at both primary time points in Protocol 006 and at Day 7 in Protocol 008. The Flex 10 group was also significantly better than placebo at both primary time points in Protocol 006. The FLEX 2.5 group was significantly better than placebo on Day 3 but not Day 7 in Protocol 008. There were no significant differences between Flex 10 and FLEX 5, or between Flex 5 and Flex 2.5 on Days 3 or 7 with respect to mean scores.

Comparison of mean scores on days other than 3 and 7 were considered secondary. The results in Table 17 suggest that, in Protocol 006, Flex 10 and Flex 5 maintained a significant difference ($p \leq 0.050$) in mean scores versus placebo through Day 7 after initially achieving statistical significance on Study Days 1 and 2, respectively. In Protocol 008, Flex 5 was significantly different than placebo on Study Days 4 through 7. In contrast, the Flex 2.5 group in Protocol 008 was significantly different from placebo on Days 3, 4, and 5 but not on Days 6 or 7.

Table 17: Patient Diary Rating-Relief from Starting Backache (Days 1-7)

	N ¹	1	2	3 ²	4	5	6	7 ²
Protocol 006								
FLEX 10	242	1.12**	1.56**	1.83**	1.98**	2.11**	2.22**	2.38**
FLEX 5	238	0.81	1.40**	1.74**	1.88**	2.13**	2.27**	2.37**
Placebo	245	0.74	1.08	1.41	1.60	1.77	1.92	2.00
Protocol 008								
FLEX 5	220	0.94	1.44	1.62	1.85**	2.01**	2.15**	2.24**
FLEX 2.5	221	0.95	1.35	1.63**	1.73*	1.86*	1.98	2.03
Placebo	218	0.81	1.19	1.29	1.45	1.57	1.66	1.72

1. Rated as 4=complete relief, 3=a lot of relief, 2=some relief, 1=a little relief, 0=no relief. Results from Table C-11 Worldwide Clinical Summary and Table 24a of Protocol 006 and Table 23 of Protocol 008.
2. Recall that study days 3 and 7 were specified as primary parameters.
3. ** = $p \leq 0.03$ vs. placebo * = $p \leq 0.05$ vs. placebo
4. Number of patients evaluated were smaller on study day 1 than the rest of the study.

Physician Rating of Muscle Spasm:

Muscle spasm was rated by the physician at each visit in protocols 006 and 008 (not the use study, 009). This evaluation was based on a five-point categorical scale as follows: 0=none; 1=mild; 2=moderate; 3=moderately severe; and 4=severe. A rating of moderate or moderately severe at Baseline (Visit 1) was required for entry into the study. Tables 18 and 19 show the distribution of spasm severity by treatment and visit for Protocols 006 and 008, respectively.

As can be seen in Table 18, baseline severity was comparable across all groups. Patients receiving Flex 10 or Flex 5 had less muscle spasm at Visits 2 and 3 than patients treated with placebo. For example, the proportion of patients with no spasm at Visit 3 was approximately 10 percentage points greater in the FLEX 5 group than the placebo group.

Table 18 : Physician Rating of Muscle Spasm-Protocol 006¹

Visit 1—Baseline	FLEX 10 (N=249)		FLEX 5 (N=242)		Placebo (N=246)	
	n	%	n	%	n	%
None (0)	0	-	0	-	0	-
Mild (1)	0	-	0	-	0	-
Moderate (2)	177	71	169	70	187	76
Moderately Severe (3)	72	29	73	30	59	24
Severe (4)	0	-	0	-	0	-
	(N=238)		(N=235)		(N=239)	
Visit 2	n	%	n	%	n	%
None (0)	20	8	15	6	14	6
Mild (1)	100	42	108	46	76	32
Moderate (2)	97	41	91	39	117	49
Moderately Severe (3)	19	8	19	8	32	13
Severe (4)	2	1	2	1	0	-
	(N=244)		(N=239)		(N=244)	
Visit 3	n	%	n	%	n	%
None (0)	90	37	89	37	65	27
Mild (1)	89	37	95	40	93	38
Moderate (2)	55	23	42	18	68	28
Moderately Severe (3)	8	3	10	4	18	7
Severe (4)	2	1	3	1	0	-

1. From Table C-13, Worldwide Clinical Summary

As noted in Table 19, baseline severity was not entirely comparable across all groups. There were 2 patients in the placebo group (ANS 2294; site 006 and 2128; site 010) who had a baseline physician rating of severe muscle spasm. However, patients receiving Flex 5 had less muscle spasm at Visits 2 and 3 than patients treated with placebo. For example, the proportion of patients with no spasm at Visit 3 was again approximately 10 percentage points greater in the FLEX 5 group than the placebo group.

Reviewer's comment: It should be noted that there are no results in the NDA that attempted to correlate, at the level of each patient, the patient driven primary endpoints with those of the physician rating of muscle spasm. One could argue that this is an important aspect of efficacy to help understand the proposed mechanism of action of Flexeril.

Table 19: Physician Rating of Muscle Spasm-Protocol 008¹

	FLEX 5 (N=222)		FLEX 2.5 (N=223)		Placebo (N=223)	
	n	%	n	%	n	%
Visit 1—Baseline						
None (0)	0	-	0	-	0	-
Mild (1)	0	-	0	-	0	-
Moderate (2)	145	65	137	61	145	65
Moderately Severe (3)	77	35	86	39	76	34
Severe (4)	0	-	0	-	2	1
	(N=215)		(N=215)		(N=217)	
Visit 2						
None (0)	9	4	10	5	6	3
Mild (1)	84	39	78	36	80	37
Moderate (2)	97	45	99	46	97	45
Moderately Severe (3)	25	12	28	13	34	16
Severe (4)	0	-	0	-	0	-
	(N=217)		(N=219)		(N=217)	
Visit 3						
None (0)	88	41	78	36	65	30
Mild (1)	74	34	75	34	71	33
Moderate (2)	45	21	49	22	64	30
Moderately Severe (3)	10	5	17	8	17	8
Severe (4)	0	-	0	-	0	-

1. From Table C-14, Worldwide Clinical Summary

Both protocols included analyses of mean change from baseline. As shown in Table 20, the Flex 10 and Flex 5 groups had significantly greater decreases in spasm at both follow-up visits in protocol 006. Flex 5 was significantly different than placebo only at Visit 3 in protocol 008; the Flex 2.5 group was not significantly different from placebo. However, there did not appear to be significant differences observed between the 2 active treatments within either study.

Table 20: Physician Rating of Muscle Spasm-Results

	Mean (S.D.) Change from Baseline ¹						
	N	Baseline ²	Visit 2 score	Visit 2 change	N	Visit 3 score	Visit 3 change
Protocol 006							
FLEX 10	238	2.28 (0.45)	1.51 (0.79)	-0.77 *(0.72)	244	0.95 (0.89)	-1.34* (0.90)
FLEX 5	235	2.31 (0.46)	1.51 (0.77)	-0.80*(0.75)	239	0.92 (0.91)	-1.38* (0.94)
Placebo	239	2.24 (0.43)	3.70 (0.77)	-0.54 (0.73)	244	1.16 (0.90)	-1.08 (0.89)
Protocol 008							
FLEX 5	215	2.35 (0.48)	1.64 (0.74)	-0.71 (0.66)	217	0.89 (0.89)	-1.45*
FLEX 2.5	215	2.38 (0.49)	1.67 (0.76)	-0.70 (0.73)	219	1.02 (0.95)	-1.36
Placebo	217	2.35 (0.50)	1.73 (0.75)	-0.62 (0.68)	217	1.15 (0.94)	-1.20

- * = p≤0.05 vs. placebo. From Table C-15 Worldwide Clinical Summary and Table 27a of Protocol 006 and Table 34 of Protocol 008.
- Baseline scores are only presented for Visit 2, the baseline values for visit are essentially identical.

Onset and Consistency of Effect:

Results for the Flex 5 group as compared to placebo are summarized in Table 21 for both protocols 006 and 008. These results suggest there is generally both an onset of response and a consistent efficacy across time. For example, evidence of onset of response was suggested by the patient diary rating of relief from starting backache parameter. These evaluations occurred nightly prior to the bedtime dose. The first evidence of response was on Study Day 2, approximately 24 to 32 hours after the first dose. In terms of mean response and proportion of responders at this time point, Flex 5 appeared significantly more efficacious than placebo. This represents patient experience after 3 to 4 doses of study medication. Further evidence of onset of efficacy was provided by the patient-rated global impression of change and patient rating of medication helpfulness parameters. Overall, there appears to be a positive and increasing difference observed as time progresses for each parameter.

The only apparent efficacy difference of note between Flex 5 and Flex 10 (data not shown) is that Flex 10 appears to have a slightly more rapid onset of action in the relief from starting backache data in Protocol 006. Relief with Flex 10 appeared to occur within the first 2 doses on Day 1, whereas Flex 5 was not significantly better than placebo until Day 2 (24 to 32 hours after the first dose).

Table 21: Onset/Consistency of Response for Flex 5 vs. Placebo-Protocols 006/8¹

Parameter	Time Point	Difference Between Means and Significance ²		Difference Between Proportion of Responders and Significance ²	
		P-006	P-008	P-006	P-008
Pt-Rated Global Impression of Change	Clinic Visit 2 ³	0.38 **	0.22	17% **	12% **
	Clinic Visit 3 ³	0.41 **	0.41 **	13% **	13% **
Pt Rating of Medication Helpfulness	Clinic Visit 2 ³	0.38 **	0.29	17% **	14% **
	Clinic Visit 3 ³	0.44 **	0.50 **	11% *	20% *
Pt Diary Rating of Relief from Starting Backache	Study Day 1	0.07	0.13	ND	ND
	Study Day 2	0.32 **	0.25	12% **	8%
	Study Day 3 ³	0.33 **	0.33	15% **	15% **
	Study Day 4	0.28 *	0.40 **	ND	ND
	Study Day 5	0.36 **	0.44 **	ND	ND
	Study Day 6	0.35 **	0.49 **	ND	ND
	Study Day 7 ³	0.37 **	0.52 **	13% **	12% **
Physician Rating of Muscle Spasm (Chg. from Baseline)	Clinic Visit 2	0.26 **	0.09	ND	ND
	Clinic Visit 3	0.30 **	0.25 *	ND	ND

1. From Table 39 and 45 of protocols 006 and 008 respectively.
2. * = 0.01 < p ≤ 0.05 ** = p ≤ 0.01 ND = not done for this parameter/time point.
3. Recall that these time points were designated as primary by the Sponsor.

Dose Response:

A dose-response relationship between the Flex treatment groups was generally evident when comparing results between protocols 006 and 008. In Protocol 006 the dose response between FLEX 5 and FLEX 10 was relatively shallow. The only significant difference between FLEX 10 and FLEX 5 was in relief from starting backache on Study Day 1. Protocol 008 was then conducted with the FLEX 2.5 group replacing the FLEX 10 group in order to more fully characterize the dose-response curve for FLEX. The most notable suggestion of a dose-response relationship was seen when comparing the Flex 2.5 dose with that of the Flex 10 dose. There were some primarily numerical trends of a dose-related response between the Flex treatments with most parameters and time points within the individual studies but there were generally no significant mean differences were observed between the various doses of Flex within the studies.

All-Patients-Treated Versus Per-Protocol Approach:

The three primary parameters were each analyzed at the 2 primary time points using the per-protocol approach in both protocols. Results (mean changes and statistical significance) of these analyses were consistent with those of the all-patients-treated (ITT) approach for all three primary parameters. Thus, the per-protocol approach leads to the same conclusions as the all-patients-treated approach.

Subgroup Analyses:

The three primary efficacy parameters were also summarized and analyzed using the ITT approach for various subgroups of the patient population including duration of muscle spasm (≤ 3 or 7 days), severity of muscle spasm at baseline (as rated by the physician-moderate or moderately severe) and location of muscle spasm (lumbar, cervical, or both). It would appear from these analyses that only the duration of muscle spasm may have had an influence on the outcomes in protocol 008. However, in protocol 006, the duration of muscle spasm (≤ 3 or 7 days) did not seem to differ from the mean differences of all patients combined (≤ 14 days duration). Therefore, the efficacy of FLEX 5 was greater than placebo regardless of duration of spasm (<14 days, <7 days, <3 days). The results also appeared similar to the overall study results with respect to the severity and location of spasms in both protocols.

Drug-Demographic Interactions for Efficacy:

Drug-demographic interactions for the three primary efficacy parameters were analyzed with respect to age (<65 or ≥ 65 years), gender, and race. For patients who were <65 years old, differences between treatment groups were similar to those for all patients combined in both protocols. In protocol 008, only 45 patients were ≥ 65 years old. For these patients, either the Flex 2.5 or placebo treatment group had a higher mean response than the Flex 5 group; no statistical analysis was done. On the other hand in protocol 006, the 40 patients ≥ 65 years old, suggested there were no differences in treatment group means between this age group and the entire study; therefore, it was difficult to draw conclusions with regard to age.

Differences between treatment group means were similar for males and females across most parameters in both protocols. Similarly, differences between treatment group means were consistent across the 3 race categories in both protocols.

Availability of cyclobenzaprine without prescription could have benefits for society as a whole in addition to the individual patient who chooses to use the product. Self-treatment for acute painful muscle spasm of the back or neck could reduce direct medical costs. Back pain is the second most common symptomatic reason expressed by patients for office visits to primary care physicians. The availability of cyclobenzaprine without prescription could reduce the number of patients who need to see a physician because of acute, uncomplicated, back pain. The indirect costs of back pain have been estimated to be several billion dollars]. Every year 14% of all U.S. workers lose 1 or more days because of back pain. Appropriate use of a muscle relaxant could reduce the number of days it takes a worker to recover enough to return to work. An earlier return to work should decrease the indirect costs of back pain.

Cyclobenzaprine has been shown to be an effective muscle relaxant in patients with acute back pain with muscle spasm. Acute back pain is an appropriate OTC condition as it is self-recognizable and usually not associated with any complicating conditions. Nonprescription analgesics are not universally effective when used to relieve acute back pain. Cyclobenzaprine has a different mechanism of action than analgesics, and the muscle relaxant would be a valuable option for consumers with acute back pain. Other muscle relaxants are available without prescription in Canada and have apparently been safely used by consumers. Availability of cyclobenzaprine without prescription would provide efficacy and convenience benefits to consumers, and could produce societal benefits as well.

Painful Muscle Spasm of the Back as a Self-Treatable Condition

Since all medications have risks of some type, it is good clinical medicine, and common sense, to use medications only when necessary and for the correct reason. As noted above, the Sponsor states that acute back pain is an appropriate OTC condition as it is self-recognizable. However, it is unknown what percentage of acute back pain is due to paraspinal muscle spasm or how much such spasm contributes to back pain even when present; in either case, it is probably not 100%.

The placebo-controlled protocols (006 and 008) required (as noted in the inclusion criteria, above) acute (≤ 7 days, P-008; ≤ 14 days, P-006), physician-rated moderate or moderately severe painful muscle spasm of the lumbar and/or cervical region for entry into the trial. In contrast, in the use trial (009), people must have believed they were experiencing painful muscle spasm, tightness, or soreness, due to strain, overexertion, and minor injuries to the back or neck. However, without physician confirmation of muscle spasm of any severity, it could be argued that these people are not "patients" but "subjects".

This distinction between a subject being able to identify acute back pain vs. the cause of their acute back pain as due to a muscle spasm is not a minor one. As noted by the Sponsor, cyclobenzaprine appears to have a different mechanism of action than analgesics. Therefore, one could argue that this compound should not be used as an analgesic but only to relieve symptoms associated with muscle spasms. Although its muscle relaxant qualities are not well understood, results in protocols 006 and 008 do lend support to the clinical observation that Flex 5 can lead to an improvement in physician-defined muscle spasms and patient-identified pain and discomfort. Unfortunately, how these different clinical endpoints correlate in each patient (i.e.

responder type analysis) was not determined in these trials, comparisons are only possible on mean scores. Nonetheless, it would appear that all the patients in these placebo-controlled protocols were being appropriately treated with Flex 5 since they did have documented paraspinal muscle spasm. The same can NOT be said for the subjects in protocol 009. Without confirmation that the subject identified back pain is actually associated with some degree of muscle spasm, these subjects are placing themselves at unnecessary risk when using Flex 5. Until proven otherwise, it may be true that these subjects would have no better than a 50-50 chance of properly diagnosing their acute back pain as due to, or even associated with, a muscle spasm. Therefore, it would appear that acute back pain due to muscle spasm is not a self-diagnosable condition.

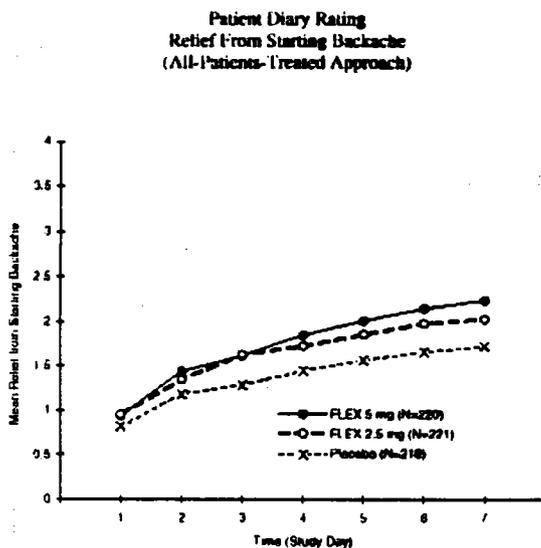
Clinical characteristics of Flex 5 efficacy:

The onset, effect size, duration and dose-response characteristics of Flex 5 were studied in the placebo-controlled trials.

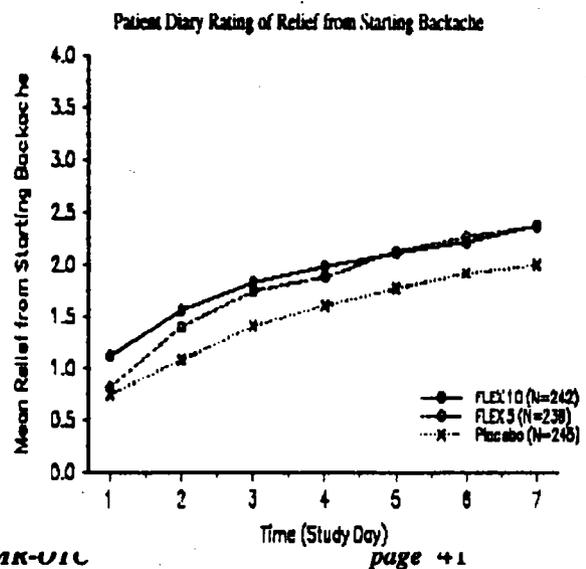
The Sponsor calculated (Table C-18, Worldwide Clinical Summary) the "Time-to-A Lot or Complete Relief" based on the relief from starting backache question answered daily. It was postulated that, since acute musculoskeletal spasm tends to resolve over time, treatment with Flex 5 might hasten the resolution of the spasm and pain. According to this post-hoc analysis, the median time to these endpoints was approximately 2 days less for FLEX 5 (and Flex 10) than placebo; FLEX 2.5 was not significantly different than placebo.

However, this analysis is difficult to place in perspective. Figures 1 and 2, for example, are the results from the patient daily rating of relief from starting backache for both protocols 006 and 008. Recalling that the scale runs from 0=no relief to 4=complete relief, these (mean) results suggest there is a general improvement in all groups, including the placebo arm.

Protocol 008 (Figure 1)



Protocol 006 (Figure 2)



One does not get the impression from the data in these figures that there is a substantial treatment response in any Flex group. Rather, the improvements seem to run a very similar course, with the Flex groups tending to be somewhat better on average. While, Flex 10 seems to have the most consistent efficacy, Flex 2.5 seems to have the least consistent responses associated with its use. At times, Flex 5 and 10 appear similar in relief of symptoms in trial 006, and at times, Flex 5 and 2.5 also appear equally able to relieve symptoms in trial 008. How much any back pain symptom relief correlated with a patients' ability to perform their activities of daily living was not addressed in these protocols.

Somnolence was the most common adverse experience for patients taking FLEX 5, occurring in 29% of that population in the Phase III studies. To determine if Flex 5 efficacy was independent of somnolence, the Sponsor examined the combined efficacy data from Protocols 006 and 008 for the FLEX 5 and placebo treatments by excluding those patients who did not report somnolence. The magnitude of effect for all parameters and time points, and the significance results for patients who did not report somnolence, seemed consistent with the analyses that included all patients. These analyses suggest that FLEX 5 may be efficacious in some patients without inducing somnolence.

Comparison of protocols 006 and 008 shows that the former had an apparent greater sensitivity to demonstrate differences between treatments with regard to onset and magnitude of effect. Since the design and endpoints of these two studies differed only slightly, it is unclear why the results of study 008 were not the same as those of study 006. Analyses of various subgroups based on demographics, pre-study duration of spasm, location of spasm, and baseline severity offered no ready explanation. Nevertheless, while protocol 008 did not exactly reproduce the results of protocol 006, it does provide confirmation that FLEX 5 is efficacious compared to placebo.

The overall efficacy of Flex 5, therefore, seems to be one in which the effect sizes, onset, and duration, though statistically significant from placebo, are clinically modest. However, it is worth noting that relief was generally obtained even though use of analgesics or anti-inflammatory drugs was prohibited. Nonetheless, there do not appear to be any outstandingly robust treatment effects noted with any Flex dose for any parameter (primary or secondary). Similarly, any time-to-response- advantage for Flex 5 over placebo does not seem to be associated with any notable clinical gain. While there are no statistically significant differences between the Flex 5 and the other Flex groups within a study, there are some general numeric trends to suggest the higher dose of Flex is more efficacious at certain time points with certain parameters.

Efficacy vs. Effectiveness:

It is widely accepted that in a randomized clinical trial, efficacy means that the therapy produces a reduction in the probability of experiencing the adverse outcome in the study group being investigated. Efficacy, however, needs to be distinguished from effectiveness. Effectiveness implies that the therapy works under usual conditions of practice as opposed to the conditions of the investigation. It is possible to perform a

randomized clinical trial to assess effectiveness of therapy by using a representative sample of the types of patients to be treated with the therapy and the usual methods that are being used clinically. Therefore, it appears that the efficacy of Flex 5 was established in the placebo-controlled trials (006, 008).

However, it does not appear that the effectiveness of Flex 5 has been demonstrated. As discussed already, without physician confirmation of paraspinal muscle spasm, there is no way to know if the subjects in the use trial would have been patients in the placebo-controlled trial. Furthermore, without a placebo control in the use trial, there is no way to know how the subjects that received Flex 5 compared to subjects that received placebo. As seen in trials 006 and 008, placebo also seems to decrease back pain symptoms over time. This "robust" placebo response seems to reflect the natural history of acute back pain as discussed above by the Sponsor. Of note, it would be useful to compare Flex 5 to other potential therapies for acute back pain (i.e. NSAIDs, acetaminophen, possibly diphenhydramine). The effectiveness of Flex 5 should probably also be established by conducting at least one trial looking at longer-term patterns of use and continued relief of symptoms since subjects will, undoubtedly, repeat use (rather than the single use as studied in trial 009) of Flex 5 if available OTC.

The interpretation of relief of symptoms of back pain in the use trial is further complicated by the fact that subjects were allowed to use concomitant analgesics. In fact, during the study sixty-three percent of patients took concomitant therapies. Those "reported" most often were hormones (21%), central nervous system drugs (21%) and analgesics (21%); most common analgesics were ibuprofen (16%) and acetaminophen (11%). One patient took a skeletal muscle relaxant (methocarbamol). One hundred fifty-eight (35%) of the 449 patients took analgesics for one or more days during the study. The mean number of days was 3.5 with a median of 2 days. Of the 158 patients who used analgesics, 16% used them for more than 7 days.

The pattern of analgesic use by study day is shown in following table. As can be seen, during the study's first 7 days, between 13% and 16% of the 449 patients used a concomitant analgesic. This percentage remained fairly steady over the first 7 days and then decreased. A subset of patients took analgesics daily. The remaining patients took analgesics sporadically without a discernible pattern.

Table 22: Analgesic Use by Study Day in Protocol 009

Study Day	Study Day Number of Patients (N=449)	
	n	%
1	62	14
2	74	16
3	62	14
4	65	14
5	74	16
6	59	13
7	62	14
8	44	10

Finally, how much "bang for the buck" is there with Flex 5 and is this worth the risk. For example, as noted in Table 5 of the use study (009), one of the questions in the baseline pain characteristics of these subjects asked "How much has muscle pain impaired the ability to do usual activities?" Only 24% noted "very much", 4% noted "extremely", while the remainder of the subjects noted "somewhat", "a little" or "not at all". Especially for consideration of OTC use, there should probably be more of a need to justify use of Flex 5 and more attention, in future effectiveness trials, to understand how these important patient parameters of daily living are influenced.

Efficacy/Effectiveness-Conclusions:

Based on the results of the two double-blind, placebo-controlled trials for Flex 5, it can be concluded that:

- Flex 5 mg provides symptomatic relief from painful muscle spasm of the back and/or neck over a 1-week course of treatment i.e. it is efficacious.
- Improvement of paraspinal muscle spasm occurs more quickly with Flex 5 mg than with placebo.
- There is evidence to suggest a modest dose-related response for efficacy between Flex 2.5 and 10.
- Flex 2.5 is not a consistently efficacious dose.
- Flex 5 may demonstrate efficacy within 24 to 48 hours of initiating treatment.
- The efficacy of Flex 5 may not be dependent on the presence of sedation.
- Somnolence and dry mouth are the most common adverse experiences with Flex 5; the incidence of severe somnolence is approximately 2.6%. Somnolence may resolve in some patients.
- It is unclear whether exclusive use of patient-derived primary endpoints is sufficient to characterize the response to treatment with Flex 5 in the absence of physician-derived variables in back pain studies.
- It is unclear whether physician-defined clinical assessment of back spasm is sufficient to characterize paraspinal muscle spasm in the absence of a more objective assessment.

Based on the results of the "pattern-of-use" trial for Flex 5, it can be concluded that:

- Flex 5 does not appear to be effective.

Safety Review (Limited):

As indicated at the beginning of the NDA review, the primary (including overall) review of the safety of Flex 5 will be done by Dr. Neuner of OTC. This brief safety review will focus on the two placebo-controlled trials and conclude with some discussion of labeling/OTC use issues.

Overview:

Table 23 lists the adverse event (AE) experience in protocols 006 and 008. It should be recalled that there were no laboratory tests done in either study, therefore, there are no laboratory AEs listed.

Table 23: Summary of Adverse Events in Protocols 006 and 008

Safety Event	Flex 10 (P-006) n=249	Flex 5 (P-006) n=242	Flex 5 (P-008) n=222	Flex 2.5 (P-008) n=223	Placebo (P-006) n=246	Placebo (P-008) n=223
Clinical AE	154 (62%) ¹	131 (54%) ¹	124 (56%) ¹	98 (44%)	87 (35%)	79 (35%)
Drug-related AE	143 (57%) ¹	118 (49%) ¹	106 (48%) ^{1,3}	79 (35%) ¹	57 (23%)	50 (22%)
Discontinued due to AE	20 (8%) ¹	12 (5%)	9 (4%)	5 (2%)	6 (2%)	4 (2%)
SAEs	0	0	1	1	0	4 (2%)
Death	0	0	0	0	0	1
Somnolence						
Total	94 (38%) ¹	77 (32%) ¹	58 (26%) ¹	44 (20%) ¹	28 (11%)	17 (8%)
Severe	9 (4%)	7 (3%)	4 (2%)	4 (2%)	2 (1%)	1
Dry Mouth						
Total	79 (32%) ^{1,2}	50 (21%) ¹	48 (22%) ^{1,3}	31 (14%) ¹	16 (7%)	15 (7%)
Severe	5 (2%)	2 (1%)	5 (2%)	0	0	0

1. Significantly different from placebo ($p \leq 0.05$).
2. Significantly different from Flex 5 ($p \leq 0.05$).
3. Significantly different from Flex 2.5 ($p \leq 0.05$).

Table 24 summarizes the AEs by body system in these same two protocols. The most common AE under the Digestive System, as seen in Table 23, was dry mouth in all groups. Similarly, as suggested by the prior table (Table 23), the most common AE under Nervous System and Psychiatric was somnolence in all groups. **Somnolence and dry mouth** were the most frequently reported AEs in all the Flex treatment groups and they were significantly more prevalent in the Flex groups than the placebo group. Of note, the "specific" terms of drowsiness, sleepiness, sedation, and lethargy were all mapped to the "preferred" term of somnolence and so somnolence was the term used throughout the NDA.

Reviewer's comment: Dr. Laughren's review specifically addresses the issue of psychomotor impairment with cyclobenzaprine.

Table 24: Summary of Adverse Events by Body System-Protocols 006 and 008

System ²	Flex 10 (P-006) n=249	Flex 5 (P-006) n=242	Flex 5 (P-008) n=222	Flex 2.5 (P-008) n=223	Placebo (P-006) n=246	Placebo (P-008) n=223
Body as Whole	20 (8%)	18 (7%)	21 (10%)	14 (6%)	11 (5%)	12 (5%)
Digestive System	83 (33%) ¹	72 (30%) ¹	59 (27%) ¹	46 (21%)	33 (13%)	36 (16%)
Musculoskeletal System	3 (1%)	3 (1%)	6 (3%)	10 (5%)	6 (2%)	7 (3%)
Special	9 (4%)	5 (2%)	7 (3%)	6 (3%)	5 (2%)	1
Respiratory	11 (4%)	6 (3%)	14 (6%)	10 (5%)	12 (5%)	8 (4%)
Skin and Appendage	4 (2%)	4 (2%)	4 (2%)	2 (1%)	3 (1%)	3 (1%)
Nervous/ Psychiatric	111 (45%)	91 (38%)	75 (34%)	61 (27%)	51 (21%)	39 (18%)

1. Significantly different than placebo (p,0.05)
2. See Table 23 for more detail on differences among treatment groups.

Adverse Events:

Protocol 006:

As noted in Tables 23 and 24, in protocol 006, there were three hundred and seventy-two (372) patients who reported as least one AE; patients in the Flex 10 and 5 groups reported significantly more AEs than patients in the placebo group. In fact, there were significantly more patients in the Flex10 (57%) and Flex 5 (49%) groups with drug-related AEs than on placebo (23%). Also, significantly more patients on Flex 10 (8%) discontinued this study due to an AE than patients on placebo (2%).

In study 006, there were 199 (27%) patients who reported at least one incidence of somnolence: 94 (38%) in the Flex 10 group, 77 (32%) in the Flex 5 group. Both of these incidence rates were statistically significantly different than the rate noted in the placebo group, i.e. 28 (11%). Although not shown here, most of the somnolence AEs were of mild intensity: 64 (26%) in the Flex 10 group, 43 (18%) in the Flex 5 group, and 18 (7%)

in the placebo group. As noted in Table 23, seven (3%) patients in the Flex 5 group had somnolence rated as severe, and 9 patients (4%) in the Flex 10 group reported severe somnolence, as compared to 2 patients (1%) in the placebo group.

In protocol 006, there were 145 (20%) patients who reported at least one incidence of dry mouth: 79 (32%) in the Flex10 group, 50 (21%) in the Flex 5 group, and 16 (7%) in the placebo group. These Flex incidence rates were statistically significantly different than the placebo rates. Although not shown here, most of the dry mouth AEs were of mild intensity: 46 (19%) in the Flex 10 group, 33 (14%) in the Flex 5 group, and 13 (5%) in the placebo group. There were five (2%), two (1%), and zero patients in the Flex 10, 5 and placebo groups respectively that had their dry mouth AE rated as severe.

Therefore, in protocol 006, **there were significantly more patients in the Flex 10 and 5 groups that experienced somnolence, dry mouth, and asthenia/fatigue** (data not shown, NDA Table 42, protocol 006) than placebo. In fact, the Flex 10 group also had a higher incidence of dry mouth than the Flex 5 group (NDA Table 42, protocol 006).

Protocol 008:

As noted in Tables 23 and 24, three hundred and one patients (301) reported at least one adverse experience. Patients in the Flex 5 group reported significantly more AEs (56%) than patients in the placebo group (35%). Further, patients on Flex 5 and Flex 2.5 had significantly more drug-related AEs than on placebo (48%, 35%, and 22%, respectively). In fact, there was also a significant difference between the Flex 5 and 2.5 groups with regard to these drug-related AEs. There were no significant differences between any of the treatment groups with respect to discontinuing the study due to an AE.

Once again, as seen in Table 24, the highest percentage of AEs were in the nervous system/psychiatric and digestive systems. For these body systems, plus the special senses body system, patients on Flex 5 experienced more AEs than patients on placebo. For nervous system/psychiatric system, patients in the Flex 2.5 treatment group also experienced more AEs than patients in the placebo group.

As seen in Table 23, the most frequently reported AE on Flex 5, Flex 2.5 and placebo were as follows: somnolence (26%, 20%, 8%), dry mouth (22%, 14%, 7%). Not included in Table 23 but noted in the Sponsor review (NDA Table 47) were headache (5%, 7%, 7%), asthenia/fatigue (5%, 4%, 3%), nausea (1%, 4%, 5%), and dizziness (3%, 3%, 3%) for Flex 5, Flex 2.5 and placebo, respectively. Significantly more patients in the Flex 5 and 2.5 groups experienced somnolence and dry mouth than patients in the placebo group. The Flex 5 group also had a significantly higher incidence of dry mouth than the Flex 2.5-mg group.

Withdrawals:

Protocol 006:

Of the 38 patients in protocol 006 who discontinued due to clinical AEs, twenty one (21) patients had somnolence listed as the only, of at least one of the adverse experiences as follows: 13 (5%) on Flex 10, six (3%) on Flex 5 and two (1%) on placebo. In fact, the Flex 10 group had significantly more patients discontinue the study with at least one incidence of somnolence than the placebo group. The Sponsor generated table (NDA Table 43) listed all patients who discontinued along with the adverse experiences, duration, severity, and outcome of the event.

The reasons for discontinuation in the Flex 5 groups included: **somnolence***, **headache***, **dizziness***, **blurred vision***, **confusion***, **decreased mental acuity***, **hypesthesia***, **nausea***, **dry mouth***, **asthenia/fatigue***, taste perversion (one patient), and neuritis (one patient). These are the same reasons patients in the Flex 10 group discontinued the study with the addition of the following AEs: **apprehension***, herpes zoster, vertigo, **anxiety***, disorientation, **irritability***, **dysarthria*** (this was along with somnolence, **nervousness*** and **abdominal pain*** in one patient-AN 0461), **dyspepsia***, urinary frequency, influenza, and **ataxia*** (along with somnolence in one patient). In the placebo group, the reasons were the same as above with the addition of back pain, **diarrhea***, and emotional changes. The severity of these AEs ranged from mild to severe with most being moderate. All these AEs resolved by the end of the study with the exception of hypesthesia (in one Flex 5 patient-AN 0220, neuritis in one Flex 5 patient-AN 0578) and headache/back pain in one placebo patient-AN 0238).

Protocol 008:

In protocol 008, there were 18 patients total (9, 5 and 4 patients in the Flex 5, Flex 2.5, and placebo groups, respectively) who discontinued because of a clinical AE. Reasons for leaving the study in the Flex 5 included **somnolence***, **dry mouth***, constipation, neck/back pain, **dizziness***, paresthesia, headache, trauma, sinusitis, URI, **dyspnea*** (along with somnolence and dry mouth in one patient) and **decreases in mental acuity***. These AEs were generally of moderate duration and only the somnolence, decreased acuity, dyspnea and dry mouth were "probably" attributed to drug. In the Flex 2.5 group, reasons also included **asthenia/fatigue***, and dizziness with nausea and fasciculation in one patient. The four placebo patients discontinued for the same type of reasons as listed for the Flex groups (i.e. nausea, asthenia/fatigue, somnolence, and headache). Eight of these 18 patients had at least one incidence of somnolence (4, 3, and 1 in the Flex 5, Flex 2.5, and placebo groups, respectively). There were no apparent significant differences between treatment groups with respect to the number of patients who discontinued due to an AE and had at least one instance of somnolence.

Reviewer's comment: The AEs noted with the () next to them were considered by the investigators as probably or definitely related to study drug in any particular patient.*

Serious Adverse Events:

None of the SAEs that follow were considered drug related by the investigators.

As noted in Table 23, there were no serious adverse events (SAEs) in protocol 006. However, there were a total of six (6) AEs in protocol 008 considered serious by the investigators. Three of these patients were from the disqualified investigator (Dr. Fiddes, site 021). One patient from this disqualified site (AN 2489, further described below under the "Deaths" section) was a 33 year old (y/o) female who experienced a myocardial infarction and died (day 5) in the Flex 5 group. Two other patients from this disqualified site also discontinued the study (patient AN 2502 from each of the Flex 2.5 group and patient AN 2471 from the placebo group).

The other three SAEs included an 81 y/o female with back pain (AN 2325), a 41 y/o male with chest pain and syncope and labyrinthitis (AN 2326) and a 56 y/o female (AN 2357) with a breast mass. The Sponsor generated report on these patients (all from study site 008-003, Dr. Bianchi) are as follows:

Patient AN 2326: Labyrinthitis, Chest Pain, PreSyncope

This 41-year-old male presented to the physician's office for Visit 3 (Study Day 8) with complaints of dizziness, chest pain, nausea, vomiting, diaphoresis, pallor, and near-syncope. He was admitted to the hospital for observation. Myocardial infarction was ruled out and he was discharged 3 days later. The investigator considered these adverse experiences to be definitely not related to study medication.

Patient AN 2325: Pain, back

This 81-year-old female presented to the emergency room, on Study Day 2, complaining of worsening of back pain. She was admitted for evaluation and treatment of the back pain and was started on intravenous fluids and ROBAXIN (A. H. Robins). Follow-up was done by the investigator. The back pain was resolved by 12/20/94, as reported in the Case Report Form. The investigator felt that the back pain was definitely not related to study drug.

Patient AN 2357: Breast, malignant neoplasm

This 56-year-old female was entered into the study. On Study Day 2, she had a mammogram that indicated a mass in the right breast. A biopsy was performed and cancer detected. The patient was hospitalized and underwent a modified right radical mastectomy. The investigator considers this adverse experience to be definitely not related to study drug.

Deaths:

As noted above, there was one death during these short-term, placebo-controlled trials. The following is the summary as prepared by the Sponsor for this patient (AN 2489):

This 33-year-old female, with a history of obesity and insulin-dependent diabetes mellitus was shopping on Study Day 5. She became agitated and complained of shortness of breath. She was transported to the emergency room (ER) by ambulance. She was awake, combative, diaphoretic, pale and had low blood pressure upon arrival at the ER. Her blood glucose was 450 mg/dL and an ECG revealed widened complexes. The patient suddenly experienced ventricular fibrillation, lost consciousness and was determined to be in asystolic arrest. She was treated with CPR, bicarbonate, epinephrine, dopamine, atropine, lidocaine bretylium, and insulin. A pulse was never established and the patient was pronounced dead. The attending physician stated that the patient's diabetes was out of control. She experienced a myocardial infarction, went into cardiac arrest, and died. It was later discovered the patient had a history of cocaine use. An autopsy revealed the presence of the cocaine metabolite, benzoylecgonine, at a concentration of 0.1 µg/mL. This can be considered an amount great enough to cause arterial occlusion. Cyclobenzaprine levels were not measured at autopsy and study drug supplies could not be returned to determine compliance with study medication. Also, upon examination it was found that the patient had markedly severe atherosclerotic heart disease, worsened by her diabetes mellitus. The investigator considers the patient's death to be definitely not related to study medication.

Discussion/Conclusions for Flex 5 safety:

It seems difficult, if not impossible, to dissociate how Flexeril "works" from the adverse event profile it elicits during its use; i.e. the "therapeutic margin" appears small. This undoubtedly has to do with the "black box" mechanism of action; Flexeril relaxes muscle spasm but does not directly relax muscle spasm. As noted earlier in this review, there have been various suggestions offered as to how Flexeril might act and many of these involve poorly understood mechanisms (i.e. inhibition of serotonergic vs. noradrenergic systems) involving the CNS. Therefore, it is not surprising, as noted above in the placebo-controlled trials, that this "tricyclic-like" drug shares many of the adverse events in this class including sedation and anti-cholinergic effects such as dry mouth, confusion and blurred vision. It is worth noting that the other potential anti-cholinergic effects of constipation and urinary retention were among the exclusions for patients in these trials.

Considering the shared properties with tricyclics, side effects of potentially more concern relate to the cardiovascular system and seizure threshold. Actions of the adrenergic and cholinergic systems may contribute to direct cardiac actions (i.e. alterations in rate, delays in conduction, decreases in myocardial contractility) as well as hypotensive effects. For example, the dysrhythmic potential of cyclobenzaprine has been noted in the literature. This may be especially true when cyclobenzaprine is used in combination with

agents that are P-450 inhibitors and known to prolong the QT interval and so predisposing to torsade de pointe. Similarly, the seizure threshold can be lowered increasing the frequency of epileptic convulsions. These side effects can occur in therapeutic dosages in susceptible populations such as the elderly, children, and cardiac or epileptic patients. These were generally NOT the type of patients studied in any of these trials, either because of exclusion, or because they were present in small numbers (only about 100 patients were > 65 years in these two trials).

The safety questions and issues that surround use of Flexeril, especially in combination with other medications and recreational "drugs" or alcohol, needs be answered more thoroughly than in these short-term trials that did not adequately sample the intended OTC population. For example, a recent case report notes the high concentrations of cyclobenzaprine and alcohol can be fatal. Certainly, it seems true that in these carefully controlled clinical trial settings, one did not see any apparent effects on things like blood pressure or pulse rate, seizures, torsades de pointes, worsened constipation, and increased urinary hesitancy (to name a few). Similarly, there did not appear to be any serious adverse events or deaths directly attributable to Flex 5. It also appears that gender and race did not seem to influence the safety profile of Flex 5. However, these very limited observations can be no convincing reassurance that all these (and many more) safety concerns will not mushroom into major public health issues once released for general use by the real "all-comers" as found in an OTC population. Finally, the concern for safety issues for OTC use of Flex 5 may easily dovetail into the safety concerns about the prescription dose of Flex 10 if patients exhibit dose-creep". In fact, this was suggested in protocol 009 since about 10% of patients used twice the labeled dose of Flex 5. The saying, "The devil we know is better than the devil we don't know" may very well apply to the situation of OTC use of Flexeril.

Therefore, without even considering the potential psychomotor impairment associated with cyclobenzaprine, it would appear that the safety of Flex 5 for OTC use has not been adequately explored in this NDA.