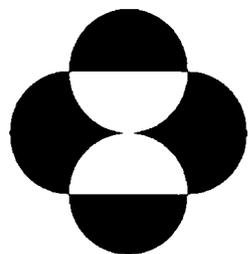


NONPRESCRIPTION DRUGS
ADVISORY COMMITTEE AND
ARTHRITIS ADVISORY
COMMITTEE

JULY 20, 1999

MERCK BRIEFING PACKAGE



MERCK

Research Laboratories

**NDA 21-070:
Nonprescription FLEXERIL MR™
5 mg Tablets**

(Cyclobenzaprine Hydrochloride)

**FDA Advisory Committee
Background Information**

Presented to:

Nonprescription Drugs
and Arthritis Advisory Committees

July 20, 1999

NONPRESCRIPTION DRUGS
ADVISORY COMMITTEE AND
ARTHRITIS ADVISORY
COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

GUIDE TO THE READER

NDA 21-070: Nonprescription FLEXERIL 5-mg Tablets
Advisory Committee Background Information
Guide to the Reader

This volume provides a comprehensive summary of the development program undertaken by Merck Research Laboratories to generate the New Drug Application (NDA) supporting nonprescription availability of the 5-mg dose of FLEXERIL (cyclobenzaprine hydrochloride) as a muscle relaxant. All of the information contained within this summary is extracted from documents provided to the FDA as part of the NDA. In some cases, material has been reordered or reformatted to accommodate the need to condense the information into a manageable package.

Synopsis: This package represents a large amount of information including results from 13 clinical studies and post-marketing safety information from over 20 years experience with the 10-mg prescription dose. The synopsis distills the information further, and is intended to orient the reader to the key elements of the more detailed presentation that follows. Annotations are provided to the page numbers of the sections of the main summary where the expanded information is located.

Introduction: A brief overview of the program and rationale for OTC availability of a lower dose of cyclobenzaprine is provided.

Efficacy: The design, analysis methods, and results of the 2 pivotal efficacy studies are summarized. This includes a prespecified analysis of the combined study data and an examination of the clinical relevance of the statistically significant findings.

Safety: The safety profile of cyclobenzaprine is examined from several perspectives. First, **clinical trial results** from the OTC program supporting the 5-mg dose are examined. Second, the extensive **marketing experience** with the 10-mg dose is reviewed with special attention focused on adverse experiences, **potential for abuse**, and the **overdose profile**. Finally, we review the results of the 6 clinical pharmacology studies designed to characterize the **sedative potential** associated with the lower 5-mg dose of cyclobenzaprine. The section ends with a discussion of the overall safety profile as it relates to nonprescription use.

In subsequent sections we review (1) the results of the **pattern-of-use study** which assessed consumer ability to take the product according to OTC labeling, (2) the **clinical pharmacokinetics** of the 5-mg dose, (3) the **rationale for the proposed labeling**, and (4) the **benefit-to-risk relationship**.

A **list of references**, denoted in the text by numbers within brackets [], follows the conclusions of the main summary. **Appendix 1** provides a more detailed description of the psychomotor performance test parameters. Additional **attachments** include copies of the current **prescription label** for the 10-mg product, the **proposed OTC label** and package insert, and copies of relevant **publications**.

NONPRESCRIPTION DRUGS
ADVISORY COMMITTEE AND
ARTHRITIS ADVISORY
COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

TABLE OF CONTENTS

Nonprescription FLEXERIL™
FDA Advisory Committee Background Information

	<u>PAGE</u>
Synopsis	S-1
1. Introduction	1
1.1 Rationale For Nonprescription Cyclobenzaprine in the Marketplace	1
1.2 Overview of Clinical Program	2
2. Efficacy	4
2.1 Rationale for Studies Conducted	4
2.2 Design of Clinical Studies	5
2.2.1 Rationale for Dose Selection in Clinical Studies	5
2.2.2 Overview of Protocol Designs	6
2.2.3 Description of Statistical Methods	9
2.3 Demographics of the Study Population	11
2.4 Efficacy Results	12
2.4.1 Double-Blind, Controlled Phase III Studies	12
2.4.2 Overall Efficacy	12
2.4.2.1 Patient-Rated Clinical Global Impression of Change	13
2.4.2.2 Patient Rating of Medication Helpfulness	14
2.4.2.3 Patient Diary Rating of Relief From Starting Backache	15
2.4.2.4 Physician Rating of Muscle Spasm	16
2.4.2.5 Magnitude of Effect	19
2.4.2.6 Onset of Effect	25
2.4.2.7 Dose Response	26
2.4.2.8 Efficacy Independent of Somnolence	28
2.4.2.9 Location of Muscle Spasm: Lumbar Versus Cervical	29
2.4.2.10 Drug-Demographic Interactions for Efficacy	30
2.4.2.11 Open-Label Pattern-of-Use Study	30
2.5 Efficacy Discussion	31
2.6 Efficacy Conclusions	33
3. Safety	34
3.1 Introduction	34
3.2 Overall Extent of Exposure of the Study Population	34
3.3 Demographics and Other Characteristics of the Study Population	35
3.4 Clinical Adverse Experiences in Nonprescription NDA Studies	37
3.4.1 Incidence of Clinical Adverse Experiences	38
3.4.2 Time Course and Intensity of Somnolence	41
3.4.3 Serious Clinical Adverse Experiences	43
3.4.4 Discontinuations Due to Clinical Adverse Experiences	44
3.4.5 Drug-Demographic Interactions	46
3.4.6 Drug-Disease Interactions	46
3.4.7 Drug-Drug Interactions	47
3.5 Laboratory Adverse Experiences	47
3.6 Special Examination Adverse Experiences	48

Nonprescription FLEXERIL™
FDA Advisory Committee Background Information

	<u>PAGE</u>
3.7 Clinical Safety Measurements	48
3.8 Experience with Marketed Prescription Dose (10 mg)	48
3.8.1 Prescription Marketing Application Studies	48
3.8.2 Postmarketing Surveillance Studies	51
3.8.3 Spontaneous Reports	53
3.8.3.1 Deaths	54
3.8.3.2 Body as a Whole	55
3.8.3.3 Cardiovascular System	55
3.8.3.4 Digestive Body System	56
3.8.3.5 Hepatobiliary System	56
3.8.3.6 Nervous System	56
3.8.3.7 Psychiatric Disorders	56
3.8.3.8 Trauma	57
3.8.3.9 Use During Pregnancy	58
3.8.3.10 Withdrawal Effects	58
3.8.3.11 Drug-Drug Interactions	59
3.8.4 Drug Abuse and Overdosage Information	60
3.9 Psychomotor Studies	63
3.9.1 Overview	63
3.9.2 Sedation in Young Subjects	69
3.9.2.1 Protocol 012	69
3.9.2.2 Protocol 001	73
3.9.2.3 Protocol 002	75
3.9.2.4 Protocol 015	76
3.9.2.5 Summary of Sedation in Young Subjects	78
3.9.3 Sedation in Elderly Subjects	79
3.9.3.1 Protocol 003	79
3.9.3.2 Protocol 014	80
3.9.3.3 Summary of Sedation in Elderly	81
3.9.4 Psychomotor Performance in Young Subjects	81
3.9.4.1 Protocol 012	82
3.9.4.2 Protocol 015	83
3.9.4.3 Protocol 001	85
3.9.4.4 Protocol 002	86
3.9.4.5 Summary of Psychomotor Performance in Young Subjects	86
3.9.5 Psychomotor Performance in Elderly Subjects	87
3.9.5.1 Protocol 014	87
3.9.5.2 Protocol 003	89
3.9.5.3 Summary of Psychomotor Performance in Elderly Subjects	90
3.9.6 Conclusions From Psychomotor Studies	90
3.10 Safety Discussion	91
3.11 Safety Conclusions	93

Nonprescription FLEXERIL™
FDA Advisory Committee Background Information

	<u>PAGE</u>
4. Pattern-of-Use Data	95
5. Clinical Pharmacology—Human Pharmacokinetics and Bioavailability	99
5.1 In Vitro Metabolism	99
5.2 Human Metabolism	99
5.3 Pharmacokinetics	100
5.4 Pharmacokinetics in Different Subpopulations	102
5.4.1 Effect of Age	102
5.4.2 Effect of Hepatic Insufficiency	104
5.4.3 Effect of Gender	105
5.5 Drug-Drug Interactions	106
5.6 Clinical Pharmacology Conclusions	107
6. Label Development	108
6.1 Rationale for Information in Label	108
6.2 Label Comprehension Study	111
7. Benefits Versus Risks Relationship	118
7.1 Potential Benefits of Nonprescription Cyclobenzaprine	118
7.2 Potential Risks of Nonprescription Cyclobenzaprine	119
7.2.1 Risks Related to Sedation	119
7.2.2 Risks of Neuropsychiatric Adverse Experiences Other Than Sedation	120
7.2.3 Risks Related to Anticholinergic Properties	121
7.2.4 Risks Related to Drug Interactions	121
7.2.5 Risks of Abuse/Misuse	121
7.2.6 Risks Related to Age	122
7.3 Benefit-to-Risk Conclusions	123
8. List of References	124
APPENDIX 1 Descriptions of Performance Tests in Psychomotor Studies	127

NONPRESCRIPTION DRUGS
ADVISORY COMMITTEE AND
ARTHRITIS ADVISORY
COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

SYNOPSIS

FLEXERIL OTC

Advisory Committee Background Information

SYNOPSIS

Rationale For Nonprescription Availability of FLEXERIL 5 mg (pp. 1-2)

FLEXERIL (cyclobenzaprine hydrochloride) has been marketed as a prescription drug in the United States since 1977 at a recommended dose of 10 mg three times daily. It is indicated as an adjunct to rest and physical therapy for the relief of muscle spasm associated with acute, painful musculoskeletal conditions such as back pain. Merck Research Labs, in collaboration with Johnson & Johnson-Merck Consumer Pharmaceuticals, is now seeking marketing authorization for a 5-mg t.i.d. dose for nonprescription (over-the-counter, OTC) use for relief of painful muscle tightness and spasm of the back or neck due to recent strain, overuse, or minor injury.

Acute back pain, often accompanied by spasm, is a common disorder that can result in significant functional disability leading to decreased work productivity and impaired activities of daily living. Up to 75% of the adult population report back problems at some time in their lives, with 50% of working-age people surveyed admitting to back symptoms at least once a year. While acute back pain is usually not serious, it often disrupts the patient's normal work and social activities for several days. The currently available OTC medications used to treat acute back pain with spasm are largely analgesics and local balms, but these agents often do not provide adequate relief for muscle spasm. Cyclobenzaprine 10 mg t.i.d. has been shown to relieve acute back pain with muscle spasm, and has been widely prescribed with or without analgesics/NSAIDs for over 20 years. Over 10,000,000 prescriptions are dispensed on an annual basis with over 100,000,000 total prescription dispensed since cyclobenzaprine was first introduced.

Patients with acute back pain may benefit from motion and early mobilization. Convenient access to an effective muscle relaxant with an acceptable tolerability profile would be a valuable addition to currently available OTC therapy options. Data presented in this document show that cyclobenzaprine shortens recovery time, therefore offering the opportunity for early treatment and decreased time lost from daily responsibilities. Thus, such a product may be expected to improve quality of life in what is often a recurring condition.

Rationale For Nonprescription Availability of FLEXERIL 5 mg (pp. 1-2) (Cont.)

It is well established that conservative care without aggressive diagnostic testing is appropriate for the initial treatment of acute uncomplicated back pain and associated spasms. Given the consumer trend toward self care and the current need to consult a physician before one can obtain the benefit of a muscle relaxant, Merck undertook the development of cyclobenzaprine for nonprescription use.

Overview of Clinical Program (pp. 2-3)

Recognizing that drowsiness is one of the main side effects of the prescription dose, a program was designed to test whether lower doses of cyclobenzaprine (2.5 and 5 mg t.i.d.) would cause less drowsiness while retaining efficacy in painful muscle spasm of the back or neck. Thirteen clinical studies were conducted in support of the Rx-to-OTC switch of cyclobenzaprine. These studies are summarized according to the type of study in Table 1 (p. 4). They included four pharmacokinetic studies, six psychomotor studies designed to characterize the drowsiness reported by some patients taking cyclobenzaprine, two definitive Phase III efficacy studies and one open-label Pattern-of-Use study.

Efficacy of Cyclobenzaprine 5 mg (pp. 4-33)

Study Design: The placebo-controlled Phase III clinical efficacy program was based on the hypothesis that cyclobenzaprine 5 mg t.i.d. for 7 days would be effective in treating patients with painful acute musculoskeletal spasm of the lower back or neck. The objective and subjective criteria that were tested are standard criteria that have been shown to be sensitive measures of muscle-relaxant activity. Pivotal efficacy information was obtained from two double-blind, placebo-controlled trials (Protocol 006, N=737; Protocol 008, N=668). In Protocol 006 a third arm using the 10 mg t.i.d. prescription dose was included, and in Protocol 008 the third arm was a potentially suboptimal dose of 2.5 mg t.i.d. Concomitant use of analgesics or anti-inflammatory drugs was prohibited. Patients entered with acute back or neck pain with moderate to moderately severe muscle spasm. Subjective and objective measures were rated at baseline (Visit 1 on Day 1), mid-point (Visit 2 on Day 3 or 4) and the end of the trials (Visit 3 on Day 8). Time to onset of relief was assessed by obtaining daily Diary Card ratings of relief. The three primary endpoints involved patient-reported assessments of relief and are listed as follows:

Primary Efficacy Endpoints (Protocols 006 and 008)

Patient-Rated Global Impression of Change	Clinic Visits 2 and 3
Patient Rating of Medication Helpfulness	Clinic Visits 2 and 3
Patient-Rated Relief from Starting Backache	Diary Data on Days 3 and 7

Efficacy of Cyclobenzaprine 5 mg (pp. 4-33) (Cont.)

Statistical significance was required a priori for at least two of the three primary endpoint parameters for at least one of the two time points in order to conclude superior efficacy for cyclobenzaprine 5 mg over placebo. Each of the six comparisons was made at the 0.030 level in order to adjust for multiplicity.

In order to verify the presence and extent of palpable muscle spasm, physician examination was included as one of the two secondary endpoints as follows:

Secondary Efficacy Endpoints (Protocols 006 and 008)

Physician Rating of Muscle Spasm	Clinic Visits 2 and 3
Patient-Rated Relief from Starting Backache	Diary Data on Days 1,2,4-6

Overall Efficacy Results: Pairwise comparisons of the cyclobenzaprine 5 mg and placebo groups in both studies demonstrated statistically significant differences ($p \leq 0.030$) for all three primary endpoints at Visit 3 and/or Day 7 (for Diary data) of treatment (Table A). Cyclobenzaprine 5 mg was also significantly better than placebo in all three primary parameters at the earlier Visit 2 time point in Protocol 006, but not Protocol 008. Protocol 006 demonstrated that cyclobenzaprine 10 mg (prescription dose) was also significantly better than placebo in the three primary endpoints at both primary time points with an effect similar to that of the 5 mg proposed OTC dose. Protocol 008 showed that cyclobenzaprine 2.5 mg was significantly better than placebo in one of three endpoints at the first primary time point but not at the second primary time point.

Both protocols demonstrated statistically significant ($p \leq 0.030$) efficacy for the primary endpoints. Differences between cyclobenzaprine 5 mg and placebo were larger and appeared earlier in Protocol 006 than Protocol 008, although the design, patient enrollment, and endpoints of the two studies differed only slightly.

Efficacy of Cyclobenzaprine 5 mg (pp. 4-33) (Cont.)

Table A

**Double Blind Efficacy Studies: Summary of Comparisons Versus Placebo
 for Primary Efficacy Parameters**

**Estimate of CYC versus Placebo Difference (95% C.I.)
 p-value for CYC versus Placebo Comparison**

		Protocol 006		Protocol 008	
		CYC 10 (n=238)	CYC 5 (n=238)	CYC 5 (n=220)	CYC 2.5 (n=221)
Patient-Rated Global Impression of Change	Visit 2	0.42 (.24, .60) <0.001	0.45 (.27, .63) <0.001	0.12 (-.08, .32) 0.242	0.06 (-.14, 0.26) 0.548
	Visit 3	0.41 (.20, .62) <0.001	0.49 (.28, .71) <0.001	0.35 (.11, .59) 0.004	0.22 (-.02, .46) 0.074
Patient Rating of Medication Helpfulness	Visit 2	0.45 (.24, .66) <0.001	0.48 (.27, .70) <0.001	0.17 (-.06, .39) 0.145	0.02 (-.20, .25) 0.845
	Visit 3	0.53 (.29, .78) <0.001	0.49 (.24, .74) <0.001	0.36 (.09, .62) 0.009	0.20 (-.07, .47) 0.147
Relief from Starting Backache	Day 3	0.44 (.24, .64) <0.001	0.38 (.17, .58) <0.001	0.22 (-.00, .44) 0.051	0.32 (.10, .54) 0.004
	Day 7	0.45 (.22, .69) <0.001	0.45 (.21, .69) <0.001	0.42 (.16, .69) 0.002	0.24 (-.03, .50) 0.081

Each parameter was evaluated using a 5-point ordered categorical scale where "0" represents the worst outcome and "4" represents the best outcome. A positive difference for CYC versus placebo indicates a more favorable outcome for cyclobenzaprine.
Bolded p-values indicate a statistically significant difference for CYC versus placebo comparison, $p \leq 0.030$.

The secondary endpoint physician assessments performed at baseline and subsequent visits, confirmed that cyclobenzaprine 5 mg was associated with a greater reduction in palpable muscle spasm compared to that seen in patients treated with placebo. This finding in both placebo-controlled trials helped to validate the subjective assessments provided by the patients.

The prespecified combined statistical analysis of Protocols 006 and 008 characterized the dose-response for cyclobenzaprine, and provided further validation of the study results. The combined analysis also showed that the onset of effect for the 5 mg dose occurs within 24 to 48 hours of initiating treatment, with mean relief from starting backache for cyclobenzaprine 5 mg being significantly better than placebo beginning on Study Day 2. The overall efficacy of the 5-mg dose differed only slightly from that of the 10-mg prescription dose, with the higher dose having a faster onset of action. The lower 2.5-mg dose was associated with suboptimal efficacy results.

Efficacy of Cyclobenzaprine 5 mg (pp. 4-33) (Cont.)

The differences between cyclobenzaprine 5 mg and placebo in the primary endpoints were large enough to be considered clinically meaningful. In both studies at both primary time points, there was an 11- to 20-percentage-point difference in proportion of predefined responders between cyclobenzaprine 5 mg and placebo. Additionally, the median Time-to-A-Lot or Complete Relief was approximately 2 days less for cyclobenzaprine 5 mg than placebo. The "effect sizes" (an analysis undertaken in consultation with FDA which is calculated by dividing the difference in means by the pooled standard deviation) for cyclobenzaprine 5 mg compare favorably with those of other nonprescription medications approved for indications that have a high placebo response and rely on subjective self-assessment of symptoms.

Drowsiness, most often mild in intensity, was reported by approximately 30% of patients receiving the 5-mg dose. While drowsiness may be therapeutically useful for patients with severe back or neck pain with spasm, drowsiness was not required for cyclobenzaprine 5 mg to be effective. The combined data from Protocols 006 and 008 showed that the statistically significant efficacy advantage for cyclobenzaprine 5 mg relative to placebo was retained for all parameters and time points when only patients who did not report drowsiness were analyzed.

Efficacy Conclusions:

- Both the 5 mg and 10 mg t.i.d. dose of cyclobenzaprine provide clinically meaningful symptomatic relief from painful muscle spasm of the back and/or neck over a 1-week course of treatment.
- Resolution of paraspinal muscle spasm occurs more quickly with cyclobenzaprine 5 mg t.i.d. or 10 mg t.i.d. than with placebo.
- Cyclobenzaprine shows evidence of a dose-related response for efficacy in the range of 2.5 mg t.i.d. to 10 mg t.i.d. However, 2.5 mg t.i.d. is not a consistently effective dose.
- Cyclobenzaprine 5 mg t.i.d. is effective within 24 to 48 hours of initiating treatment.
- The relative efficacy of cyclobenzaprine 5 mg t.i.d. is not dependent on the presence of drowsiness.

Safety of Cyclobenzaprine (pp. 34-94)

The safety profile of nonprescription cyclobenzaprine was assessed through a comprehensive examination of controlled clinical trial data, extensive post-marketing experience with cyclobenzaprine 10 mg, independent drug abuse and poison control databases, and ten clinical pharmacology studies aimed at defining pharmacokinetics in special populations and characterizing the potential for cyclobenzaprine to produce drowsiness.

Nonprescription Clinical Studies (pp. 34-48): Cyclobenzaprine 5 mg was generally well tolerated in the nonprescription clinical studies which included a total of 2106 patients/subjects of whom 1632 received at least one dose of cyclobenzaprine. There were no serious drug-related clinical or laboratory adverse experiences. One patient died; her death was attributed to diabetes, coronary artery disease, and cocaine use. There were no drug-related adverse experiences that have not already been reported to occur with the prescription dose of cyclobenzaprine 10 mg. Gender, age, and race were not significant factors in the adverse experience profile of cyclobenzaprine 5 mg in the OTC studies.

The most common adverse experience was somnolence which was dose related in the placebo-controlled Phase III studies. Verbatim terms categorized as "somnolence" were reported by 38% of patients receiving cyclobenzaprine 10 mg, 29% receiving cyclobenzaprine 5 mg, 20% receiving cyclobenzaprine 2.5 mg, and 10% receiving placebo. Somnolence generally began within two days of initiating treatment, and most patients reported their most intense somnolence as mild or moderate, with only 2.6% of patients receiving cyclobenzaprine 5 mg reporting severe somnolence. Of those patients who received cyclobenzaprine 5 mg, 2.5% discontinued treatment because of an adverse experience of somnolence. The second most common adverse experience with cyclobenzaprine was dry mouth. This anticholinergic effect was also dose related with incidences of 32%, 21%, 14%, and 7% reported with cyclobenzaprine 10 mg, 5 mg, 2.5 mg, and placebo, respectively, in the two Phase III studies. Dry mouth prompted discontinuation of treatment in $\leq 1\%$ of the patients/subjects who received cyclobenzaprine 5 mg t.i.d.

Asthenia, fatigue, confusion, disorientation, dizziness, and decreased mental acuity were reported less frequently than somnolence or dry mouth. The same pharmacologic effect which may be responsible for somnolence may also be responsible for these other relatively nonspecific central nervous system disturbances. The data suggest that asthenia/fatigue and dizziness are also dose related, although the relationship is less apparent than for the more common events of somnolence and dry mouth.

Safety of Cyclobenzaprine (pp. 34-94)

Post-marketing Prescription Experience (pp. 48-59): Cyclobenzaprine 10 mg has been marketed in the U.S. and Canada as Flexeril by Merck and Co., Inc. since 1977, and has been available in generic form since 1989. Over 100,000,000 prescriptions for cyclobenzaprine have been dispensed. As of February 1, 1999, 993 adverse experience reports were entered into Merck's Worldwide Adverse Experience System (WAES) database. This document reviews this experience in detail in Section 3.8.3. When classified according to body system, the majority of these reports were categorized into body as a whole, psychiatric disorder, respiratory system, cardiovascular system, and digestive system.

Post-marketing data is also available from two uncontrolled post-marketing surveillance studies in 7607 patients. One set of results (n=6311) was based on elicited (not spontaneous) reports focusing on the central nervous system and psychiatric adverse experiences that may occur with cyclobenzaprine 10 mg. Hallucinations were reported by 0.2% of the patients who were asked specifically whether they had experienced them, a procedure generally recognized as likely to induce over-reporting. There have been 82 reports of patients with hallucinations reported spontaneously to the WAES database over the 20 years of marketed use. If, as postulated, the anticholinergic effect of cyclobenzaprine is responsible for hallucinations seen with cyclobenzaprine, it is reasonable to assume that they would be dose related.

Since 1977, Merck has received 52 reports of deaths associated with taking cyclobenzaprine. Fifteen of these reports were intentional overdoses often with other drugs, and many of the others were people with serious medical problems who were on multiple medications. Merck is also aware of an additional 36 death reports in FDA databases for which fewer details are available. Taken together, there appears to be no pattern or common underlying cause for deaths temporally associated with therapeutic use of cyclobenzaprine.

Drug Abuse and Overdosage Information (pp. 60-62): Data from the American Association of Poison Control Centers (AAPCC), Merck's Worldwide Adverse Experience System (WAES), and published literature support the conclusion that there is a wide margin of safety with cyclobenzaprine. The lowest known fatal dose of cyclobenzaprine is estimated to be approximately 13 mg/kg. This is substantially greater than the proposed nonprescription dose of 0.1 mg/kg (based on 50 kg body weight).

Safety of Cyclobenzaprine (pp. 34-94)

Although cyclobenzaprine is structurally related to tricyclic antidepressants, it should be noted that it is substantially safer in overdose than this class of agents. According to the AAPCC, the mortality rate with exposures to cyclobenzaprine alone was 0.02% (3 of 16,996). This is notably different from the 1.0% mortality rate reported for five common tricyclic antidepressants. The most common symptoms reported to AAPCC with single-agent cyclobenzaprine exposures related to the cardiovascular, gastrointestinal, and nervous systems. Of the cyclobenzaprine exposures reported to the AAPCC database, the percentages of patients who experienced tachycardia and hypertension were 9.5% and 1.5%, respectively. For CNS symptoms, the percentages of patients who experienced drowsiness/lethargy were 31.5%, agitated/irritable, 5.2%, and confusion, 2.4%.

The potential for cyclobenzaprine to be a recreational and/or abused drug was assessed by examining Merck WAES reports, the published literature, and data supplied by the Substances Abuse and Mental Health Services Administration, which monitors drug abuse through the Drug Abuse Warning Network (DAWN). There are no published reports on the recreational use of cyclobenzaprine. Furthermore, there are no WAES reports that could be construed as evidence of drug abuse with cyclobenzaprine. These data suggest that cyclobenzaprine is not used for recreational purposes.

Clinical Pharmacology Studies of Sedation Potential (pp. 63-90): The most commonly reported side effect of cyclobenzaprine is somnolence or drowsiness. In order to further characterize this effect as it relates to psychomotor performance, six studies were performed. The somnolence associated with cyclobenzaprine is believed to be mediated by antihistaminic and antimuscarinic properties. OTC antihistamines were included as controls to compare the degree of drowsiness with cyclobenzaprine 5 mg to that of other sedating nonprescription medications. Three of the six studies (Protocols 001,002,003) were exploratory in nature and do not offer firm conclusions. However, the three subsequent studies (Protocols 012, 014, 015) employed validated methodologies and appropriate controls.

Protocol 012 measured sedation using an Alert/Drowsy Visual Analog Scale (VAS) at multiple time points post-dose. The degree of drowsiness with cyclobenzaprine 5 mg, as measured by the VAS, was similar to that with diphenhydramine 50 mg and clemastine 1 mg. The study also included the Multiple Sleep Latency Test (MSLT). This test measures the time it takes to fall asleep in an unstimulated environment. The test indicated that single doses of cyclobenzaprine 5 mg, diphenhydramine 50 mg, and clemastine 1 mg all similarly shortened the time to fall asleep. Multiple doses of cyclobenzaprine 5 mg shortened the time to fall asleep 1 to 2 minutes more than did diphenhydramine 50 mg or clemastine 1 mg.

Safety of Cyclobenzaprine (pp. 34-94)

Neither the VAS nor MSLT have been shown to predict performance impairment. A subject's ability to perform simple or complex psychomotor tasks cannot be inferred from measures of sedation. Therefore, batteries of performance tests were also included in the 6 psychomotor studies. Cyclobenzaprine 5 mg was not associated with any consistent pattern of impairment relative to placebo in the laboratory measures of performance tested in the 6 studies. Two studies recommended by FDA, one in young adults (Protocol 014) and one in subjects over 65 years of age (Protocol 015), specifically assessed skills relevant to driving a motor vehicle. The battery of tests employed in these studies evaluated the ability to control movement of a machine in use (Critical Tracking), ability to simultaneously perform tracking and visual search (Divided Attention), and ability to maintain attention to a boring task over a long period of time (Vigilance). Both studies included both amitriptyline and diphenhydramine as positive controls. In both studies, amitriptyline 50 mg was associated with more impairment of skills than either cyclobenzaprine 5 mg or diphenhydramine 50 mg, which were similar to each other and generally not different from placebo. These results suggest that cyclobenzaprine- or diphenhydramine-induced drowsiness does not impair peoples' ability to perform specific tasks. These data also support the assertion that OTC use of cyclobenzaprine 5 mg should not be associated with psychomotor impairment that is any greater than that associated with current nonprescription medications known to produce sedation. Regardless, proposed OTC labeling strongly warns against operating a motor vehicle or using cyclobenzaprine together with other sedating drugs, including alcohol.

Safety Conclusions

- Cyclobenzaprine 5 mg t.i.d. is generally well tolerated when used for up to 10 days to treat acute painful muscle spasm of the back or neck.
- Drowsiness and dry mouth are the most common adverse experiences with cyclobenzaprine. These effects are dose-related in a range between 2.5 mg t.i.d. and 10 mg t.i.d. Most patients who report drowsiness initially notice the effect on the first or second day of dosing. Most episodes of somnolence are mild or moderate in intensity; the incidence of severe somnolence is approximately 2.6% in patients treated with cyclobenzaprine 5 mg t.i.d. Somnolence resolves in some patients with continued dosing, suggesting adaptation may occur.
- Drowsiness, as subjectively measured by self-report, with cyclobenzaprine 5 mg is similar to that with diphenhydramine 50 mg and clemastine 1 mg and less than that with amitriptyline 50 mg in young, healthy subjects. Drowsiness occurs sooner with diphenhydramine 50 mg than with cyclobenzaprine 5 mg. Drowsiness does not continue to increase with multiple doses of cyclobenzaprine 5 mg.

Safety Conclusions (Cont.)

- Cyclobenzaprine 5 mg shortens the time to fall asleep, as measured by the Multiple Sleep Latency Test, to a greater extent than does diphenhydramine 50 mg and clemastine 1 mg.
- Cyclobenzaprine 5 mg t.i.d. generally does not produce performance impairment in young or elderly subjects. Psychomotor performance with cyclobenzaprine 5 mg is better than with amitriptyline 50 mg, and not different from placebo or diphenhydramine 50 mg.
- There are no clinically meaningful differences in the safety profile of cyclobenzaprine 5 mg t.i.d. with regard to age, race, or gender.
- Cyclobenzaprine has very low potential for abuse and a high margin of safety in overdose.

Pattern-of-Use Study (pp. 95-98)

Study Design: Protocol 009 was conducted to assess the degree to which consumers will self-medicate with cyclobenzaprine 5 mg in accordance with an earlier version of the proposed labeling. This open-label, uncontrolled, 15-site study enrolled 468 patients with self-diagnosed painful muscle spasm, tightness, or soreness of the back or neck. Patients were interviewed by a physician but not examined. After giving informed consent, patients were given a bottle containing 30 5-mg tablets of cyclobenzaprine. They also received a diary card containing Indications, Directions, and Warnings consistent with the proposed label, which has since been revised to incorporate the knowledge gained from this study. The Directions read "Take one tablet every 6 to 8 hours. Do not exceed 3 tablets in 24 hours. Do not take continuously for more than 7 days." Patients recorded their medication use on the diary and provided a Global Impression of Change at the return visit to the clinic.

Results: The mean number of treatment days was 7.4 with a range of 1 to 15 days. Ninety-two percent of patients used the medication for 10 days or less, although only 44% used it as instructed for 7 days or less. Approximately half the patients (57%) used medication for 7 to 9 days. The majority of patients (87%) did not take more than 3 tablets per day. Although 13% of patients took more than 3 tablets on at least 1 day, more than 3 tablets in a single day were taken on only 3% of total treatment days. Eleven percent of patients took more than 1 tablet per dose at least once, but less than 1% of doses consisted of more than 1 tablet.

Pattern-of-Use Study (pp. 95-98) (Cont.)

Conclusions:

- The majority of patients will self-medicate with 3 or fewer tablets per day.
- It appears that a 10-day period may be more consistent with the way patients will actually use the product than the 7 days recommended in the version of the label used in this study.

Clinical Pharmacology—Human Pharmacokinetics and Bioavailability (pp. 99-107)

Disposition studies conducted previously in animals and man have shown that cyclobenzaprine hydrochloride is well absorbed, is widely distributed among body tissues, and is extensively metabolized. Peak plasma concentration is reached approximately 4 hours post-dose, and the effective half-life is estimated to be 18 hours. Cyclobenzaprine is about 93% bound to human plasma proteins. Cyclobenzaprine or its metabolites are secreted in the bile and are subject to enterohepatic circulation.

Four new pharmacokinetic studies were conducted to support the OTC switch program and better characterize the pharmacokinetic profile of cyclobenzaprine in elderly and hepatically impaired patients. The conclusions from these and the previously available data are as follows:

- Cyclobenzaprine N-demethylation is mediated primarily via cytochrome P-450s 3A4 and 1A2, while cytochrome P-450 2D6 plays a minor role.
- Cyclobenzaprine has very little potential for inhibition of cytochrome P-450-mediated reactions at clinically relevant concentrations based on the relatively high K_i values obtained for human liver microsomes.
- The bioavailability of cyclobenzaprine hydrochloride 5-mg tablets is 0.55.
- Plasma concentrations increase proportionally to dose over the dose range 2.5 to 10 mg, indicating the pharmacokinetics of cyclobenzaprine are linear over this dose range.
- There is approximately fourfold accumulation of cyclobenzaprine in plasma when dosed every 8 hours.
- Steady-state plasma concentrations of cyclobenzaprine are increased in the elderly as the result of increased effective half-life.

Clinical Pharmacology—Human Pharmacokinetics and Bioavailability (pp. 99-107)
(Cont.)

- Mild-to-moderate hepatic impairment increases steady-state plasma concentrations of cyclobenzaprine as the result of increased effective half-life.
- The magnitude of any differences in steady-state plasma concentrations of cyclobenzaprine between males and females is relatively small.

OTC Label Development (pp. 108-117)

The proposed label was developed in an iterative manner incorporating knowledge gained from the Pattern-of-Use study, label comprehension studies, and input from FDA experts. The proposed carton back-panel includes all standard and required language for the safe use of the product. Additionally a package insert has been developed to further educate the consumer about the safe use of the product and provide general information about avoidance and management of back and neck strain.

Indication: The proposed indication or “use” for FLEXERIL MR is *for relief of painful muscle tightness and spasm of the back or neck due to recent strain, overuse, or minor injury*. This is the condition that was studied in the nonprescription trials, and is consistent with the current indication for the prescription dose.

Dose and Duration of Use: The proposed nonprescription dose is 5 mg three times a day; half of the current prescription dose. The label instructs patients not to medicate for longer than 10 consecutive days; consistent with usage in the clinical studies and the maximum duration of treatment for OTC analgesics which may also be used to treat acute back pain. Consumers are instructed to consult a physician if the condition persists after 10 days.

Warnings and Precautions: Standard warnings common to other OTC products relating to sedation, concomitant medications, pregnancy, and preexisting conditions are provided. Also a statement warning of the potential to cause drowsiness is provided on the front display panel of the outer carton. Additionally warnings are included about specific conditions relating to the origin and duration of preexisting back pain for which the patient should seek a doctors advice. Finally, consumers with liver disease or over age 65 are advised to consult their doctor before using this product

Benefit/Risk Relationship (pp. 118-123)

Overall Benefits: Acute painful muscle spasm of the back and neck is a highly prevalent condition among adults and a major contributor to morbidity and lost productivity in this society. An effective treatment should hasten the resolution of the spasm and pain. The

Benefit/Risk Relationship (pp. 118-123) (Cont.)

two pivotal Phase III studies showed that relief occurred approximately 2 days faster with cyclobenzaprine 5 mg t.i.d. than with placebo. The effect of the 5 mg t.i.d. dose paralleled that of the 10 mg t.i.d. prescription dose, with the exception of having about a one day delay in achieving statistical superiority to placebo. The median Time-to-A Lot or Complete Relief was approximately 2 days less for cyclobenzaprine 5 mg than placebo. Because patients often must restrict their activities because of their pain and spasm, earlier relief should allow patients to resume their normal activities sooner.

With greater access to cyclobenzaprine, without the cost and inconvenience of a physician visit, many people could effectively self-treat who might not be adequately relieved with currently available OTC analgesic products only. Reducing the period of morbidity by 1 to 2 days could yield a large cumulative benefit to individual patients (quality of life and wages) and society as a whole (productivity and direct health-care costs). Having an effective OTC product available represents an important option to consumers seeking to quickly self-treat a commonly occurring, self-recognizable condition.

Risk Due to Drowsiness: The safety profile of cyclobenzaprine has been well characterized in clinical trials and through post-marketing surveillance. The substantial marketing experience with cyclobenzaprine 10 mg also provides information about the margin of safety with cyclobenzaprine 5 mg. While the studies supporting this application showed subjective drowsiness with cyclobenzaprine 5 mg, there was no consistent pattern of impairment of psychomotor performance as measured by standard computerized test batteries. Two studies validated to assess driving-related skills under conditions of drug- or alcohol-induced impairment showed that subjects receiving cyclobenzaprine 5 mg were able to perform driving-related skills during the time of peak drowsiness. Consumers should still be clearly warned against driving or operating dangerous machinery while taking OTC cyclobenzaprine. The precedent with sedating OTC antihistamines indicates that the risk associated with cyclobenzaprine-induced drowsiness can be managed with appropriate label warnings.

Risk Due to Other CNS Effects: Review of post-marketing adverse experiences, reported to the sponsor over two decades of experience with over 100,000,000 prescriptions of cyclobenzaprine 10 mg, reveals a small number of reports of acute psychiatric disturbance, most frequently coded as "hallucinations". While the risk of hallucination cannot be eliminated by OTC labeling, it is not prohibitive to OTC use because it is likely to be extremely rare, dose related, and reversible. The risk should be lower with the OTC dose as it is only one-half that of the prescription dose.

Benefit/Risk Relationship (pp. 118-123) (Cont.)

Risks of Abuse/Misuse: The risks of cyclobenzaprine being abused or misused are small. Cyclobenzaprine has not been reported to produce euphoria or other desired psychoactive effects, and therefore has no identifiable abuse potential. Data from the Drug Abuse Warning Network (DAWN) show that there is no pattern of widespread recreational use of cyclobenzaprine.

There is extensive information about overdoses of cyclobenzaprine. Sedation and sinus tachycardia are the most common manifestations. Serious cardiovascular effects are rare and occur substantially less often than with overdoses of tricyclic antidepressants. Fatality is very rare (0.02% of the nearly 17,000 single-agent ingestions reported to the poison control centers), and the therapeutic margin is wide.

Acute back pain is a self-recognizable condition, and self-medication is medically appropriate for initial treatment. OTC products labeled for use in back pain and/or muscle spasm are already being used by consumers. Use of the product for painful conditions other than acute back or neck pain is unlikely to have clinical consequences other than a lack of effectiveness. The likelihood of off-label use can be minimized by clear labeling. The proposed nonprescription package will include an insert that provides additional information about conditions for which use of cyclobenzaprine is inappropriate (e.g., leg cramps). The label includes additional warnings about signs of infection or nerve entrapment. This additional information should further reduce the potential for inappropriate self-medication.

Overall Conclusions on OTC Availability of Cyclobenzaprine

Acute back pain is a highly prevalent condition that represents the second most common reason for an office visit to a primary care physician. The large number of physician visits indicates the limited effectiveness of currently available nonprescription treatments. Other muscle relaxant drugs have been available for nonprescription use in Canada for over 20 years, and were granted open-shelf unrestricted status in 1995. This attests to the consumer need for such a product, their ability to recognize the condition of acute back pain, and the acceptability of such treatment without physician involvement.

Many people who now self-medicate with nonspecific analgesics for symptomatic relief of acute painful muscle spasm of the back could benefit from the substantial efficacy provided by cyclobenzaprine. Not only would OTC availability eliminate the delays encountered in consulting a physician and obtaining a prescription, but, as shown in this program, relief of symptoms could occur up to two days earlier than with normal non-pharmacologic intervention. A foreshortening of the clinical course with this product could curtail suffering, boost productivity, and permit early mobilization which could provide an additional benefit in tending to prevent progression to chronicity.

Overall Conclusions on OTC Availability of Cyclobenzaprine (Cont.)

The drowsiness reported by some users of cyclobenzaprine should not preclude OTC availability. Somnolence, which is reported in about a third of people in clinical trials at the 5-mg t.i.d. dose, has been shown to be generally mild, comparable to that seen with existing OTC products and unlikely to substantially impair psychomotor performance or interfere with necessary daily tasks. While drowsiness and efficacy are independent effects, drowsiness appearing early in treatment may be useful to those whose back pain interferes with sleep. Clear labeling can warn consumers of the risk of drowsiness, guide against inappropriate use for conditions other than the intended or with prohibited drugs, differentiate from OTC analgesics, and direct people to their physicians for treatment as needed.

In conclusion, the potential risks of nonprescription availability of cyclobenzaprine 5 mg can be effectively managed by optimal labeling and are outweighed by the benefits of this important adjunctive treatment option. In today's environment of increased concern about the efficiency of healthcare delivery and consumer involvement in self-care, it is therefore reasonable and beneficial to expand access to this treatment option beyond the current prescription-only restrictions

NONPRESCRIPTION DRUGS
ADVISORY COMMITTEE AND
ARTHRITIS ADVISORY
COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

INTRODUCTION

1. Introduction

Acute back pain is a common disorder that results in significant functional disability, i.e., decreased work productivity and impaired activities of daily living. In 1977, FLEXERIL™† (cyclobenzaprine) 10 mg three times daily was approved by the United States Food and Drug Administration as an adjunct to rest and physical therapy for the relief of muscle spasm, associated with acute, painful musculoskeletal conditions such as back pain. Merck is now seeking marketing authorization for a 5-mg nonprescription dose.

1.1 Rationale For Nonprescription Cyclobenzaprine in the Marketplace

Up to 75% of the adult population report back problems at some time in their lives [17; 30]. Among the working-age people surveyed, 50% admit to back symptoms at least once a year. Nonprescription analgesics and anti-inflammatory drugs (NSAIDs) are commonly used to treat acute back pain, but these agents do not provide adequate relief for everyone. Cyclobenzaprine 10 mg t.i.d. has been shown to relieve acute muscle spasm, and the drug has been widely prescribed with or without analgesics/NSAIDs over the past 20 years for treatment of neck and back pain [29]. Although experimental studies have defined the possible mode of action of cyclobenzaprine in animals, the mechanism responsible for its muscle-relaxant activity in man remains unknown [5]. Cyclobenzaprine has no activity at the neuromuscular junction and no direct effect on skeletal muscle. Experts have hypothesized that cyclobenzaprine provides relief by interrupting a self-reinforcing pathway of muscle spasm and local pain.

Several muscle relaxants (methocarbamol, chlorzoxazone, orphenadrine citrate) are available without prescription in Canada. Combination products consisting of a muscle relaxant and an analgesic are also sold open-shelf without prescription in Canada. Since none of the muscle relaxants have been reclassified as prescription-only products, it can be concluded that they have been safely used by consumers to self-medicate for acute back pain. The Canadian experience with other muscle relaxants provides support for the proposal to consider making cyclobenzaprine available without prescription.

Given the recognition that conservative care without aggressive diagnostic testing is appropriate for the initial treatment of acute uncomplicated back pain, Merck undertook the development of cyclobenzaprine for nonprescription use. Since drowsiness was recognized as one of the main side effects of the prescription dose, a program was designed to test whether lower doses of cyclobenzaprine (2.5 and 5 mg t.i.d.) would be effective but less sedating for the treatment of acute painful muscle spasm of the back or neck.

† FLEXERIL is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

1.1 Rationale For Nonprescription Cyclobenzaprine in the Marketplace (Cont.)

While acute back pain is usually not serious, it often disrupts the patient's normal work and social activities for several days [3]. By relieving the symptoms of painful muscle spasm of the back or neck, muscle relaxants may allow early ambulation and return to normal activity. Such return to normal activities is advisable because it prevents the development of muscle atrophy, deconditioning, and in some cases the progression to chronic low back disability [4]. Acute musculoskeletal conditions may benefit from motion and early mobilization. The currently available OTC medications used to treat acute back pain with spasm are NSAIDs, nonspecific analgesics, and local balms. An effective muscle relaxant with specific action and an acceptable tolerability profile would be a valuable addition to currently available OTC therapy options. Convenient access to an effective muscle relaxant offers the opportunity for early treatment with the potential to decrease time lost from daily responsibilities, leading to a positive effect on quality of life.

1.2 Overview of Clinical Program

The clinical program was designed to characterize the efficacy and safety of the proposed nonprescription dose of cyclobenzaprine. The key program objectives were to:

- Demonstrate the efficacy of cyclobenzaprine in patients with acute pain and muscle spasm of the cervical or lumbar areas.
- Define the dose-response relationship for cyclobenzaprine for both efficacy and safety in order to select the optimal nonprescription dose.
- Examine patterns of medication use when patients are allowed to self-medicate with the proposed nonprescription dose.
- Characterize the drowsiness associated with use of the proposed nonprescription dose and compare it with currently available OTC products also known to cause drowsiness. Examine whether the OTC dose of cyclobenzaprine has an effect on psychomotor performance.
- Update information on the pharmacokinetics of cyclobenzaprine.

Merck sponsored 13 clinical studies in support of the Rx-to-OTC switch of cyclobenzaprine. They are summarized according to the type of study in Table 1 (Protocols 004 and 013 were never conducted). Three of the studies were conducted in the United Kingdom (Protocols 001, 002, 003); the other 10 were conducted in the United States. Each of the studies included orally administered cyclobenzaprine 5 mg.

1.2 Overview of Clinical Program (Cont.)

Table 1

List of All Nonprescription Cyclobenzaprine Clinical Studies by Type of Study

Protocol Number	Short Study Description	Drug	Duration	Number Evaluable for Safety
Clinical Pharmacology - Pharmacokinetic				
005	Open-label crossover study of single- and multiple-dose pharmacokinetics and dose proportionality of cyclobenzaprine in young healthy volunteers	CYC 2.5 mg, 5 mg, 10 mg	2 weeks	18
007	Open-label multiple-dose parallel study of pharmacokinetics of cyclobenzaprine in hepatically impaired patients and healthy subjects	CYC 5 mg	1 week	24
010	Open-label multiple-dose study of pharmacokinetics of cyclobenzaprine in elderly subjects	CYC 5 mg	1 week	12
011	Open-label crossover bioequivalence/bioavailability study of cyclobenzaprine tablets made by 2 different processes	CYC 5 mg P.O. (planetary process); CYC 5 mg P.O. (high shear process); CYC 1.25 mg I.V.	1 dose	24
Psychomotor				
001	Double-blind, single-dose, crossover psychomotor study of cyclobenzaprine, diphenhydramine, and placebo in young subjects	CYC 2.5 mg, 5 mg; DPH 50 mg; Placebo	1 dose	24
002	Double-blind, multiple-dose, crossover psychomotor study of cyclobenzaprine in young subjects	CYC 5 mg; Placebo	4 days	18
003	Double-blind, multiple-dose, crossover psychomotor study of cyclobenzaprine, diphenhydramine, and placebo in elderly subjects	CYC 5 mg; DPH 50 mg; Placebo	4 days	20
012	Double-blind, multiple-dose, crossover psychomotor study of cyclobenzaprine, diphenhydramine, clemastine, and placebo in young subjects	CYC 5 mg; Clemastine 1 mg; DPH 50 mg; Placebo t.i.d.	2 days	28
014	Double-blind, multiple-dose crossover study to compare effects of cyclobenzaprine, diphenhydramine, and amitriptyline on driving-related psychomotor skills in elderly subjects	CYC 5 mg (t.i.d. x 4 doses); DPH 50 mg; Amitriptyline 50 mg; Placebo	2 days	32
015	Double-blind, multiple-dose crossover study to compare effects of cyclobenzaprine, diphenhydramine, and amitriptyline on driving-related psychomotor skills in young subjects	CYC 5 mg (t.i.d. x 4 doses); DPH 50 mg; Amitriptyline 50 mg; Placebo	2 days	33
Phase III				
006	Double-blind, multiple-dose, parallel-group efficacy and safety study in patients with acute skeletal muscle spasm	CYC 5 mg, 10 mg; Placebo t.i.d.	1 week	737
008	Double-blind, multiple-dose, parallel-group dose-confirmation-study in patients with acute skeletal muscle spasm	CYC 2.5 mg, 5 mg; Placebo t.i.d.	1 week	668
009	Open-label, multiple-dose, pattern-of-use study in patients with self-diagnosed muscle spasm	CYC 5 mg	≤10 days	468
CYC = cyclobenzaprine, DPH = diphenhydramine.				

NONPRESCRIPTION DRUGS
ADVISORY COMMITTEE AND
ARTHRITIS ADVISORY
COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

EFFICACY

2. Efficacy

2.1 Rationale for Studies Conducted

The clinical study program for cyclobenzaprine over-the-counter (OTC) was based on the hypothesis that cyclobenzaprine 5 mg t.i.d. for 7 days is more efficacious than placebo in treating patients with acute musculoskeletal spasm. The model used in the OTC development program for cyclobenzaprine is an enhanced version (involving daily diary ratings) of the musculoskeletal spasm model that was used in obtaining approval for the prescription (Rx) product. The objective and subjective criteria that were tested are standard criteria that have been shown to be sensitive measures of muscle-relaxant activity [3].

In order to obtain pivotal efficacy and safety information, cyclobenzaprine 5 mg t.i.d. was tested in two double-blind, placebo-controlled trials (Protocols 006 and 008). The condition treated was acute back or neck pain with moderate to moderately severe muscle spasm. Subjective and objective measures were rated at baseline (Day 1), mid-point (Day 3 or 4) and the end of the trials (Day 8). Daily ratings of relief were included to allow description of time to onset. Because this program was intended to support approval of a nonprescription dose, the primary endpoints involved patient-reported assessments of relief. Physician examination to document the presence and extent of palpable muscle spasm was included as a secondary endpoint.

The clinical study program also included an open-label Pattern-of-Use study (Protocol 009). Thirty cyclobenzaprine 5-mg tablets were dispensed to patients who, after reading the label, decided for themselves if they met the labeled inclusion and exclusion criteria. Patients were not examined by a physician. The main objective of this study was to examine each patient's pattern of drug usage and compliance with the directions. While efficacy determination was not a primary objective in this study, some efficacy data (global impression of change) were collected and are included in this integrated summary.

The duration of treatment in the 2 pivotal OTC Phase III clinical efficacy trials was 7 days (21 doses). Musculoskeletal spasm is a self-limiting illness, with 90% of sufferers recovering within 4 weeks. Clinical trials show there is a consistent improvement over time in musculoskeletal spasm symptoms in all treatment groups, including placebo. It was felt that a 7-day treatment duration would differentiate the efficacy of the various doses of cyclobenzaprine when compared to placebo. Dosing for 7 days would also allow characterization of the safety profile for the various doses of cyclobenzaprine after plasma concentrations had been at steady state for several days.

2.2 Design of Clinical Studies

2.2.1 Rationale for Dose Selection in Clinical Studies

The 10-mg Dose (30 mg Per Day)

The 10-mg t.i.d. dose is the approved prescription dose that has been marketed for the past 20 years. This dose has demonstrated efficacy and was included in the first OTC efficacy study as a reference standard. The 10-mg t.i.d. dose will be referred to as CYC 10 in this summary. In the prescription application clinical trials at 30 mg per day, the most commonly reported clinical adverse experiences were drowsiness (39%), dry mouth (27%), and dizziness (11%). The corresponding incidences on placebo were 14, 5, and 6%, respectively. It was anticipated that at lower total daily dosages efficacy would be acceptable while the rates of adverse experiences would be lower.

The 5-mg Dose (15 mg Per Day)

Clinical experience with a reduced dosage of cyclobenzaprine at 10 mg per day (5 mg b.i.d.) was obtained in 3 multiclinic studies as part of an earlier development program. In 2 of the 3 studies cyclobenzaprine 5 mg b.i.d. was superior to placebo as assessed by the physician's assessment of global improvement. However, the evaluations of the patient's symptoms of muscle spasm and local pain showed inconsistent results compared to placebo. In these studies the incidences of drowsiness (6 to 19%) were lower than those observed in the prescription application studies of 30 mg per day. It was concluded that the total dosage of cyclobenzaprine 10 mg per day was associated with lower incidences of adverse experiences but marginal efficacy. It was therefore expected that a total dose of 15 mg per day (5 mg t.i.d.) would be required to obtain clinically relevant efficacy while having lower incidences of adverse experiences than the prescription dose. This proposed OTC dose was evaluated in both pivotal efficacy studies and the Pattern-of-Use study. The 5-mg t.i.d. dose is referred to as CYC 5 in this summary.

The 2.5-mg Dose (7.5 mg Per Day)

Total doses of less than 10 mg per day (5 mg b.i.d.) had not previously been evaluated in controlled trials. After the first OTC efficacy study showed that 5 mg t.i.d. was more effective than placebo, the FDA requested that the 2.5-mg t.i.d. dose be included in the second OTC efficacy study, which used an essentially identical protocol to explore the lower end of the dose response. Taken together, the 2 studies would allow the dose response for efficacy and safety to be fully characterized. A combined analysis of both studies was pre-planned to facilitate this. It was anticipated that the 15 mg per day (5 mg t.i.d.) would be the lowest acceptably effective dose and that the total dose of 7.5 mg per day (2.5 mg t.i.d.) would not demonstrate clinically and statistically significant efficacy. The 2.5-mg t.i.d. dose is referred to as CYC 2.5 in this summary.

2.2.2 Overview of Protocol Designs

Controlled Trials

Two randomized, double-blind, parallel-group, placebo-controlled, multi-center, outpatient studies evaluated the efficacy of various cyclobenzaprine doses (2.5, 5, and 10 mg t.i.d.) in patients with moderate to moderately severe painful muscle spasm of the lumbar and/or cervical spine regions. Patients were recruited from physicians' practices and by newspaper advertisements targeting patients with acute neck or back pain with muscle spasm. Pregnant or nursing women were excluded from the studies. Patients were also excluded if they had any of the following:

- Vertebral body or spinous process percussive tenderness.
- Unexplained constipation, diarrhea, or urinary retention.
- Contraindication to the use of cyclobenzaprine (e.g., angle-closure glaucoma, hyperthyroidism, hypersensitivity to the drug, congestive heart failure, history of arrhythmias).
- Current evidence of depression, psychosis, alcohol or drug abuse.
- Workman's compensation case or other litigation related to the cause of the cervical or lumbar spasm.
- Sustained systolic blood pressure >160 mm Hg or diastolic blood pressure >105 mm Hg at baseline.
- Myocardial infarction within 1 year prior to the study.

In each study there were approximately 234 patients per treatment group. Differences in study design are shown in Table 2. The FDA requested that Protocol 008 enroll patients with more acute pain. In Protocol 006 the double-dummy technique was used to maintain the double blind; patients were given two bottles of medication and took 1 tablet from each bottle t.i.d. In Protocol 008 the treatments were three tablets that appeared identical; patients received 1 bottle of medication and took 1 tablet t.i.d.

Patients had 3 study visits: Visit 1 (Baseline/ Study Day 1), Visit 2 (mid-course/Study Day 3 or 4), 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 to have physician assessments for a given patient performed by the same physician at all visits.

2.2.2 Overview of Protocol Designs (Cont.)

Table 2

Differences in Designs of Double-Blind Efficacy Studies

	Protocol 006	Protocol 008
Cyclobenzaprine 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 prestudy	≤14 days	≤7 days
Stratification by prestudy duration of spasm	≤7, >7 days	≤3, >3 days
Number of sites enrolling patients	20	19†
† One investigator was disqualified by the United States Food and Drug Administration because of fraud in prior non-Merck studies; therefore, the data from that investigator are not included in this efficacy summary.		

Prestudy, prospective patients were instructed to discontinue acetaminophen use for 8 hours prior to presentation to the clinic, and any other analgesic, nonsteroidal anti-inflammatories and muscle relaxants for 24 hours prior to presentation to the clinic.

Patients who met all study entry criteria were assigned to 1 of 3 treatment groups according to a randomized allocation schedule. Allocation to study group was stratified based on duration of spasm at time of study entry (see Table 2). Patients received a diary card and bottle of study medication. The bottle was labeled with instructions stating "Take 1 tablet upon awakening, at approximately 2 PM and at bedtime." The first dose of study medication 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 of medication was taken and, if the patient's clinic visit was after 2 PM, the afternoon (2 PM) dose was also taken.

The following agents were prohibited throughout the study: all analgesics (including nonsteroidal anti-inflammatories), all psychotropic agents (e.g., antidepressants, antipsychotics), and any prescription or OTC product known to produce sedation. No muscle relaxants except study drug were permitted during the study. Nonpharmacologic therapies (e.g., physical therapy, manipulation, ultrasound, external ointments) were prohibited throughout the course of the study, except local application of heat.

The evaluations listed below were performed in both studies according to the schedule in Table 3:

- 1) **Physician Rating of 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. (Visits 1, 2, and 3; secondary efficacy parameter).

2.2.2 Overview of Protocol Designs (Cont.)

- 2) Patient-Rated Clinical Global Impression of Change - 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." (Visits 2 and 3; primary efficacy parameter).
- 3) Patient Rating of Medication Helpfulness - the following question was asked: "How would you rate this study medication in improving your condition? Excellent = 4; Very good = 3; Good = 2; Fair = 1; Poor = 0." (Visits 2 and 3; primary efficacy parameter).
- 4) Diary Card: Relief From Starting Backache - 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; primary efficacy parameter)."

Table 3

Schedule of Evaluations in Double-Blind Efficacy Studies

	Clinic Visit 1	Clinic Visit 2	Clinic Visit 3
	Baseline/ Study Day 1	Study Day 3 or 4	End of Treatment/ Study Day 8
Evaluation of inclusion/exclusion criteria	X		
Physical/neurologic exam	X		X
Vital signs	X		X
Physician rating of spasm	X	X	X
Patient-rated clinical global impression of change		X	X
Patient rating of medication helpfulness		X	X
Patient diary (relief from starting backache)†	X		X
Adverse experiences‡	X		X
Study medication administration§	X		X
Tablet counts	X	X	X

† Evaluated after initiation of double-blind therapy. Study Days 1 through 7.
 ‡ Begun after study drug administration.
 § Medication was taken upon awakening, at approximately 2 PM, and at bedtime, with at least 6 hours between doses.

Criteria for an effective treatment were predefined. Statistical significance was required for at least 2 of the 3 patient-rated parameters at either Visit 2 (Day 3 diary) or Visit 3 (Day 7 diary) in order to conclude a treatment was effective.

2.2.2 Overview of Protocol Designs (Cont.)

Uncontrolled Pattern-of-Use Trial

The open-label, uncontrolled, 15-site Pattern-of-Use study enrolled 468 patients with self-diagnosed painful muscle spasm, tightness, or soreness of the back or neck. Patients were interviewed by a physician but not examined or advised on drug administration. After giving informed consent, patients were given a bottle containing 30 cyclobenzaprine 5-mg tablets. They also received a diary card containing Indications, Directions, and Warnings consistent with the proposed label. The Directions read "Take one tablet every 6 to 8 hours. Do not exceed 3 tablets in 24 hours. Do not take continuously for more than 7 days." Patients recorded their medication use on the diary and answered the following question at the follow-up visit: "Compared to how you felt prior to starting medication, 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." This is the same Clinical Global Impression of Change rating as in the two Phase III controlled trials.

2.2.3 Description of Statistical Methods

Primary Efficacy Endpoints

The primary efficacy endpoints were the same in both Phase III controlled trials. Three primary parameters were assessed by the patient at two primary time points:

Clinical Global Impression of Change Clinic Visits 2 and 3

Rating of Medication Helpfulness Clinic Visits 2 and 3

Relief from Starting Backache Diary on Study Days 3 and 7

Mean scores were calculated by treatment group for each parameter and time point. A multiplicity adjustment was defined a priori. Statistical significance in favor of CYC 5 was required for at least two of the three parameters for at least 1 of the 2 time points in order to conclude superior efficacy for CYC 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. This is based on computer simulations assuming a high correlation ($\rho=0.90$) between the parameters. A nominal Type I error rate <0.025 at each time point assures an overall Type I error rate ≤ 0.050 across the 2 time points based on Bonferroni's inequality. In this document the word "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 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 $p \leq 0.050$.

2.2.3 Description of Statistical Methods (Cont.)

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 2 and 3

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. 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.

In this summary, the following convention is used to denote the level of statistical significance for primary and secondary endpoints from a single study:

*** $p \leq 0.001$

** $0.001 < p \leq 0.030$

* $0.030 < p \leq 0.050$

The legend for each table identifies the convention used in that table.

The all-patients-treated approach was the primary approach used to analyze the efficacy parameters and is presented in this summary. All patients who took at least 1 dose of study medication and had at least one efficacy evaluation after taking study medication were included in the analysis.

Combined Analysis

An *a priori* analysis of the combined data from both efficacy trials was conducted. The primary purpose of this analysis was to fully characterize the dose-response curves for both efficacy and safety endpoints within the range of doses studied across both protocols (placebo, 2.5, 5, and 10 mg). Both mean response and proportion of responders were analyzed.

2.3 Demographics of the Study Population

Patients in the double-blind efficacy studies had acute, painful muscle spasm of the lumbar and/or cervical region rated as moderate or moderately severe by the physician. The patients had an otherwise normal physical examination. Patients were enrolled in the Pattern-of-Use study if, by their own assessment, they felt they were experiencing painful muscle spasm, tightness, or soreness of the back or neck.

The populations in the 3 studies had similar baseline characteristics. Approximately 56% of the patients were female. The mean age of the patients was approximately 42 years. The majority of patients were Caucasian (~89%). In both pivotal trials, approximately two-thirds of the patients had low back pain and one-third had neck pain. Within the two controlled efficacy trials, the treatment groups were balanced with respect to baseline characteristics. Approximately 40% of the patients in each treatment group used some form of heat therapy during the studies.

2.4 Efficacy Results

2.4.1 Double-Blind, Controlled Phase III Studies

2.4.2 Overall Efficacy

Comparisons of the CYC 5 and placebo groups in both studies demonstrated statistically significant differences ($p \leq 0.030$) for all three primary parameters at Visit 3 and/or Day 7 of treatment (Table 4). In Protocol 006, CYC 5 was significantly better than placebo in all three primary parameters at the earlier time point as well. 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 demonstrated that CYC 10 was also significantly better than placebo in the three primary parameters at both primary time points. Protocol 008 showed that CYC 2.5 was significantly better than placebo in one of three parameters at the first primary time point but none at the second primary time point. The results obtained for each endpoint at each time point are discussed in the following sections. Results from the double-blind efficacy studies are subsequently presented side-by-side to facilitate visual comparison. Magnitude of effect, onset of effect, and dose response are subsequently discussed.

Cofactor analyses on overall efficacy were also conducted. The CYC 5 group had consistently higher mean responses than placebo regardless of duration of spasm (<14 days, <7 days, <3 days), severity of spasm (moderate versus moderately severe), or location (cervical versus lumbar).

Table 4

Double-Blind Efficacy Studies: Summary of Comparisons Versus Placebo
 for Primary Efficacy Parameters

		Protocol 006		Protocol 008	
		CYC 10	CYC 5	CYC 5	CYC 2.5
		(n=245)	(n=240)	(n=220)	(n=221)
Patient-rated global impression of change	Visit 2	***	***	NS	NS
	Visit 3	***	***	**	NS
Patient rating of medication Helpfulness	Visit 2	***	***	NS	NS
	Visit 3	***	***	**	NS
Relief from starting backache	Day 3	***	***	NS	**
	Day 7	***	***	**	NS

*** $p \leq 0.001$.
 ** $0.001 < p \leq 0.030$.
 NS Not Significant.

2.4.2.1 Patient-Rated Clinical Global Impression of Change

Patients who received CYC 10 or CYC 5 assigned more favorable global evaluations of change than did patients who received placebo (Table 4 and Table 5). The primary analysis of mean scores showed significant differences ($p \leq 0.030$) for CYC 5 in both studies at Visit 3 and in Protocol 006 at Visit 2. There were no significant differences between CYC 10 and CYC 5, or between CYC 5 and CYC 2.5.

The secondary analysis classified patients as responders (marked, moderate, or mild improvement) or nonresponders (no change, worsening). In both studies the proportion of responders in the CYC 5 group was significantly greater ($p \leq 0.050$) than placebo at both time points (Table 5). There were no significant differences between the CYC doses within either study.

Table 5

Double-Blind Efficacy Studies: Patient-Rated Clinical Global Impression of Change

	Visit 2			Visit 3		
	N	Mean	Std. Dev.	N	Mean	Std. Dev.
<u>Mean Score</u>						
Protocol 006						
CYC 10	238	2.30***	0.94	244	2.82***	1.13
CYC 5	238	2.29***	0.90	239	2.88***	1.06
Placebo	241	1.91	0.97	244	2.47	1.16
Protocol 008						
CYC 5	215	2.19	0.88	217	2.82**	1.07
CYC 2.5	216	2.05	0.96	219	2.63	1.19
Placebo	217	1.97	0.98	217	2.41	1.19
<u>% Responders (Mild, Moderate or Marked Improvement)</u>	N	%	95% C.I.	N	%	95% C.I.
Protocol 006						
CYC 10	238	81%***	(76.86%)	244	86%*	(81.90%)
CYC 5	238	83%***	(78.88%)	239	90%***	(85.93%)
Placebo	241	66%	(60.72%)	244	77%	(71.82%)
Protocol 008						
CYC 5	215	78%**	(72.83%)	217	88%***	(83.92%)
CYC 2.5	216	72%	(65.78%)	219	81%	(75.86%)
Placebo	217	66%	(60.73%)	217	75%	(69.81%)
*** $p \leq 0.001$ vs. placebo. ** $0.001 < p \leq 0.030$ vs. placebo. * $0.030 < p \leq 0.050$ vs. placebo. 4 = Marked improvement. 3 = Moderate improvement. 2 = Mild improvement. 1 = No change. 0 = Worsening.						

2.4.2.2 Patient Rating of Medication Helpfulness

Patients who received CYC 10 or CYC 5 assigned greater medication helpfulness scores than did patients who received placebo (Table 6). The primary analysis of mean scores showed significant differences ($p \leq 0.030$) for CYC 5 in both studies at Visit 3 and in Protocol 006 at Visit 2. There were no significant differences between CYC 10 and CYC 5, or between CYC 5 and CYC 2.5.

The secondary analysis classified patients as responders (excellent, very good, good) or nonresponders (fair, poor). The proportion of responders in the CYC 5 group was significantly ($p \leq 0.050$) greater than placebo in both studies at both time points (Table 6). There were no significant differences between the CYC doses within either study with respect to proportion of responders.

Table 6

Double-Blind Efficacy Studies: Patient Rating of Medication Helpfulness

	Visit 2			Visit 3		
	N	Mean	Std. Dev.	N	Mean	Std. Dev.
Mean Score Protocol 006						
CYC 10	238	1.62***	1.13	244	2.13***	1.32
CYC 5	238	1.62***	1.10	239	2.09***	1.27
Placebo	240	1.24	1.14	243	1.65	1.33
Protocol 008						
CYC 5	215	1.49	1.07	217	2.00**	1.28
CYC 2.5	216	1.25	1.05	219	1.72	1.35
Placebo	217	1.20	1.11	217	1.50	1.30
% Responders (Excellent, Very Good, Good)	N	%	95% C.I.	N		95% C.I.
Protocol 006						
CYC 10	238	53***	(46.59%)	244	65**	(59.71%)
CYC 5	238	54***	(48.61%)	239	64**	(58.70%)
Placebo	240	37	(31.43%)	243	53	(46.59%)
Protocol 008						
CYC 5	215	50**	(43.57%)	217	64***	(57.70%)
CYC 2.5	216	38	(31.45%)	219	50	(43.57%)
Placebo	217	36	(30.43%)	217	44	(38.51%)
*** $p \leq 0.001$ vs. placebo. ** $0.001 < p \leq 0.030$ vs. placebo. * $0.030 < p \leq 0.050$ vs. placebo. 4 = Excellent. 3 = Very good. 2 = Good. 1 = Fair. 0 = Poor.						

2.4.2.3 Patient Diary Rating of Relief From Starting Backache

Descriptive statistics and 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 7. Study Days 3 and 7 are considered primary time points for the analysis of mean scores. The CYC 5 group was significantly better ($p \leq 0.030$) than placebo at both primary time points in Protocol 006 and at Day 7 in Protocol 008 (Table 7). The CYC 10 group was also significantly better than placebo at both primary time points in Protocol 006. The CYC 2.5 group was significantly better than placebo on Day 3 but not Day 7 in Protocol 008. There were no significant differences between CYC 10 and CYC 5, or between CYC 5 and CYC 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. Table 7 shows that, in Protocol 006, CYC 10 and CYC 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, CYC 5 was significantly different than placebo on Study Days 4 through 7. In contrast, the CYC 2.5 group in Protocol 008 was significantly different from placebo on Days 3, 4, and 5 but not on Days 6 or 7.

Proportion of responders (complete, a lot, some relief) and nonresponders (a little, no relief) was a secondary analysis. Each CYC group was significantly better ($p \leq 0.050$) than placebo on Days 3 and 7 (Table 8). There were no significant differences between CYC 10 and CYC 5, or between CYC 5 and CYC 2.5 with respect to the proportion of responders on Days 3 or 7.

Table 7

Double-Blind Efficacy Studies: Patient Diary Rating[†] of Relief From Starting Backache—Days 1 through 7

	Study Day [‡]							
	N	1	2	3	4	5	6	7
Protocol 006								
CYC 10	242	1.12**	1.56**	1.83**	1.98**	2.11**	2.22**	2.38**
CYC 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								
CYC 5	220	0.94	1.44	1.62	1.85**	2.01**	2.15**	2.24**
CYC 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

[†] 4=complete relief, 3=a lot of relief, 2=some relief, 1=a little relief, 0=no relief.
[‡] Study Days 3 and 7 were primary parameters.
 ** $p \leq 0.030$ vs. placebo.
 * $p \leq 0.050$ vs. placebo.

2.4.2.3 Patient Diary Rating of Relief From Starting Backache (Cont.)

Table 8

Double-Blind Efficacy Studies: Patient Diary Rating of Relief from Starting Backache—
 Days 3 and 7

	% Responders† (95% C.I.)		
	N	Study Day 3	Study Day 7
Protocol 006			
CYC 10	242	62* (55.68)	76* (71.82)
CYC 5	238	59* (52.65)	75* (69.81)
Placebo	245	44 (38.51)	62 (56.69)
Protocol 008			
CYC 5	220	57* (50.63)	69* (62.75)
CYC 2.5	221	54* (47.61)	66* (59.72)
Placebo	218	42 (36.49)	57 (50.64)

† Responder = Some, a lot, or complete relief.
 * p≤0.050 vs. placebo.

2.4.2.4 Physician Rating of Muscle Spasm

Muscle spasm was rated by the physician at each visit. Table 9 and Table 10 show the distribution of spasm severity by treatment and visit for Protocols 006 and 008, respectively. Patients receiving CYC 10 or CYC 5 had less muscle spasm at Visits 2 and 3 than patients treated with placebo. In both studies, the proportion of patients with no spasm at Visit 3 was approximately 10 percentage points greater in the CYC 5 group than the placebo group.

2.4.2.4 Physician Rating of Muscle Spasm (Cont.)

Table 9

Protocol 006: Descriptive Statistics for the Proportion of Patients in Each Category
 Physician Rating of Muscle Spasm by Visit

Visit 1—Baseline Category	CYC 10-mg (N=249)		CYC 5-mg (N=242)		Placebo (N=246)	
	n	%	n	%	n	%
Moderate (2)	177	71.1	169	69.8	187	76.0
Moderately Severe (3)	72	28.9	73	30.2	59	24.0

Visit 2 Category	CYC 10-mg (N=238)			CYC 5-mg (N=235)			Placebo (N=239)		
	n	%	Cum. %	n	%	Cum. %	n	%	Cum. %
None (0)	20	8.4	8.4	15	6.4	6.4	14	5.9	5.9
Mild (1)	100	42.0	50.4	108	46.0	52.3	76	31.8	37.7
Moderate (2)	97	40.8	91.2	91	38.7	91.1	117	49.0	86.6
Moderately Severe (3)	19	8.0	99.2	19	8.1	99.2	32	13.4	100.0
Severe (4)	2	1.0	100.0	2	1.0	100.0	0	0.0	100.0

Visit 3 Category	CYC 10-mg (N=244)			CYC 5-mg (N=239)			Placebo (N=244)		
	n	%	Cum. %	n	%	Cum. %	n	%	Cum. %
None (0)	90	36.9	36.9	89	37.2	37.2	65	26.6	26.6
Mild (1)	89	36.5	73.4	95	39.8	77.0	93	38.1	64.8
Moderate (2)	55	22.5	95.9	42	17.6	94.6	68	27.9	92.6
Moderately Severe (3)	8	3.3	99.2	10	4.2	98.7	18	7.4	100.0
Severe (4)	2	1.0	100.0	3	1.3	100.0	0	0.0	100.0

2.4.2.4 Physician Rating of Muscle Spasm (Cont.)

Table 10

Protocol 008: Descriptive Statistics for the Proportion of Patients in Each Category
 Physician Rating of Muscle Spasm by Visit

Visit 1—Baseline Category	CYC 5-mg (N=222)		CYC 2.5-mg (N=223)		Placebo (N=223)	
	n	%	n	%	n	%
Moderate (2)	145	65.3	137	61.4	145	65.0
Moderately Severe (3)	77	34.7	86	38.6	76	34.1
Severe	0	0	0	0	2	0.9

Visit 2 Category	CYC 5-mg (N=215)			CYC 2.5-mg (N=215)			Placebo (N=217)		
	n	%	Cum. %	n	%	Cum. %	n	%	Cum. %
None (0)	9	4.2	4.2	10	4.7	4.7	6	2.8	2.8
Mild (1)	84	39.1	43.3	78	36.3	40.9	80	36.9	39.6
Moderate (2)	97	45.1	88.4	99	46.1	87.0	97	44.7	84.3
Moderately Severe (3)	25	11.6	100.0	28	13.0	100.0	34	15.7	100.0
Severe (4)	0	0.0	100.0	0	0.0	100.0	0	0.0	100.0

Visit 3 Category	CYC 5-mg (N=217)			CYC 2.5-mg (N=219)			Placebo (N=217)		
	n	%	Cum. %	n	%	Cum. %	n	%	Cum. %
None (0)	88	40.6	0.6	78	35.6	35.6	65	30.0	30.0
Mild (1)	74	34.1	74.7	75	34.3	69.9	71	32.7	62.7
Moderate (2)	45	20.7	95.4	49	22.4	92.2	64	29.5	92.2
Moderately Severe (3)	10	4.6	100.0	17	7.8	100.0	17	7.8	100.0
Severe (4)	0	0.0	100.0	0	0.0	100.0	0	0.0	100.0

The protocols included analyses of mean change from baseline. The CYC 10 and CYC 5 groups had significantly greater decreases in spasm at one or both follow-up visits (Table 11). The CYC 2.5 group was not significantly different from placebo. There were no significant differences observed between the 2 active treatments in either study.

2.4.2.4 Physician Rating of Muscle Spasm (Cont.)

Table 11

Double-Blind Efficacy Studies: Change in Physician Rating of Muscle Spasm

	Mean Change From Baseline (Std. Dev.)				
	N	Visit 2		Visit 3	
Protocol 006					
CYC 10	238	-0.77*	0.72	244	-1.34* 0.90
CYC 5	235	-0.80*	0.75	239	-1.38* 0.94
Placebo	239	-0.54	0.73	244	-1.08 0.89
Protocol 008					
CYC 5	215	-0.71	0.66	217	-1.45* 0.88
CYC 2.5	215	-0.70	0.73	219	-1.36 0.97
Placebo	217	-0.62	0.68	217	-1.20 0.94

* p≤0.050 vs. placebo.

2.4.2.5 Magnitude of Effect

Three different approaches were used to characterize the magnitude of effect for the 3 CYC doses: proportion of responders, Time-to-A Lot or Complete Relief, and calculation of effect size. All three approaches showed that the magnitude of the difference between CYC 5 mg t.i.d. (or CYC 10 mg t.i.d.) and placebo was clinically meaningful.

Proportion of Responders

The magnitude of effect was assessed by calculating the percentage point difference between the proportion of responders for each primary parameter in the active and placebo groups (Table 12). In both studies at both primary time points, there was an 11- to 20-percentage-point difference between CYC 5 and placebo in the 3 primary parameters. In Protocol 006 the difference between CYC 10 and placebo ranged from 9 to 18 percentage points. In Protocol 008 the difference between CYC 2.5 and placebo was 2 to 12 percentage points.

2.4.2.5 Magnitude of Effect (Cont.)

Table 12

Double-Blind Efficacy Studies:
 Difference Versus Placebo-Proportion of Responders (%)

		Protocol 006		Protocol 008	
		CYC 10 (n=245)	CYC 5 (n=240)	CYC 5 (n=220)	CYC 2.5 (n=221)
Patient-rated global impression of change	Visit 2	15	17	12	6
	Visit 3	9	13	13	6
Patient rating of medication helpfulness	Visit 2	16	17	14	2
	Visit 3	12	11	20	6
Relief from starting backache	Day 3	18	15	15	12
	Day 7	14	13	12	9

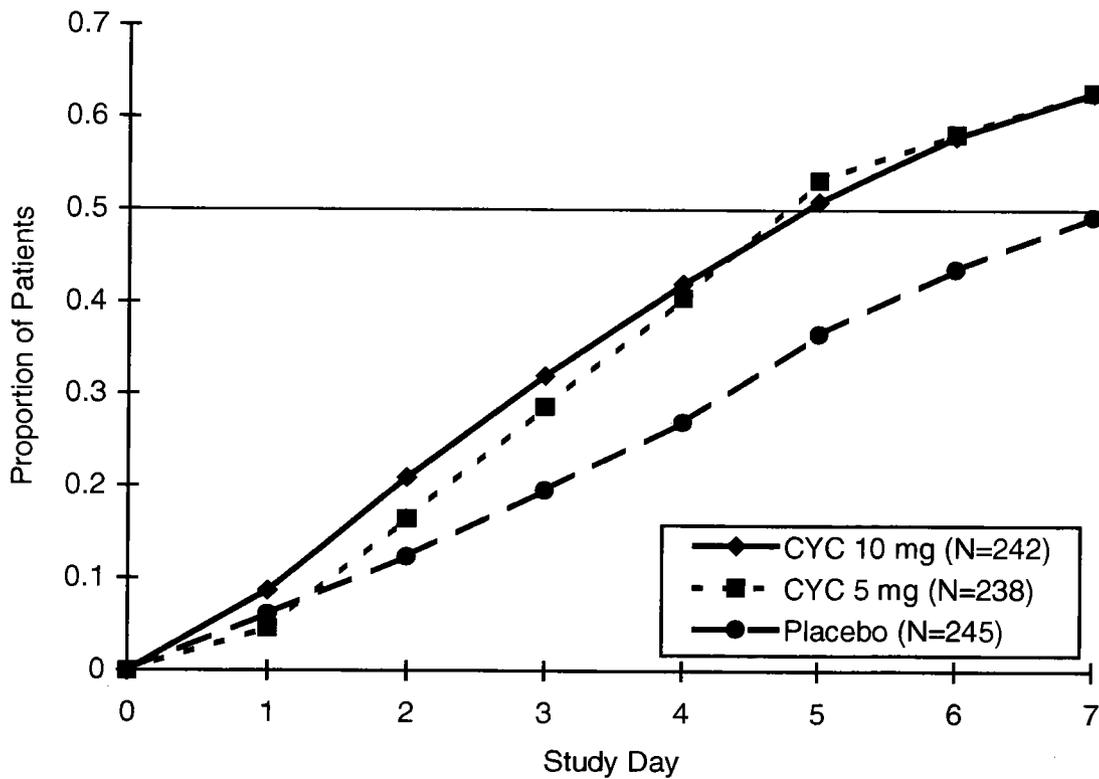
Time-to-A Lot or Complete Relief

This method of estimating the magnitude of effect is based on the relief from starting backache question answered daily in diary cards. Acute musculoskeletal spasm tends to resolve over time. It is reasonable to postulate that treatment with cyclobenzaprine will hasten the resolution of the spasm and pain. In order to examine how much cyclobenzaprine hastens recovery, a post-hoc analysis determined the Time-to-A Lot or Complete Relief. Figure 1 and Figure 2 show that in both protocols, the median Time-to-A Lot or Complete Relief was approximately 2 days less for CYC 5 than placebo. The Time-to-A Lot or Complete Relief with CYC 10 was similar to CYC 5, while CYC 2.5 was not significantly different than placebo.

2.4.2.5 Magnitude of Effect (Cont.)

Figure 1

Time to "A Lot of" or "Complete" Relief
Protocol 006

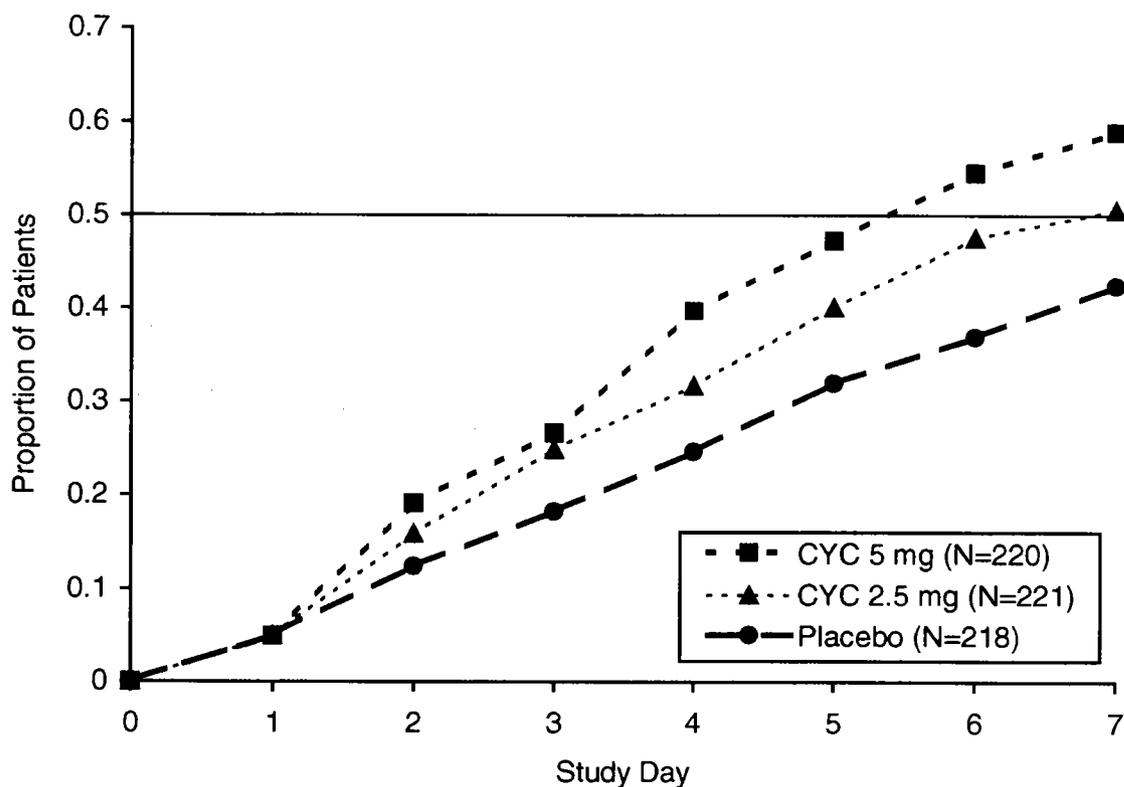


CYC 5 versus Placebo: Hazard ratio = 1.61, p=0.001
CYC 10 versus Placebo: Hazard ratio = 1.56, p=0.001
CYC 5 versus CYC 10: Hazard ratio = 1.03, p=0.811

2.4.2.5 Magnitude of Effect (Cont.)

Figure 2

Time to "A Lot of" or "Complete Relief"
Protocol 008



CYC 5 versus Placebo: Hazard ratio = 1.68, p=0.001
CYC 2.5 versus Placebo: Hazard Ratio = 1.33, p=0.065
CYC 5 versus CYC 2.5: Hazard Ratio = 1.23, p=0.092

2.4.2.5 Magnitude of Effect (Cont.)

Effect Size

After discussion with the FDA reviewers of this NDA, a post hoc evaluation of “effect size” was performed for the two double-blind efficacy trials. An effect size represents a standardized difference between a test group and a control group calculated by dividing the difference in means by the pooled standard deviation. The resulting measure has no units associated with it and can therefore be used to compare magnitude of effect across different endpoints. Arbitrary criteria for interpreting effect size have been proposed [23]: 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 (a small-to-moderate effect based on the proposed criteria).

Table 13 presents effect sizes for the comparisons of CYC 10, CYC 5, and CYC 2.5 versus placebo. The table also provides the pooled standard deviations used in calculating the effect size. For CYC 10 and 5, all effect sizes fell between 0.20 and 0.50 except 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 5-mg group. In contrast, the effect sizes for the 2.5 mg comparison all fell below 0.32 with 8 of the 13 falling below 0.20. The effect sizes for CYC 5 and CYC 10 compare favorably with those for famotidine 10 mg, an approved nonprescription medication. In the 2 most recent studies which administered famotidine 10 mg before a meal to prevent heartburn, the effect sizes were calculated as 0.21 and 0.31 for the comparison of famotidine to placebo. The effect sizes for CYC also compare favorably with those for antihistamines used to treat runny nose and sneezing. In a published meta-analysis, D’Agostino and Weintraub et al reported that the pooled effect sizes for nonprescription antihistamines ranged from 0.19 to 0.35. [238][26]. The above data indicate that the effect size of cyclobenzaprine is comparable to that of at least two categories of presently available OTC medications that rely upon subjective assessments to demonstrate efficacy.

2.4.2.5 Magnitude of Effect (Cont.)

Table 13
 Effect Sizes and Pooled Standard Deviation for Efficacy Parameters

Parameter	Time Point	Study 006 CYC 10 Versus Placebo Effect Size (SD pool)	Study 006 CYC 5 Versus Placebo Effect Size (SD pool)	Study 008 CYC 5 Versus Placebo Effect Size (SD pool)	Study 008 CYC 2.5 Versus Placebo Effect Size (SD pool)
Patient-Rated Clinical 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)
Patient 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)
Patient 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)

2.4.2.6 Onset of Effect

The daily diary rating and evaluations at the first follow-up visit provide information to characterize the onset of treatment effect. For each parameter, comparisons of the mean score (primary analysis) and proportion of responders (secondary analysis) versus placebo help describe time to onset of effect. In Protocol 006, Clinic Visit 2 assessments were made within 48 hours of the first dose in 54% of patients and 48 to 72 hours in an additional 42% of patients. In Protocol 008, Visit 2 occurred within 48 hours of the first dose. Patient Diary Card ratings were completed each evening starting with the first day medication was taken. Table 14 summarizes comparisons of CYC 5 versus placebo for the means and proportion of responders for the patient ratings at the first primary time point.

Protocol 006 provides strong evidence that CYC 5 has onset within 24 to 48 hours of starting treatment. Mean Relief from starting backache was significantly better ($p \leq 0.050$) for CYC 5 than placebo beginning on Study Day 2 (Table 7). This time point occurred after 3 to 4 doses (24 to 32 hours after the first dose). Mean Clinical Global Impression of Change and Medication Helpfulness were significantly greater ($p \leq 0.030$) for CYC 5 than placebo at Clinic Visit 2 (Table 14). Results from the subgroup of patients who returned for Clinic Visit 2 on Study Day 3 (approximately 48 hours after the first dose) also showed a significant mean difference favoring CYC 5 over placebo for both parameters. Analysis of proportion of responders showed that CYC 5 was significantly better ($p \leq 0.050$) than placebo in all three primary parameters at the first primary time point.

Protocol 008 also provides data that CYC 5 begins to have efficacy within 48 hours of initiating treatment. The mean scores for the primary endpoints at the first primary time point were greater for CYC 5 than for placebo. The responders analysis of Clinical Global Impression of Change, Medication Helpfulness, and Relief from Starting Backache showed CYC 5 had significantly more responders ($p \leq 0.050$) than placebo at Visit 2, which was within 48 hours after the first dose.

The pre-planned combined analysis of Protocols 006 and 008 showed that mean relief from starting backache with CYC 5 was significantly better than placebo beginning on Study Day 2. This finding is consistent with the conclusion that CYC 5 has onset within 24 to 48 hours of starting treatment.

2.4.2.6 Onset of Effect (Cont.)

Table 14

Double-Blind Trials: Differences Between CYC 5 and Placebo at Early Time Point

	Difference in Mean Score		Difference in Proportion of Responders (%)	
	006	008	006	008
Patient rated Global Impression of Change (Visit 2)	0.38**	0.22	17*	12*
Patient rating of Medication Helpfulness (Visit 2)	0.38**	0.29	17*	14*
Relief from Starting Backache (Study Day 3)	0.33**	0.33+	15*	15*
** p≤0.030. * p≤0.050. + 0.050<p≤0.100.				

2.4.2.7 Dose Response

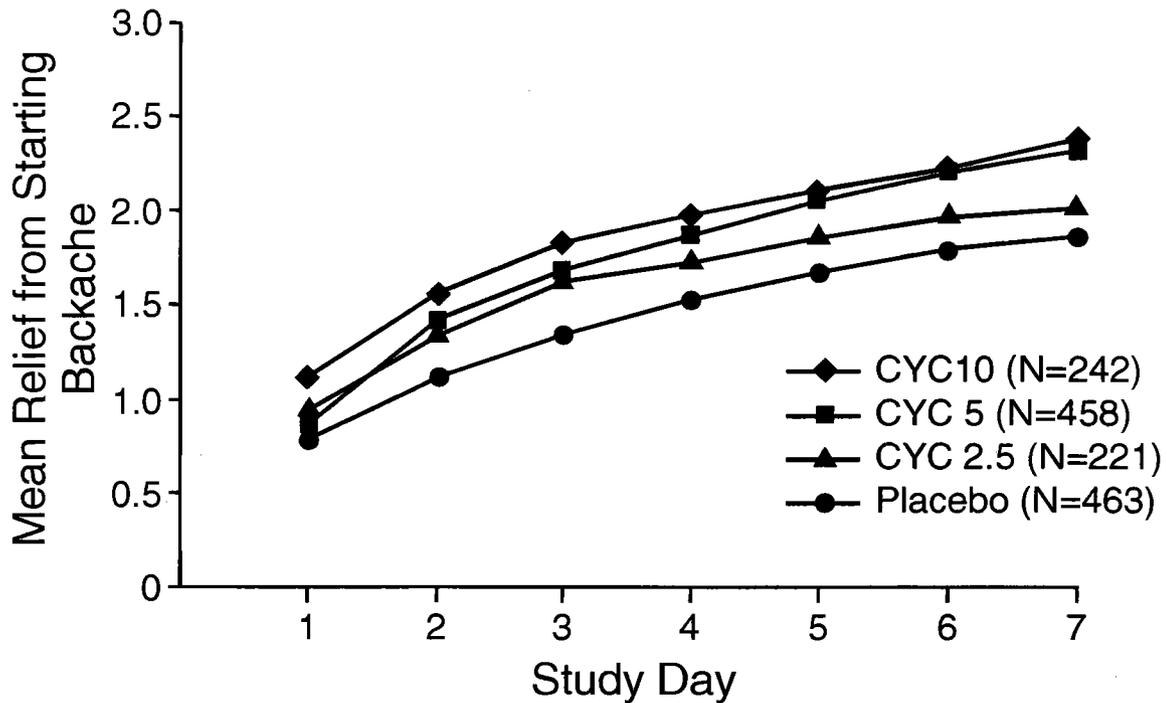
In Protocol 006 the dose response between CYC 5 and CYC 10 was relatively shallow. The only significant difference between CYC 10 and CYC 5 was in relief from starting backache on Study Day 1. Protocol 008 was conducted with the CYC 2.5 group replacing the CYC 10 group in order to more fully characterize the dose-response curve for FLEX. There was numerical evidence of a dose-related response with most parameters and time points. The preplanned combined analysis of these two protocols suggested a consistent, positive dose response.

Figure 3 presents a graphical display of mean relief versus study day for the patient diary rating of relief from starting backache for both protocols combined. The mean response increased with increasing dose for all time points except Study Day 1 when the mean response for CYC 5 was less than the mean response for CYC 2.5 (0.87 versus 0.95). The CYC 5 mean was closer to the CYC 2.5 mean at the earlier time points and closer to the CYC 10 mean at the later time points. This suggests that CYC 5 and 2.5 have a slower onset of effect than that seen with CYC 10 and that CYC 5 and 10 have a similar magnitude of effect that is greater than that seen with CYC 2.5. Statistical analysis supports this observation as the mean for CYC 10 was significantly different from placebo beginning on Day 1, while the mean for CYC 5 was significantly different from placebo beginning on Day 2.

2.4.2.7 Dose Response (Cont.)

Figure 3

Patient Diary Rating of Relief From Starting Backache—Protocols 006 and 008
Combined



Note: Study Day 1 occurs after 1 dose (8 hours after first dose). (Cont.)
Study Day 2 occurs after 3 to 4 doses (24 to 32 hours after first dose).
Study Day 3 occurs after 6 to 7 doses (48 to 56 hours after first dose).

Scale

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

2.4.2.8 Efficacy Independent of Somnolence

Somnolence was the most common adverse experience for patients taking CYC 5, occurring in 29% of that population in the Phase III studies (see 3.4.1). The prescription application contained an analysis that showed cyclobenzaprine produces clinical improvement whether or not sedation occurs. To determine if CYC 5 was effective for those patients who did not also report somnolence, the combined efficacy data from Protocols 006 and 008 for the CYC 5 and placebo treatments were analyzed excluding those patients who did not report somnolence.

Table 15 presents the proportion of responders in the CYC 5 and placebo treatment groups for the subsets of patients who did and did not report somnolence. For all primary parameters there was a meaningful treatment effect in patients who did not report somnolence. These analyses indicate that CYC 5 is effective even if patients have not reported somnolence.

Table 15

**Proportion of Responders and Pairwise Treatment Comparisons
 for Patients Without Somnolence†—Protocols 006 and 008 Combined
 CYC 5 Versus Placebo**

Parameter	Time Point	Trt Grp	All Patients		Not Reporting Somnolence		Reporting Somnolence	
			N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Clinical Global Impression of Change	Clinic Visit 2	CYC5	453	81% (77, 84%)	321	79% (74, 83%)	132	86% (79, 92%)
		PBO	458	66% (62, 71%)	413	65% (61, 70%)	45	76% (60, 87%)
	Clinic Visit 3	CYC5	456	89% (86, 92%)	323	88% (84, 92%)	133	91% (85, 95%)
		PBO	461	76% (72, 80%)	416	75% (70, 79%)	45	89% (76, 96%)
Medication Helpfulness	Clinic Visit 2	CYC5	453	52% (47, 57%)	321	50% (44, 55%)	132	58% (49, 66%)
		PBO	457	37% (32, 41%)	412	35% (31, 40%)	45	47% (32, 62%)
	Clinic Visit 3	CYC5	456	64% (59, 68%)	323	63% (57, 68%)	133	67% (58, 75%)
		PBO	460	49% (44, 53%)	415	46% (41, 51%)	45	71% (56, 84%)
Relief from Starting Backache	Study Day 3	CYC5	458	58% (53, 62%)	326	56% (51, 62%)	132	62% (53, 70%)
		PBO	463	43% (39, 48%)	418	42% (37, 47%)	45	56% (40, 70%)
	Study Day 7	CYC5	458	72% (68, 76%)	326	72% (67, 77%)	132	73% (64, 80%)
		PBO	463	60% (55, 64%)	418	58% (53, 63%)	45	76% (60, 87%)

† The terms drowsiness, sleepiness, sedation and lethargy map to the database term "somnolence."

2.4.2.9 Location of Muscle Spasm: Lumbar Versus Cervical

Table 16 displays the mean Global Impression of Change from Protocols 006 and 008 by treatment group and location of muscle spasm (cervical versus lumbar). In both studies, the mean differences between the cyclobenzaprine groups and placebo were comparable regardless of whether the spasm was in the cervical or lumbar region. The data for the other 2 patient-rated endpoints also showed consistent differences between cyclobenzaprine and placebo for both anatomic areas. These findings indicate that CYC 5 is effective for acute muscle spasm in both the cervical and lumbar areas.

Table 16

Mean Global Impression of Change in Protocols 006 and 008—
 Cervical Compared to Lumbar Spine

	Visit 2			Visit 3		
	N	Mean	SD	N	Mean	SD
Protocol 006						
Cervical						
CYC 10	79	2.15	0.93	80	2.68	1.18
CYC 5	76	2.30	0.95	76	2.88	1.06
Placebo	84	1.74	0.91	87	2.44	1.10
Lumbar						
CYC 10	153	2.35	0.93	158	2.90	1.09
CYC 5	155	2.28	0.88	156	2.90	1.07
Placebo	154	2.00	1.00	154	2.51	1.17
Protocol 008						
Cervical						
CYC 5	56	2.21	0.89	57	2.98	0.92
CYC 2.5	85	1.98	0.90	88	2.52	1.18
Placebo	75	2.05	0.98	75	2.41	1.24
Lumbar						
CYC 5	140	2.18	0.88	141	2.80	1.12
CYC 2.5	119	2.09	0.99	119	2.72	1.19
Placebo	136	1.96	0.98	136	2.41	1.17
4 = Marked improvement. 3 = Moderate improvement. 2 = Mild improvement. 1 = No change. 0 = Worsening.						

2.4.2.10 Drug-Demographic Interactions for Efficacy

Drug-demographic interactions for efficacy were investigated in the analyses of the individual controlled trials and the combined analysis of these two trials.

Age: <65/≥65 Years

In Protocol 006 the differences between treatment-group means were similar across the two age categories. In Protocol 008 and the combined analysis, the means for CYC 2.5 or placebo were higher than for CYC 5 in the older group. Given the small number of patients who were ≥65 years old (only 86 patients in the combined analysis), it is difficult to draw conclusions regarding treatment effect in the elderly.

Gender: Male/Female

In the combined analysis and within each of the two controlled trials, differences between treatment-group means were similar for males and females across most parameters.

Race: Caucasian/Black/Other

In the combined analysis and within each of the two controlled trials, differences between treatment-group means were consistent across the two largest race categories (Caucasian and Black). There were only 44 patients (3%) whose race was "other". As a result, conclusions regarding treatment effect in non-Caucasians and non-Blacks are probably not meaningful.

2.4.2.11 Open-Label Pattern-of-Use Study

Four hundred and fifty-two (452) patients in Protocol 009 rated their Clinical Global Impression of Change at the end of the open-label pattern-of-use study. The distribution of responses is summarized in Table 17. Eighty-eight percent (88%) were classified as responders (mild, moderate, or marked improvement). This proportion is very similar to the 88 to 90% responder rates for CYC 5 in the two double-blind trials (see Table 5). The pattern-of-use data for this study are presented in Section 4.

Table 17

Protocol 009
Open-Label Pattern-of-Use Study: Clinical Global Impression of Change

	N	%	Cum %
Marked improvement	172	38	38
Moderate improvement	162	36	74
Mild improvement	63	14	88
No change	53	12	100
Worsening	2	<1	100

2.5 Efficacy Discussion

The two double-blind, placebo-controlled studies (Protocols 006 and 008) reviewed in this document provide convincing evidence of the efficacy of CYC 5 for treatment of acute, painful, musculoskeletal spasm of the back or neck. The efficacy of the 5-mg dose differed only slightly from that of the already approved 10-mg prescription dose. A lower 2.5-mg dose demonstrated marginal efficacy.

Efficacy Endpoints: There were 3 primary efficacy endpoints (patient ratings at specified time points) in each study: Clinical Global Impression of Change, Medication Helpfulness, and Relief from Starting Backache. For the study results to be declared successful, it was decided *a priori* that CYC 5 should achieve significance ($p \leq 0.030$) compared with placebo in two of the above-mentioned three criteria for at least 1 of the primary time points. CYC 5 achieved significance ($p \leq 0.030$) in all three primary parameters at the second primary time point (Visit 3 or Day 7) in both studies. CYC 5 was also significantly better than placebo in all three primary parameters at the first time point in 1 of the studies (006). Cofactor analyses showed that the efficacy of CYC 5 was superior to placebo regardless of location of spasm (cervical versus lumbar). Relief was generally obtained even though use of analgesics or anti-inflammatory drugs was prohibited. Overall, these findings show a consistent pattern of results which demonstrate that patients are able to perceive a benefit versus placebo when CYC 5 is used to treat acute painful conditions of the low back or neck.

Physician assessments performed at baseline and subsequent visits confirmed that CYC 5 was associated with a greater reduction in palpable muscle spasm than found with placebo. This finding on physical examination in both placebo-controlled trials further validates the subjective assessments provided by the patients. These data also provide support for using the term "Muscle Relaxant" to describe this product.

Magnitude of Effect: The differences between CYC 5 and placebo in the primary endpoints were large enough to be clinically meaningful. In both studies at both primary time points, there was an 11- to 20-percentage-point difference in proportion of responders between CYC 5 and placebo. Analysis of Time-to-A Lot or Complete Relief from starting backache also shows an appreciable difference between CYC 5 and placebo in both studies. In both studies, the median Time-to-a-Lot or Complete Relief was approximately 2 days earlier for CYC 5 than placebo. The calculated effect sizes for CYC 5 compare favorably with those for famotidine 10 mg and OTC antihistamines (H_1), nonprescription medications approved for indications that have a high placebo response and rely on subjective assessment of symptoms.

2.5 Efficacy Discussion (Cont.)

Onset of Action: The only apparent efficacy difference of note between CYC 5 and CYC 10 is that CYC 10 appears to have a slightly more rapid onset of action. The Relief from Starting Backache data in Protocol 006 showed that onset of effect with CYC 10 appeared to occur within the first 2 doses on Day 1, whereas CYC 5 was not significantly better than placebo until Day 2 (24 to 32 hours after the first dose). Mean Clinical Global Impression of Change and Medication Helpfulness scores for CYC 5 were significantly better than for placebo at Visit 2 in Protocol 006, providing further evidence that onset of effect occurs within the first 48 hours of treatment. Protocol 008 provides data that show onset of effect with CYC 5 within 48 hours. The proportion of responders at Visit 2 was significantly higher with CYC 5 than placebo for both the Global Impression of Change and Medication Helpfulness parameters.

Dose Response: The planned combined analysis of Protocols 006 and 008 characterized the dose-related response for cyclobenzaprine. The ability to detect a dose response provides further validation of the studies' results. The combined analysis shows that onset of effect with CYC 5 occurs within 24 to 48 hours of initiating treatment. Mean relief from starting backache with CYC 5 was significantly better than placebo beginning on Study Day 2. Highly significant differences ($p < 0.001$) were demonstrated for CYC 5 versus placebo in mean scores for Clinical Global Impression of Change and Medication Helpfulness at Visit 2.

The CYC 2.5 dose was evaluated in one study. Based on the *a priori* criteria, the 2.5 dose was declared unacceptable as it achieved statistical significance compared to placebo in only one of three primary parameters (Relief from Starting Backache) at the first primary time point. The difference in the proportion of responders in Global Impression of Change and Medication Helpfulness ratings was only 6 percentage points or less when CYC 2.5 was compared to placebo at Visits 2 and 3. Physician examination also did not show significant difference for CYC 2.5 versus placebo in amount of muscle spasm.

Somnolence and Efficacy: Drowsiness, most often mild, is a frequently observed side effect of CYC 5. While drowsiness may be therapeutically useful for patients with severe back pain requiring a period of bedrest, somnolence is not required for CYC to be effective. The combined data from Protocols 006 and 008 showed that the efficacy advantage for CYC 5 relative to placebo was apparent for all patient-rated parameters when only patients who did not report somnolence were analyzed.

2.6 Efficacy Conclusions

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

1. Cyclobenzaprine 5 mg or 10 mg t.i.d. provides clinically meaningful symptomatic relief from painful muscle spasm of the back and/or neck over a 1-week course of treatment.
2. Resolution of paraspinal muscle spasm occurs more quickly with cyclobenzaprine 5 mg t.i.d. or 10 mg t.i.d. than with placebo.
3. There is evidence of a dose-related response for efficacy across the dose range of cyclobenzaprine 2.5 mg t.i.d. and 10 mg t.i.d. Cyclobenzaprine 2.5 mg t.i.d. is not a consistently effective dose.
4. Cyclobenzaprine 5 mg t.i.d. is effective within 24 to 48 hours of initiating treatment.
5. The relative efficacy of cyclobenzaprine 5 mg t.i.d. is not dependent on the presence of somnolence.

NONPRESCRIPTION DRUGS
ADVISORY COMMITTEE AND
ARTHRITIS ADVISORY
COMMITTEE

JULY 20, 1999

NDA 21070

COMPANY SUBMISSION

SAFETY

3. Safety

3.1 Introduction

Information from multiple sources was collected to examine the safety profile of cyclobenzaprine. Sections 3.2 to 3.7 summarize the adverse experience data from all patients and subjects who entered the 13 Nonprescription Cyclobenzaprine Clinical Studies. Primary safety data for the 5-mg tablet is provided by the 2 parallel-design, placebo-controlled efficacy studies (Protocols 006 and 008) and the Pattern-of-Use study (Protocol 009). These 3 studies are referred to as the Phase III studies. Patients in the Phase III studies were symptomatic and medicated as outpatients for several days to a week. One investigator in Protocol 008 was disqualified by the United States Food and Drug Administration because of fraud in prior non-Merck studies. The 40 patients enrolled at that site are excluded from all tabulations in this summary except the listings of patients with serious clinical adverse experiences.

Section 3.8 summarizes the safety profile of cyclobenzaprine 10 mg tablets during marketed use since 1977. The results of the prescription NDA studies and the Postmarketing Surveillance studies are presented first. Then information from Spontaneous Reports to Merck is summarized. Data collected by the American Association of Poison Control Centers characterizes the profile of overdosage with cyclobenzaprine.

Six clinical studies were conducted to characterize the extent of drowsiness and psychomotor impairment with cyclobenzaprine 5 mg. The drowsiness and psychomotor performance data from these studies is discussed in Section 3.9. Several medications known to produce drowsiness (diphenhydramine, clemastine, and amitriptyline) were included as active controls in the psychomotor studies.

3.2 Overall Extent of Exposure of the Study Population

A total of 2106 patients/subjects were evaluable for safety in the 13 Nonprescription Cyclobenzaprine Clinical Studies, and 2103 actually took study medication. Table 18 displays the distribution of patients/subjects exposed to cyclobenzaprine or control agents by the maximum duration of exposure. A total of 233 subjects participated in clinical pharmacology studies and they are presented separately for each different treatment received. Two-hundred thirty-one of the 233 subjects received cyclobenzaprine. A total of 1401 patients took cyclobenzaprine in the Phase III studies. Total exposures are greater than the total patients/subjects entered because subjects in crossover design studies received multiple treatments.

3.2 Overall Extent of Exposure of the Study Population (Cont.)

Table 18

Number of Subjects/Patients by Maximum Number of Treatment Days and Treatment Group in Nonprescription Cyclobenzaprine Clinical Studies

	CYC All Doses	Diphenhydramine 50 mg	Amitriptyline 50 mg	Clemastine 1 mg	Placebo
Subjects (Clinical Pharmacology Studies)					
1 to 4 Days (≤10 Doses)	177	135	65	28	152
5 to 14 Days	54	0	0	0	0
Patients (Phase III Studies)					
1 to 15 Days	1401	0	0	0	469
Total	1632	135	65	28	621

CYC = cyclobenzaprine.
 Three patients assigned to receive cyclobenzaprine did not take the study medication and are not included in this table.

A total of 230 subjects and 930 patients received the 5-mg dose. Patients in the controlled Phase III trials were instructed to take study medication for 7 days (21 doses). Patients in the Pattern-of-Use Study were instructed to medicate for as long as symptoms persisted, but not more than 7 days. One-hundred and thirty-seven patients (31%) in the Pattern-of-Use Study actually took drug for 9 to 15 days.

3.3 Demographics and Other Characteristics of the Study Population

Demographics

The demographic characteristics of the subjects and patients in Clinical Pharmacology and Phase III studies are summarized in Table 19. Slightly more than half of the subjects in the Clinical Pharmacology studies were males (52.8%). The mean age (41.7 years) was appreciably higher than the median (33.0 years), reflecting the inclusion of two studies of only elderly subjects (Protocols 010 and 014). Approximately 81% of the subjects were Caucasian, 6% were Black, and 9% were Hispanic.

In the Phase III studies, there were slightly more females than males. For those patients who took cyclobenzaprine, the mean age was 41.7 years. Approximately 89% of the patients were Caucasian, 8% were Black, and 2% were Hispanic. There were no meaningful differences in demographic characteristics between patients who received cyclobenzaprine compared to those who received placebo.

3.3 Demographics and Other Characteristics of the Study Population (Cont.)

Table 19

Baseline Demographic Characteristics for Subjects/Patients in Nonprescription Cyclobenzaprine Clinical Studies

	Patients in Phase III Studies N=1873		Subjects in Clinical Pharmacology Studies N=233
	CYC (N=1404) n (%)	Placebo (N=469) n (%)	n (%)
Gender			
Male	617 (43.9%)	200 (42.6%)	123 (52.8%)
Female	787 (56.1%)	269 (57.4%)	110 (47.2%)
Age (Years)			
<20	18 (1.3%)	5 (1.1%)	8 (3.4%)
20 to 29	233 (16.6%)	86 (18.3%)	99 (42.5%)
30 to 39	415 (29.6%)	116 (24.7%)	30 (12.9%)
40 to 49	363 (25.9%)	139 (29.6%)	15 (6.4%)
50 to 59	235 (16.7%)	75 (16.0%)	10 (4.3%)
60 to 64	66 (4.7%)	18 (3.8%)	4 (1.7%)
≥65	74 (5.3%)	30 (6.4%)	67 (28.8%)
Mean±SD	41.7 (±13.1)	41.9 (±13.1)	41.7 (±20.2)
Median	40.0	41.0	33.0
Range	18 to 85	18 to 79	18 to 82
Racial Origin			
Caucasian	1247 (88.8%)	411 (87.6%)	188 (80.7%)
Black	109 (7.8%)	43 (9.2%)	15 (6.4%)
Hispanic	33 (2.4%)	10 (2.1%)	22 (9.4%)
Other	15 (1.1%)	5 (1.1%)	8 (3.4%)
CYC = cyclobenzaprine.			

Secondary Diagnoses

All patients who entered Phase III had a primary diagnosis related to acute musculoskeletal pain and spasm of the back and/or neck. In the Phase III studies, the most common additional diagnoses for those in the cyclobenzaprine group were allergies to various drugs (~14%), hypertension (~12%), and headache (~6%). The profiles of secondary diagnoses were comparable in the cyclobenzaprine and placebo groups.

Prior Therapies

Prior therapy was defined as any therapy taken within 7 days of starting the study medication. These therapies may or may not have been taken after study medication was begun. Seventy-four percent of patients reported use of a prior therapy. The most common prior therapies were central nervous system (analgesics) and anti-inflammatory agents

3.3 Demographics and Other Characteristics of the Study Population (Cont.)

taken to treat the primary diagnosis (acute back/neck pain). Hormones were also a frequent prior therapy. Approximately 5% of the patients reported prior use of a muscle relaxant. Most of the drugs categorized as muscle relaxants were actually bronchodilators (e.g., albuterol). Seventeen patients (1%) reported taking cyclobenzaprine prior to study entry (13 were randomized to cyclobenzaprine and 4 to placebo). In general, the profiles of prior therapies were similar in the cyclobenzaprine and placebo populations.

Concomitant Therapies

Concomitant therapies are medications taken after study medication was dispensed. Prior therapies continued after study medication was dispensed are also considered to be concomitant therapies. The profile of concomitant therapies was very similar to that of prior therapies. The most common concomitant therapies were hormones and central nervous system (analgesic) agents. Concomitant use of analgesics and anti-inflammatory agents was prohibited in the placebo-controlled trials but not the Pattern-of-Use study. Seventy-two of the 75 patients who took ibuprofen were in the Pattern-of-Use study, as were 47 of the 52 patients who took acetaminophen and all 27 of the patients who took aspirin.

3.4 Clinical Adverse Experiences in Nonprescription NDA Studies

For all investigational trials, an adverse experience (AE) was defined as any unfavorable and unintended change in the structure or function of the body temporally associated with any use of the test substance, whether or not considered related to the use of the test substance. Clinical AEs were collected through spontaneous patient reporting in all of the studies. The severity of each AE was rated as mild, moderate, or severe. An assessment of drug relationship (i.e., possibly, probably, or definitely, probably not, or definitely not drug related) was made by the investigator. Those AEs that were considered possibly, probably, or definitely drug related by the investigator are designated "drug related" in tabulations in which drug-related AEs are documented. The specific term reported on the case report form was mapped to a "preferred term" using the MRL Adverse Event Dictionary.

Table 20 presents an overview of the clinical adverse experiences reported in the total population that received any dose of cyclobenzaprine in the 13 Nonprescription Cyclobenzaprine Clinical Studies. Summary data for the placebo group are also presented. Approximately 55% of patients/subjects receiving cyclobenzaprine reported one or more adverse experiences, most of which were considered drug related by the investigator. Approximately 37% of the placebo population reported an adverse experience; most of these were also considered drug related. Only three people (0.2%) in the cyclobenzaprine population and one (0.2%) in the placebo population had adverse experiences that met the regulatory definition of serious; none of the serious adverse experiences was considered drug related. Seventy-two individuals (4.4%) who received cyclobenzaprine discontinued because of an adverse experience as did 10 people (1.6%) who received placebo. Details of these events will be presented subsequently.

3.4 Clinical Adverse Experiences in Nonprescription NDA Studies (Cont.)

Table 20

Summary of Clinical Adverse Experiences in Nonprescription
 Cyclobenzaprine Clinical Studies—Number (%) of Subjects/Patients

	CYC n=1635	Placebo n=621
With any AE	905 (55.4%)	228 (36.7%)
With drug-related AE	788 (48.2%)	162 (26.1%)
With serious AE	3 (0.2%)	1 (0.2%)
With serious drug-related AE	0	0
Deaths	0†	0
Withdrawn due to AE	72 (4.4%)	10 (1.6%)
Withdrawn due to drug-related AE	62 (3.8%)	8 (1.3%)
Withdrawn due to serious AE	0	0

CYC = cyclobenzaprine.
 † One death (see 3.4.3) was reported and rated by the investigator who was disqualified as definitely not related to study drug (Protocol 008-021).

3.4.1 Incidence of Clinical Adverse Experiences

The following tables provide tabulations of AEs by body system and individual adverse experience terms. In the tabulations by body system, patients/subjects were counted more than once in the table if they had AEs classified in more than one body system. However, a patient/subject was counted only once in the overall total and in a particular body system, even if they reported multiple occurrences of different AEs within the same body system. Patients/subjects who reported multiple occurrences of the same AE were counted only once for that particular AE.

Clinical Pharmacology Studies: Table 21 summarizes the clinical adverse experiences by body system and treatment group for subjects in the clinical pharmacology studies. Adverse experiences that occurred in $\geq 1\%$ of subjects receiving cyclobenzaprine 5 mg are presented in Table 21. The highest incidence of adverse experiences occurred with amitriptyline 50 mg and cyclobenzaprine 10 mg. The incidence of adverse experiences with cyclobenzaprine appeared dose related, although the sample sizes for the 2.5- and 10-mg groups were much smaller than for the 5-mg group. Comparisons of adverse experiences related to sedation need to take into consideration that investigators used different terms to report sedation. Some of these terms map to the preferred term asthenia/fatigue, while others (e.g., drowsiness) map to the preferred term somnolence. The specific term reported on the case report form was mapped to a “preferred term” using the MRL Adverse Event Dictionary. These mappings explain why cyclobenzaprine 5 mg is associated with somnolence in Table 20, but cyclobenzaprine 10 mg (which was only included in one single-site protocol) and cyclobenzaprine 2.5 mg are not. Compared to placebo, cyclobenzaprine 10 mg and cyclobenzaprine 5 mg appeared to have a higher incidence of dry mouth and sedation (asthenia/fatigue or somnolence).

3.4.1 Incidence of Clinical Adverse Experiences (Cont.)

Table 21

Clinical Adverse Experiences by Body System in Clinical Pharmacology Studies (Incidence $\geq 1\%$ of Subjects Receiving Cyclobenzaprine 5 mg)—
 Percent of Subjects

	CYC 2.5 mg N=42	CYC 5 mg N=230	CYC 10 mg N=18	Diphen 50 mg N=135	Clem 1.0 mg N=28	Amit 50 mg N=65	Placebo N=152
Percent with any adverse experience	26.2	49.6	94.4	37.8	10.7	93.8	40.8
Body as a Whole	4.8	8.7	50.0	2.2	0	13.8	3.3
Asthenia/fatigue	4.8	7.8	44.4	0.7	0	12.3	2.6
Digestive	14.3	12.2	72.2	4.4	3.6	18.5	9.9
Constipation	0	1.7	0	0	0	0	0
Dry mouth	7.1	8.7	72.2	3.0	0	9.2	2.0
Musculoskeletal†	7.1	3.5	5.6	0.7	0	4.6	1.3
Nervous System and Psychiatric	16.7	40.4	66.7	33.3	7.1	90.8	33.6
Dizziness	4.8	3.9	22.2	8.1	0	32.3	2.6
Headache	14.3	9.1	44.4	4.4	7.1	1.5	5.9
Mental acuity decreased	0	2.2	0	0.7	0	1.5	3.9
Nervousness	0	1.3	0	0	0	0	0.7
Somnolence	0	32.2	0	22.2	0	78.5	23.7
Respiratory†	4.8	3.0	5.6	1.5	0	1.5	0
Special Senses†	4.8	1.7	0	0.7	0	0	3.9
Urogenital†	2.4	1.7	0	2.2	0	4.6	4.6

CYC = Cyclobenzaprine.
 Diphen=Diphenhydramine.
 Clem = Clemastine.
 Amit = Amitriptyline.
 † All individual AEs categorized in this body system have an incidence <1% in the cyclobenzaprine 5-mg population.
 This table is based on counts of subjects. Although a subject may have had two or more AEs, the person is counted only once in the body system total and in "Percent with any adverse experience."

Phase III Studies: The incidences of clinical adverse experiences by dose in the 3 Phase III studies are summarized in Table 22. The table presents the adverse experiences occurring in $\geq 1\%$ of the patients receiving cyclobenzaprine 5 mg in the double-blind efficacy studies (Protocols 006 and 008) or all 3 Phase III studies combined (006, 008, and 009). The profile of adverse experiences with cyclobenzaprine 5 mg is not appreciably different when the Pattern-of-Use Study data is pooled with that of the controlled trials. The incidence of adverse experiences overall, and somnolence and dry mouth in particular, was greater with cyclobenzaprine than placebo. The incidences of somnolence and dry mouth appeared to be dose related.

3.4.1 Incidence of Clinical Adverse Experiences (Cont.)

Table 22

Clinical Adverse Experiences by Body System in Phase III Studies
 (Incidence ≥1% of Patients Treated with Cyclobenzaprine 5 mg)—
 Percent of Patients

	Protocols 006 and 008				Protocols 006, 008, 009
	CYC 2.5 mg N=223	CYC 5 mg N=464	CYC 10 mg N=249	Placebo N=469	CYC 5 mg N=932
Percent with any adverse experience	43.9	55.0	61.8	35.4	56.3
Body as a Whole	6.3	8.4	8.0	4.9	8.8
Asthenia/fatigue	4.0	5.6	6.0	2.6	5.8
Pain, abdominal	0.4	1.1	0.8	0.6	1.1
Digestive	20.6	28.2	33.3	14.7	23.0
Acid regurgitation	0	1.3	0.8	0.4	1.6
Constipation	1.3	1.5	1.6	1.5	1.3
Diarrhea	1.8	1.7	0	1.7	1.1
Dry mouth	13.9	21.1	31.7	6.6	16.3
Nausea	4.0	3.0	1.6	3.6	2.8
Musculoskeletal†	4.5	1.9	1.2	2.8	2.6
Nervous System and Psychiatric	27.4	35.8	44.6	19.2	39.8
Dizziness	2.7	2.8	4.4	1.5	3.3
Headache	7.2	5.4	4.8	7.5	9.3
Irritability	0	0.9	1.2	0.2	1.0
Mental acuity decreased	0.4	1.1	0.8	0.4	0.9
Nervousness	0	0.6	1.6	0.2	1.1
Somnolence	19.7	29.1	37.8	9.6	30.6
Respiratory	4.5	4.3	4.4	4.3	4.8
Infection, upper respiratory	0.9	1.5	0.8	1.5	1.3
Pharyngitis	0.9	1.1	1.2	0.6	0.9
Skin and Skin Appendage†	0.9	1.7	1.6	1.3	1.4
Special Senses†	2.7	2.6	3.6	1.3	2.3
Urogenital†	0.4	0.6	0.8	0.9	1.2

CYC = cyclobenzaprine.
 † All individual AEs categorized in this body system have an incidence <1% in the CYC 5 population in the double-blind efficacy studies (Protocols 006 and 008) and all 3 Phase III studies combined (Protocols 006, 008 and 009).
 This table is based on counts of patients. Although a patient may have had two or more AEs, the person is counted only once in the body system total and in "Percent with any adverse experience."

3.4.2 Time Course and Intensity of Somnolence

Somnolence was the most commonly reported adverse experience in the Phase III studies. The “specific” terms drowsiness, sleepiness, sedation, and lethargy all mapped to the “preferred” term of somnolence. Patients may have reported somnolence more than once during a clinical study.

Table 23 displays the number and percent of patients who first reported somnolence on each study day. Of the 30% of patients who reported somnolence with cyclobenzaprine, 90% initially noticed the somnolence on the first or second day of dosing (within the first 4 doses in the Phase III studies).

Table 23

Incidence of First Report of Somnolence by Study Day in Phase III Studies

Study Day	CYC 2.5 mg (N=223)		CYC 5 mg (N=932)		CYC 10 mg (N=249)		Placebo (N=469)	
	n	(%)	n	(%)	n	(%)	n	(%)
1	26	11.7	162	17.4	58	23.3	20	4.3
2	14	6.3	97	10.4	28	11.2	16	3.4
3	1	0.5	14	1.5	1	0.4	7	1.5
4	2	0.9	5	0.5	4	1.6	1	0.2
5	0	0.0	4	0.4	0	0.0	1	0.2
6	1	0.5	2	0.2	1	0.4	0	0.0
7	0	0.0	0	0.0	2	0.8	0	0.0
8	0	0.0	0	0.0	0	0.0	0	0.0
9	0	0.0	1	0.1	0	0.0	0	0.0

CYC = Cyclobenzaprine.

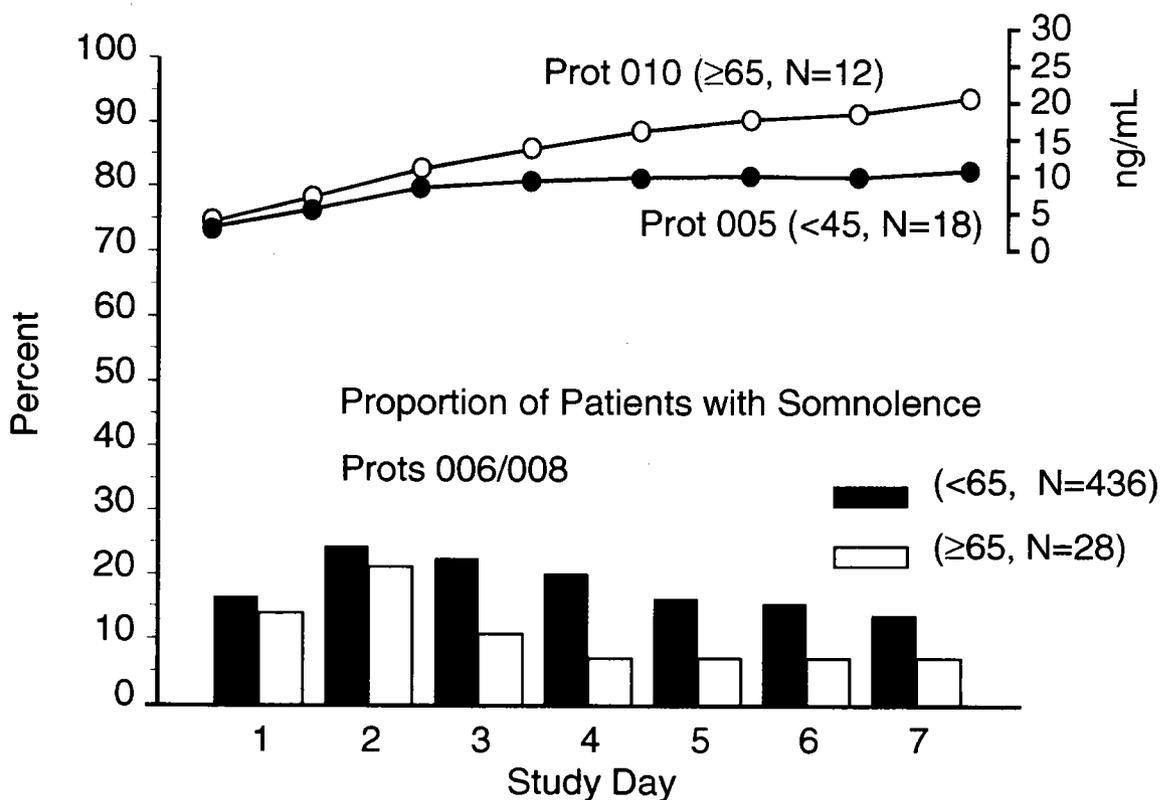
The presence or absence of somnolence was not assessed on a daily basis. Information obtained at Visits 2 and 3 indicated that once somnolence occurred, it did not necessarily persist for the remainder of the study. Somnolence resolved in some patients even though dosing continued and the plasma concentration of cyclobenzaprine was presumably increasing.

3.4.2 Time Course and Intensity of Somnolence (Cont.)

Figure 4 presents the mean plasma concentration by day from 2 cyclobenzaprine pharmacokinetic studies: Protocol 005 enrolled subjects 45 years old, Protocol 010 enrolled ≥ 65 years old subjects. Figure 4 also presents the proportion of patients who reported somnolence in the placebo-controlled Phase III studies by study day. The prevalence of somnolence in patients less than 65 years of age peaked on Study Day 2 then gradually declined. The prevalence of somnolence in patients 65 years of age or older also peaked on Study Day 2 and then decreased. These data show that somnolence does not increase with continued dosing, suggesting that adaptation to the sedating effect of cyclobenzaprine may occur.

Figure 4

Mean Trough Plasma Concentration and Proportion of Patients With Somnolence by Study Day for Patients <65 Years Old and ≥ 65 Years Old on 5-mg Dose



3.4.2 Time Course and Intensity of Somnolence (Cont.)

Patients were asked to rate the severity of each episode using the following scale:

- Mild (aware of symptom but easily tolerated)
- Moderate (interferes with usual activity)
- Severe (incapacitating with inability to work or do usual activity)

Table 24 presents the maximum intensity ratings for somnolence by treatment group in the Phase III studies. Most episodes of somnolence with cyclobenzaprine were mild or moderate in intensity. The incidence of severe somnolence with cyclobenzaprine 5 mg was 2.6%.

Table 24

Maximum Severity of Somnolence in Phase III Studies

	CYC 2.5 (N=223)	CYC 5 (N=932)	CYC 10 (N=249)	Placebo (N=469)
	n (%)	n (%)	n (%)	n (%)
Mild	30 (13.4)	156 (16.7)	64 (25.7)	31 (6.6)
Moderate	10 (4.5)	105 (11.3)	21 (8.4)	11 (2.3)
Severe	4 (1.8)	24 (2.6)	9 (3.6)	3 (0.6)

CYC = Cyclobenzaprine.
 Note: Each patient is counted only once. If a patient had somnolence more than once, the somnolence occurrence with the worst severity rating was used to count that patient.

3.4.3 Serious Clinical Adverse Experiences

Serious adverse experiences were reported in a total of 5 patients.

Deaths: One patient who was enrolled contrary to protocol defined criteria by the disqualified investigator (Protocol 008-021) died during a clinical study of nonprescription cyclobenzaprine. This 33-year-old female with a history of obesity and insulin-dependent diabetes mellitus was randomized to cyclobenzaprine 5 mg. She became agitated and complained of shortness of breath while shopping on Study Day 5. 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, then asystole. Resuscitation efforts were unsuccessful. 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

3.4.3 Serious Clinical Adverse Experiences (Cont.)

revealed the presence of the cocaine metabolite, benzoylecgonine, at a concentration of 0.1 µg/mL, an amount which has been shown to produce constriction of coronary arteries [19]. Cyclobenzaprine levels were not measured at autopsy. Upon autopsy it was found that the patient had markedly severe atherosclerotic heart disease, worsened by her diabetes mellitus. The investigator considered the patient's death to be definitely not related to study medication.

Nonfatal Serious Adverse Experiences: Table 25 lists the 4 patients with nonfatal serious adverse experiences. All the adverse experiences were considered by the investigator to be definitely not drug related, and none prompted discontinuation of treatment.

Table 25

Listing of Patients With Nonfatal Serious Clinical Adverse Experiences

Study Number	Gender/ Age	Drug/ Total Daily Dosage (mg)	Relative Day of Onset	Adverse Experience	Duration	Intensity	Drug Relation	Resolved
008	F/81	CYC/7.5	2	Pain, back, worsening	7 days	Severe	Def not	Yes
008	M/41	CYC/15	8	Pain, chest	3 days	Severe	Def not	Yes
			8	Syncope	3 days	Severe	Def not	Yes
			8	Labyrinthitis	3 days	Severe	Def not	Yes
009	F/32	CYC/5	1	Pneumonia, worsening	1 day	Severe	Def not	Yes
008	F/56	Placebo	2	mass, breast	17 days	Moderate	Def not	Yes

CYC = Cyclobenzaprine.

3.4.4 Discontinuations Due to Clinical Adverse Experiences

A total of 83 patients/subjects discontinued from the 13 Nonprescription Cyclobenzaprine Clinical Studies because of clinical adverse experiences. In addition, 3 patients enrolled by the disqualified investigator also discontinued because of adverse experiences; these 3 patients are not included in Table 26 and Table 27. Table 26 provides a breakdown of the number (%) of subjects/patients discontinued due to clinical AEs and the number (%) of subjects/patients discontinued due to drug-related clinical AEs by treatment group. No subjects discontinued treatment due to adverse experiences after receiving amitriptyline or clemastine. Discontinuations due to adverse experiences appeared to be dose related for the cyclobenzaprine groups.

3.4.4 Discontinuations Due to Clinical Adverse Experiences (Cont.)

Table 26

Subjects/Patients Discontinued Due to Clinical Adverse Experiences by Treatment Group

Treatment Group	N	Number (%) Discontinued Due to Clinical AE	Number (%) Discontinued Due to Drug-Related [†] Clinical AE
CYC 2.5 mg	265	5 (1.9%)	5 (1.9%)
CYC 5 mg	1162	47 (4.0%)	41 (3.5%)
CYC 10 mg	267	20 (7.5%)	18 (6.7%)
Placebo	621	10 (1.6%)	8 (1.3%)
Diphenhydramine 50 mg	135	1 (0.7%)	1 (0.7%)
Amitriptyline 50 mg	65	0	0
Clemastine 1.0 mg	28	0	0

[†] Considered by the investigator to be possibly, probably, or definitely drug related.

Table 27 presents the adverse experiences reported by 3 or more patients/subjects who discontinued treatment with cyclobenzaprine 5 mg because of an AE. Patients/subjects may have reported more than one adverse experience without specifying which one prompted discontinuation. Somnolence was the most common AE associated with discontinuation and appeared to be dose related. All the adverse experiences for which follow-up information is available are known to have resolved after discontinuation of study medication.

Table 27

Adverse Experiences Reported by ≥3 Subjects/Patients Who Discontinued Due to an AE—Number (%) of Subjects/Patients

Adverse Experience	CYC 2.5 N=265	CYC 5 N=1162	CYC 10 N=267	Placebo N=621
Asthenia/fatigue	1 (0.4%)	4 (0.3%)	3 (1.1%)	1 (0.2%)
Dizziness	1 (0.4%)	6 (0.5%)	2 (0.7%)	0
Dry mouth	1 (0.4%)	8 (0.7%)	3 (1.1%)	0
Headache	0	9 (0.8%)	1 (0.4%)	2 (0.3%)
Mental acuity decreased	0	3 (0.3%)	0	0
Nausea	1 (0.4%)	6 (0.5%)	1 (0.4%)	1 (0.2%)
Somnolence	3 (1.1%)	29 (2.5%)	13 (4.9%)	3 (0.5%)

3.4.5 Drug-Demographic Interactions

Incidence of Clinical Adverse Experiences by Gender: The profile of clinical adverse experiences in the Phase III studies (Protocols 006, 008, and 009 combined) was examined separately for males and females. Data from all 3 cyclobenzaprine doses (2.5, 5, and 10 mg) were combined. The type and frequency of adverse experiences were similar in the males and females treated with cyclobenzaprine. There was no evidence of a gender difference in the tolerability of cyclobenzaprine.

Incidence of Clinical Adverse Experiences by Age: The profile of clinical adverse experiences in the Phase III studies (Protocols 006, 008, and 009 combined) was examined separately for patients younger than 65 years of age and patients 65 or older. Data from all 3 cyclobenzaprine doses (2.5, 5, and 10 mg) were combined. The incidence of dry mouth was slightly higher in the elderly patients who received cyclobenzaprine, while the incidence of asthenia/fatigue was slightly lower in the older patients. Overall, however, there was little evidence of an age effect on the tolerability of cyclobenzaprine in these studies.

Incidence of Clinical Adverse Experiences by Race: The profile of clinical adverse experiences in the Phase III studies (Protocols 006, 008, and 009 combined) was examined separately for Caucasian patients and Black patients, the two largest racial groups in the trials. Data from all three cyclobenzaprine doses (2.5, 5, and 10 mg) were combined. Generally, adverse experiences occurred less often in the Black patients who received cyclobenzaprine than in the Caucasian patients. The same trend was evident in the patients who received placebo, suggesting that any differences in incidence were confounded by differences in the tendency to report events.

3.4.6 Drug-Disease Interactions

The nonprescription cyclobenzaprine trials enrolled patients who were generally healthy. Relatively few patients in the Phase III studies had medically significant concomitant conditions such as hypertension (12%), arthritis (4%), hypercholesterolemia (3%), or diabetes mellitus (2%). Given the small number of patients with significant concomitant conditions, comparisons of adverse experience profiles in patients with and without these conditions were not performed. Instead, the clinical adverse experience database was reviewed to look for reports of patients who had a worsening of a concomitant medical problem while receiving cyclobenzaprine. The only report of increased blood pressure while on cyclobenzaprine was a patient in the Pattern-of-Use Study (009). There were no adverse experiences related to changes in cholesterol level or control of diabetes.

The prescription labeling advises that cyclobenzaprine should be used with caution in patients with angle-closure glaucoma. There were no adverse experiences reported of increased intraocular pressure in patients who received cyclobenzaprine in the Phase III studies (ophthalmologic examination was not required in these studies), however patients with angle closure glaucoma were excluded from entry.

3.4.6 Drug-Disease Interactions (Cont.)

The prescription labeling also includes hyperthyroidism as a contraindication. Twenty-two patients with a history of hypothyroidism and 2 patients with a history of hyperthyroidism received cyclobenzaprine in the Phase III studies. There were no reported adverse experiences in the endocrine body system.

3.4.7 Drug-Drug Interactions

There were no drug-interaction studies conducted with cyclobenzaprine 5 mg. Since analgesics or anti-inflammatory drugs may be concomitantly used to treat acute back or neck pain, the adverse experience profiles were reviewed for the 75 patients who used ibuprofen, the 52 patients who used acetaminophen, and the 27 patients who used aspirin while taking cyclobenzaprine in the Phase III nonprescription studies. As noted earlier, concomitant analgesics were only allowed in the Pattern-of-Use Study 009. The type and frequency of adverse experiences in these groups were generally similar to the larger population that did not use concomitant analgesics, indicating that there do not appear to be interactions between cyclobenzaprine and nonprescription analgesics or anti-inflammatory drugs. The exception is headache, which was reported by 33% of patients who concomitantly used ibuprofen and 52% of patients who concomitantly used acetaminophen. In contrast, headache was reported by only 9% of all patients who received cyclobenzaprine 5 mg in the Phase III studies. It is likely that some patients were using the analgesics to treat the headaches, so it is logical that more headaches would be reported in patients who used analgesics than in patients who did not use them.

3.5 Laboratory Adverse Experiences

Seven of the clinical pharmacology trials included both prestudy and poststudy laboratory tests; routine laboratory tests were not included in the Phase III trials. The incidence of laboratory adverse experiences was based on the number of subjects who underwent each laboratory test. Table 28 lists the laboratory adverse experiences that occurred. No serious laboratory adverse experiences were reported. One subject discontinued due to a laboratory adverse experience (ALT increased) that was considered possibly drug related.

Table 28

Listing of Subjects With Laboratory Adverse Experiences

AN	Age	Gender	Treatment Group	Study Day	Total Daily Dose mg	Adverse Experience	Drug Relation
0013†	67	F	CYC 5.0 mg	3	5.0 mg	ALT increased	Possibly
0005	76	M	DPH 50 mg	10	Off Drug	ALT increased	Possibly
0008	40	F	CYC 2.5 mg	49	Off Drug	Hematuria	Def. Not
				76	Off Drug	Pyuria Hematuria	Prob Not

CYC = cyclobenzaprine.
 DPH = diphenhydramine.
 † Discontinued because of laboratory adverse experience.

3.6 Special Examination Adverse Experiences

Electrocardiograms (ECG) were performed prestudy and poststudy in 140 subjects as part of 7 Clinical Pharmacology studies. There were no appreciable changes in mean QT interval after treatment with cyclobenzaprine. Only one ECG adverse experience was reported. A 40-year-old female in Study 005 was noted to have premature ventricular contractions on her poststudy ECG. She also reported palpitations and anxiety that resolved. The subject received cyclobenzaprine 10 mg, cyclobenzaprine 5 mg, and cyclobenzaprine 2.5 mg in the 3 treatment periods. The investigator considered the ECG changes to be possibly related to study medication.

3.7 Clinical Safety Measurements

Changes in pulse and blood pressure were analyzed in the two double-blind Phase III studies. Changes that the investigator considered to be clinically meaningful were to be reported as clinical adverse experiences. There was only one reported adverse experience of tachycardia (in the placebo group), and there were no reports of increased blood pressure in Protocols 006 and 008.

Blood Pressure: Sitting systolic and diastolic blood pressure were measured at the baseline and final visits in Protocols 006 and 008. Cyclobenzaprine did not have a consistent effect on blood pressure. All treatment mean changes were within 2.3 mm Hg of their baseline and were not considered clinically important.

Pulse: Sitting pulse was measured at the baseline and final visits in Protocols 006 and 008. Cyclobenzaprine was associated with a small increase in pulse rate compared to placebo. All treatment mean changes were within 4.3 beats/minute of their baseline means and were not considered clinically important.

3.8 Experience with Marketed Prescription Dose (10 mg)

This section reviews the safety profile of the currently marketed cyclobenzaprine 10-mg tablet. Data from three sources is summarized in the sections that follow:

- Controlled clinical trials included in the original prescription marketing application
- Postmarketing Surveillance Studies
- Spontaneous reports to the manufacturer arising from marketed use.

3.8.1 Prescription Marketing Application Studies

The prescription marketing application included data from clinical studies of acute muscle spasm with a 2-week duration of treatment. The application also included 8 long-term safety studies of cyclobenzaprine in which patients with various neurologic disorders (e.g., Parkinson's Disease) received up to 80 mg per day for 1 month to 3 years. Data from these long-term high-dose studies are not presented in the summary.

3.8.1 Prescription Marketing Application Studies (Cont.)

The acute muscle spasm trials included placebo and diazepam 5 mg as control groups. Four hundred seventy-three patients received cyclobenzaprine 10 mg t.i.d. and 19 patients received cyclobenzaprine 5 mg t.i.d. Approximately 50% of the patients were males. The ages ranged from 10 to 70 years with the majority in the 21 to 60 year age group. Table 29 displays the clinical adverse experiences (AEs) by body system. (The mapping of individual adverse experiences to a body system has changed since 1977). Adverse experiences occurring in $\geq 1\%$ of patients receiving cyclobenzaprine 10 mg t.i.d. are presented. Somnolence was the most frequent adverse experience (39% for cyclobenzaprine 10 mg and 38% for diazepam). Somnolence was rated severe in 12 of the 185 patients treated with cyclobenzaprine 10 mg who reported somnolence, and 10 of the 107 patients treated with diazepam who reported somnolence. Dry mouth occurred most frequently in the cyclobenzaprine 10-mg group (27%), while dizziness was most common in the diazepam group (18%). The number of patients who received cyclobenzaprine 5 mg is too small (n=19) to provide accurate incidence rates for adverse experiences with that treatment.

3.8.1 Prescription Marketing Application Studies (Cont.)

Table 29

Incidences of Clinical Adverse Experiences in $\geq 1\%$ of Patients Treated With
 Cyclobenzaprine (CYC) 10 mg in Prescription Application Clinical Trials—
 Number (%) of Patients

	CYC 10 mg N = 473	CYC 5 mg N = 19	Diazepam 5 mg N = 280	Placebo N = 496
Patients with Any Adverse Experience	263 (56)	13 (68)	129 (46)	135(27)
Body as a Whole	20 (4)	1 (5)	7 (3)	11 (2)
Asthenia/fatigue	7 (1)	0	0	4 (1)
Headache	6 (1)	0	5 (2)	4 (1)
Integumentary	131 (28)	4 (21)	29 (10)	30 (6)
Dry mouth/tongue	128 (27)	4 (21)	27 (10)	26 (5)
Digestive	30 (6)	0	6 (2)	23 (4)
Constipation	5 (1)	0	1 (0.3)	0
Dyspepsia	7 (1)	0	0	3 (1)
Nausea	8 (2)	0	3 (1)	13 (3)
Nervous System	58 (12)	5 (26)	52 (19)	34 (7)
Dizziness	51 (11)	2 (11)	50 (18)	29 (6)
Special Senses	22 (5)	3 (16)	7 (3)	10 (2)
Taste Perversion	14 (3)	2 (11)	2 (1)	2 (0.4)
Amblyopia	5 (1)	1 (5)	1 (0.3)	2 (0.4)
Psychiatric	194 (41)	9 (47)	113 (40)	80 (16)
Nervousness	5 (1)	1 (5)	3 (1)	4 (1)
Somnolence	185 (39)	7 (37)	107 (38)	69 (14)
CYC = Cyclobenzaprine. This table contains counts of patients. Although a patient may have had two or more AEs, the person is counted only once in the body system total and "Percent with any AE."				

3.8.2 Postmarketing Surveillance Studies

Two studies were conducted in 1977 and 1978 as part of the postmarketing surveillance program for cyclobenzaprine: a Postmarketing Surveillance Study [2], and a Comparative Survey. The design of these studies is summarized below:

- **Surveillance Study**—6311 patients with acute muscle spasm were enrolled by 1991 physicians. Each patient initially received enough medication for 14 days. Most patients (80%) took 10 mg t.i.d., although they were allowed to titrate the dose up or down. (The publication summarizing this study is included as an Attachment to this document.)
- **Comparative Survey**—1296 patients with acute muscle spasm were allocated to cyclobenzaprine 10 mg t.i.d. by 685 physicians. Each physician was asked to treat half of the eligible patients with cyclobenzaprine and the other half with other available medications. Patients were to be alternately assigned to open-label cyclobenzaprine or standard care. Safety data were collected from the standard care group but were not included in the final report, and therefore were not available for this summary.

In both studies, patients were asked an open-ended question about adverse experiences. The severity of these volunteered events was then assessed through directed questioning. Patients were also directly asked whether they experienced any of the following: confusion, tachycardia, disorientation, hallucinations, arrhythmia, or seizure. These were considered elicited adverse experiences.

Table 30 summarizes the adverse experiences (volunteered and elicited) in each study and for both studies combined. Specific adverse experiences that occurred in $\geq 1\%$ of patients in either study are presented. The adverse experience profiles in the 2 studies were nearly identical. The most common adverse experiences were somnolence (16.3%), dry mucous membranes (6.7%), and dizziness (3.3%). The incidence of each of these events was appreciably lower in these open-label postmarketing studies than in the double-blind, prescription marketing application studies. The incidence of somnolence rated severe, however, was similar in the postmarketing studies (3.4%) and the cyclobenzaprine 10-mg group in the nonprescription studies (3.6%) (see Table 24).

Elicited adverse experiences were reported in 2.7% of patients. Table 31 summarizes the elicited adverse experiences from each study and for the studies combined. Episodes of confusion (1.4%), disorientation (0.9%), and tachycardia (0.9%) were most common. Hallucinations were reported by 0.2% of patients. In discussions with the investigators at that time, it was noted that the terms confusion, disorientation, and tachycardia were defined by the physicians to include subjective feelings and sensations in addition to the medical definition of the terms. Many of the confusion episodes were described as feeling strange or "spaced out." Disorientation was often reported when the patient felt forgetful or lightheaded. Tachycardia was the subjective sensation of a rapid heart rate; only 2 patients had documented pulse rates of 100 or more.

3.8.2 Postmarketing Surveillance Studies (Cont.)

Table 30

Adverse Experiences by Body System With Incidence $\geq 1\%$ in Cyclobenzaprine 10-mg Surveillance Study, Comparative Survey, and Total—Number (%) of Patients

AE by Body System	Surveillance Study	Comparative Survey	Total
	N=6311	N=1296	N = 7607
No. (%) of patients with any AE	1986 (31%)	377 (29%)	2363 (31%)
No. (%) of patients without any AE	4325 (68%)	919 (71%)	5244 (69%)
Body as a Whole	237 (3.8)	41 (3.2)	278 (3.7)
Asthenia	67 (1.1)	9 (0.7)	76 (1.0)
Fatigue/tiredness	99 (1.6)	15 (1.2)	114 (1.5)
Cardiovascular System	82 (1.3)	17 (1.3)	99 (1.3)
Tachycardia	59 (0.9)	13 (1.0)	72 (0.9)
Digestive System	214 (3.4)	46 (3.5)	260 (3.4)
Nausea	93 (1.5)	23 (1.8)	116 (1.5)
Integumentary System	459 (7.3)	67 (5.2)	526 (6.9)
Dry mucous membranes	445 (7.1)	64 (4.9)	509 (6.7)
Nervous System	274 (4.3)	58 (4.5)	332 (4.4)
Dizziness	208 (3.3)	43 (3.3)	251 (3.3)
Organs of Special Senses†	90 (1.4)	11 (0.8)	101 (1.3)
Psychiatric	1225 (19.4)	237 (18.3)	1462 (19.2)
Confusion	102 (1.6)	18 (1.4)	120 (1.6)
Nervousness	75 (1.2)	5 (0.4)	80 (1.1)
Somnolence	1023 (16.2)	215 (16.6)	1238 (16.3)

This table contains counts of patients. Although a patient may have had two or more AEs, the person is counted only once in the body system total and "Percent with any AE."

† All individual AEs categorized in this body system have an incidence $<1\%$ in Surveillance Study and Comparative Survey.

Table 31

Elicited Adverse Experiences in the Cyclobenzaprine 10-mg Surveillance Study, Comparative Survey, and Total—Number (%) of Patients

AE by Body System	Surveillance Study	Comparative Survey	Total
	N=6311	N=1296	N = 7607
Confusion	88 (1.4%)	18 (1.4%)	106 (1.4%)
Tachycardia	53 (0.8%)	12 (0.9%)	65 (0.9%)
Disorientation	52 (0.8%)	10 (0.8%)	62 (0.9%)
Hallucination	13 (0.2%)	2 (0.2%)	15 (0.2%)
Arrhythmia	5 (0.1%)	2 (0.2%)	7 (0.1%)
Seizure	1 (-)	0	1 (-)

3.8.3 Spontaneous Reports

Cyclobenzaprine 10-mg tablets have been marketed in the United States since 1977. It is estimated that over 100,000,000 prescriptions have been written for cyclobenzaprine since then, and over 1,500,000,000 tablets have been distributed by Merck. It is not known how many different individuals have been exposed to cyclobenzaprine, since many may have received multiple prescriptions to treat a recurrent problem.

Spontaneous reports of adverse experiences with cyclobenzaprine received by Merck & Co., Inc., from worldwide sources are entered in the Company's Worldwide Adverse Experience System (WAES) database. Individual patients identified in the literature, where the focus of the article or abstract was a report of an adverse experience to cyclobenzaprine, have been included in the database. Reports are included in the database regardless of the outcome or the likelihood of a causal association. The terminology used in this report reflects the diagnosis or terminology used by the reporter. The reporter terminology is mapped to a Preferred Term using a Merck-developed dictionary. Due to an evolving dictionary and coding guidelines, it is possible that, over time, different Preferred Terms may have been used to identify synonymous reactions (e.g., "dry mucous membranes" in the integumentary system versus "dry mouth" in the digestive system).

The FDA has received reports of post-marketing adverse events with cyclobenzaprine from Merck and sources other than Merck (e.g., patients, healthcare professionals, manufacturers of generic cyclobenzaprine). The FDA database utilizes a different adverse experience dictionary, and source documents for events reported by entities other than Merck were not available for review. Therefore, this document focuses on data in the Merck database.

As of February 1, 1999, a total of 993 adverse experience reports were reported from marketed use and entered into the WAES database. Of the 993 patients, 238 had at least one adverse experience that was identified as meeting the regulatory definition of serious at the time of the report. Reports were not reclassified according to current criteria for serious adverse experiences. For perspective, the WAES database for famotidine contained 146 reports of serious adverse experiences (including 11 deaths) when the OTC NDA was written in 1992. As of that time, an estimated 9,000,000 prescriptions had been written for famotidine in the United States, one-tenth that of cyclobenzaprine.

Table 32 displays all 993 adverse experience reports and the serious adverse experience reports by body system, excluding overdoses. Considering both serious and nonserious reports, the most commonly affected body systems were body as a whole, nervous, and psychiatric. Serious events were most common in the body as a whole, cardiovascular, nervous, and psychiatric body systems.

3.8.3 Spontaneous Reports (Cont.)

Table 32

Number of Patients With Adverse Experiences and Serious Adverse Experiences by Body System Received as Spontaneous Reports During Marketed Use Since 1977

Body System	Number with An Adverse Experience	Number with a Serious Adverse Experience
Body as a whole/site unspecified	346	99
Cardiovascular system	138	52
Digestive system	133	20
Endocrine system	17	5
Eyes, ears, nose, throat	74	13
Hemic and lymphatic system	36	11
Hepatobiliary system	50	25
Immune system	40	4
Metabolism and nutrition	41	8
Musculoskeletal system	40	16
Nervous system	248	63
Psychiatric disorder	261	66
Respiratory system	37	16
Skin and skin appendages	88	11
Urogenital system	99	25
Total	993	238
Note: The same patient may appear in more than one body system		

The WAES database contains the ages of the patients for 487 of the 993 reports. Ninety-two of the patients (19%) were ≥ 65 years old. It is estimated that 14% of the cyclobenzaprine prescriptions are written for people ≥ 65 years old. The elderly, therefore, account for a slightly greater proportion of the WAES reports than would be expected based on proportion of prescriptions. This may reflect differences in reporting rates, or it may reflect increased plasma concentrations in the elderly (see 5.4.1).

3.8.3.1 Deaths

The WAES database contains 52 reports of deaths in people who received cyclobenzaprine. There were no reports in which therapeutic use of cyclobenzaprine was clearly the primary cause of death. Fifteen of the reports described patients who took overdoses of the product with or without other drugs. Three reports described fetal deaths where the mother had taken cyclobenzaprine at some point during the pregnancy. There was no pattern among the other 34 reports. There were 29 reports where confounding factors were present: 6 with underlying heart disease, 3 with liver disease, 3 with cancer, 4 with pulmonary disease, 9 with other medications (e.g., MAO-inhibitors, tricyclic antidepressants), 2 with intracranial bleeds, 1 with dermatomyositis, and 1 with rhabdomyolysis. The remaining 5 reports had insufficient data to assess causality.

3.8.3.1 Deaths (Cont.)

The FDA database contains 36 reports of deaths which were not reported to Merck and therefore Merck cannot verify the details. Based on the limited available information, there does not appear to be a pattern of toxicity among those reports.

3.8.3.2 Body as a Whole

The most common reports classified under Body as a Whole were dizziness (35) and dry mucous membranes (32). Neither of these are unexpected findings given the data from the controlled trials and postmarketing studies. There were 29 reports of asthenia/fatigue, which is difficult to distinguish from somnolence (which is classified in Nervous System).

3.8.3.3 Cardiovascular System

There were 74 reports of patients with one or more cardiac dysrhythmias. There were 8 reports of overdoses, 1 of which was a fatal multiple-drug ingestion. Forty-one of the remaining 66 reports were not serious (e.g., palpitations, sinus tachycardia). There were 25 reports classified as serious that were not overdoses. Eight of the 25 serious reports were deaths (4 patients had underlying cardiac disease and the other 4 had significant non-cardiac illnesses), 5 were non-fatal cardiac arrests, and 2 were intra-operative sustained ventricular tachycardia. In 1 of the intra-operative cases [24], a patient who had been taking cyclobenzaprine and fluoxetine developed torsades de pointes after receiving droperidol, a drug that has been shown to prolong the QT interval [25]. Based on the limited number of unconfounded reports and the large number of patients exposed over the past 20 years, it appears that cyclobenzaprine is associated with an extremely low risk, if any, of potentially serious ventricular arrhythmias.

Cardiac toxicity with tricyclic antidepressants is known to be dose related. An in vitro rabbit atria study conducted in 1978 demonstrated that cardiac toxicity with cyclobenzaprine is also dose related [33]. Cardiodepressant activity was observed at free unbound plasma concentrations of 3600 ng/mL but not 250 ng/mL. A free, unbound cyclobenzaprine level of 3600 ng/mL is approximately 50- to 200-fold greater than therapeutic concentrations in humans. The extremely low number of serious cardiac events is consistent with the large margin of safety demonstrated in the animal study.

3.8.3.4 Digestive Body System

Nausea (37) and vomiting (18) were the most commonly reported adverse experiences in the digestive system. There were 16 reports of dry mouth, a known anticholinergic effect of cyclobenzaprine.

3.8.3.5 Hepatobiliary System

The WAES database contains 52 reports of hepatobiliary adverse experiences, 25 of which were classified as serious. Twenty-five of the 52 reports were confounded by other medications, gall bladder disease, tumor, sarcoidosis, or prior liver function test abnormalities. Four reports described transaminase elevation that could have been causally related; in 2 cases the abnormality was reversible and the outcome is not known in the other 2. Four reports described a cholestatic picture; in 2 cases the abnormality resolved after the drug use discontinued. Given the limited number of unconfounded cases and the large number of patients exposed, there is no evidence that cyclobenzaprine has a direct hepatotoxic effect.

3.8.3.6 Nervous System

Somnolence was the most commonly reported nervous system adverse experience. There were 45 reports, 12 of which were serious. The relatively low number of reports likely reflects the fact that somnolence is a well-known effect of cyclobenzaprine and is therefore not reported routinely.

Tricyclic antidepressants have been reported to increase the risk of seizures. The WAES database contains 29 spontaneous reports of patients who experienced a seizure after administration of cyclobenzaprine. Assessment of drug relationship is confounded by concomitant medications and previous medical history (e.g., head injury) in 12 cases. There was one report in which tramadol was concomitantly used; the labeling for that analgesic includes a warning about increased risk of seizures when used with a tricyclic compound. In 2 cases, the seizure occurred after administration of contrast media for a myelogram. Two reports were overdoses of cyclobenzaprine. Based on the small number of unconfounded reports, it appears there is a very low risk for seizures with therapeutic use of cyclobenzaprine 10 mg.

3.8.3.7 Psychiatric Disorders

After the category of Body As A Whole, the category of psychiatric disorder contained the most spontaneous reports. The most commonly reported adverse experiences were mental disorder (127), hallucination (82), confusion (32), psychosis (24), disorientation (28), and depression (23). There was substantial overlap among the reports as multiple adverse experience terms were included in many of the reports. There were 41 reports where "mental disorder" was the only psychiatric or neurologic term listed. At least one other psychiatric event, most commonly hallucination, was listed in the other reports.

3.8.3.7 Psychiatric Disorders (Cont.)

There were 82 reports of hallucination, 30 (38%) of which were considered serious. Visual hallucinations were more common than auditory, which is consistent with a drug-induced phenomenon. The hallucinations began after 1 dose in some cases, and after several days in others. In all but a few cases, the hallucinations resolved within a few days of discontinuing treatment with cyclobenzaprine. Thirty-two (41%) of the reports were confounded by other medications (e.g., narcotics) or underlying illness, and 27 reports (34%) had insufficient information to assess causality. Hallucinations are known to occur with anticholinergic compounds such as the tricyclic antidepressants, atropine, scopolamine and diphenhydramine [6]. It is possible that the anticholinergic properties of cyclobenzaprine are responsible for at least some of the reported cases of hallucinations with cyclobenzaprine. In 2 cases, a diagnosis of bipolar disorder was made when the symptoms persisted after cyclobenzaprine was discontinued. In those cases, the acute event was likely a worsening of a preexisting condition.

The elderly (≥ 65 years old) account for 58% of the reports of hallucination in which the age is known. There are two possible explanations for this observation. One is that the elderly are more prone to hallucinations in general or to drug-induced disturbances of cerebral function. The second is that clearance of cyclobenzaprine is reduced in the elderly, resulting in greater plasma concentrations of cyclobenzaprine.

Based on the limited number of reports, there appears to be a low incidence of serious psychiatric events that occur while taking cyclobenzaprine 10 mg. The risk should be even lower with the proposed OTC dose of 5 mg.

3.8.3.8 Trauma

Sedation was reported by 16% of patients in the postmarketing surveillance studies. Since sedation may be associated with an increased risk for a motor vehicle accident, reports of trauma in the WAES database were reviewed to look for any association between treatment and an injury. Two elderly patients (ages 71 and 87) suffered hallucinations and injured themselves while walking or falling out of bed. Two patients were involved in motor vehicle accidents while taking cyclobenzaprine 10 mg and concomitant medications (1 patient was also taking amitriptyline and drank alcohol, the other was depressed and also taking propoxyphene). There were no reports of motor vehicle accidents in which the driver was taking only cyclobenzaprine. Given the large numbers of motor vehicle accidents in the general population and the paucity of WAES reports of accidents in patients taking cyclobenzaprine, there does not appear to be an increased incidence of motor vehicle accidents with use of cyclobenzaprine.

3.8.3.9 Use During Pregnancy

Although cyclobenzaprine is not recommended for use in pregnant women, Merck received reports of 18 women exposed to cyclobenzaprine during 19 pregnancies. Cyclobenzaprine was taken for only a few days in most of the cases. The outcomes of the pregnancies are displayed in Table 33. There were 20 outcomes as one twin pregnancy was identified. The outcome was not known in 4 cases.

Table 33

WAES Data: Outcomes for Pregnancies Exposed To Prescription Cyclobenzaprine

Outcome	Number of Cases
Unknown	4
Live Birth/Normal	5
Live Birth/Congenital Anomaly	5
Live Birth/Miscellaneous Adverse Outcome	2
Abortion (Spontaneous or Elective)	4

Five newborns were reported to have external abnormalities that are known to occur spontaneously. There was no consistent pattern of abnormalities among the 5 reports of newborns with anomalies. All of these cases were reported retrospectively. Retrospective reports are defined as those received after the outcome of the pregnancy is known (the reason for the report is the outcome of the pregnancy). It is generally recognized that adverse pregnancy outcomes, particularly congenital anomalies, are more likely to be retrospectively reported than normal pregnancy outcomes [22].

In view of the small number of retrospective reports and the absence of any apparent pattern of abnormalities among the 5 newborns with anomalies, the possibility of inadvertent usage during pregnancy (despite label warnings) does not appear to pose significant problems.

3.8.3.10 Withdrawal Effects

There were no patients who reported withdrawal effects after stopping treatment with cyclobenzaprine in the nonprescription studies. The WAES database contains eight reports of drug withdrawal disorder and one report of drug dependence. Two patients were treated concomitantly with medications known to be potentially addicting (codeine; alprazolam). Two patients had a previous history of mental disorder. In several cases, treatment with cyclobenzaprine had been ongoing for 2 to 3 years, raising a question as to the condition being treated. In at least 1 case, the reported adverse event upon discontinuation of treatment was a recurrence of the underlying chronic condition.

3.8.3.10 Withdrawal Effects (Cont.)

There is no evidence that use of cyclobenzaprine 5 mg t.i.d. for short-term treatment of acute musculoskeletal spasm can result in physiologic addiction to cyclobenzaprine. Agents with similar pharmacologic effects (antihistamine, anticholinergic) are not known to be addictive.

3.8.3.11 Drug-Drug Interactions

It has also been reported that the risk of seizures in patients taking the analgesic tramadol is increased with concomitant administration of tricyclic antidepressants. This pharmacodynamic interaction likely reflects a reduction of the seizure threshold by the tricyclic compound. A published report indicates that seizures have been reported in 4 patients who took cyclobenzaprine and tramadol concomitantly [9]. Based on this information, we will recommend avoidance of concomitant use of cyclobenzaprine and tramadol.

There are 23 WAES reports of drug interaction; three of the patients died. Four reports involved monoamine oxidase inhibitors, a known contraindication to treatment with cyclobenzaprine. Six involved alcohol, concomitant use of which is also known to be ill-advised and will be warned against in the label for nonprescription cyclobenzaprine. There was no apparent pattern among the other 11 reports. Prescribing data compiled by IMS shows that an analgesic is generally prescribed or recommended when cyclobenzaprine is prescribed. It is estimated that 72% of cyclobenzaprine prescriptions are accompanied by a prescription for an analgesic (including nonsteroidal anti-inflammatory drugs), and 7% are accompanied by a recommendation to use a nonprescription analgesic. Given the extensive concomitant use of cyclobenzaprine and nonprescription analgesics, the paucity of spontaneous reports of drug interactions attests to the safety of concomitant use with OTC and prescription analgesics.

3.8.4 Drug Abuse and Overdosage Information

Data from the American Association of Poison Control Centers (AAPCC), Merck's Worldwide Adverse Experience System (WAES), and published literature (copy attached) [8] support the conclusion that there is a wide margin of safety with cyclobenzaprine. The acute oral LD₅₀ dose of cyclobenzaprine is approximately 338 and 425 mg/kg in mice and rats respectively. The lowest known fatal overdose with cyclobenzaprine occurred in a 15-year-old male (body weight unknown) who ingested approximately 80 tablets of 10 mg cyclobenzaprine. Assuming a total dose of 800 mg in a subject who weighed 60 kg, the lowest known fatal dose of cyclobenzaprine is estimated to be approximately 13 mg/kg. This is substantially greater than the proposed nonprescription dose (15 mg per day).

The AAPCC uses the term exposure to identify calls to poison control centers since not all calls represent true cases of overdose. Table 34 summarizes the AAPCC data. There were 31,605 exposures of cyclobenzaprine reported to poison control centers from 1985 through 1997. Of those exposures, 16,996 episodes involved cyclobenzaprine as a single agent. The number of exposure reports of cyclobenzaprine as a fraction of the estimated cyclobenzaprine prescription volume has remained fairly constant, suggesting that increased availability of the drug from prescriptions has not resulted in a commensurately larger risk of overdose.

3.8.4 Drug Abuse and Overdosage Information (Cont.)

Table 34

Reports of Cyclobenzaprine Exposures From the AAPCC

	Year													Total
	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	
Estimated number of prescriptions (1000s)†	4157	4369	4912	5551	5800	6135	7037	7574	7920	8414	8685	9277	9676	89507
Exposures (including multiple-agents)	21	249	1054	1879	2194	2593	3042	3122	2812	3265	3476	3638	4260	31,605
Deaths (including multiple-agents)	0	0	1	3	3	3	1	6	3	2	4	5	5	36 (0.1%§)
Single-agent exposures	17	156	614	1082	1242	1424	1754	1661	1522	1773	1824	1906	2021	16,996
Single-agent deaths	1‡	0	0	0	1	1	0	0	0	0	0	0	0	3 (0.02%§)

† Estimates of total prescriptions for cyclobenzaprine (brand and generic products) were generated from the IMS America database and include number of prescriptions from retail pharmacies, long-term care/nursing home facilities, and mail order business [50].

‡ Data obtained from Litovitz, et al. 1985 [7] and not identified in the Toxic Exposure Surveillance System Database.

§ Mortality rate.

3.8.4 Drug Abuse and Overdosage Information (Cont.)

AAPCC defines a medical outcome as a clinical effect in a *patient* that resulted in one of the following: No effect, minor effect, moderate effect, major effect, death and an "other" category. The combined categories of "no effect" or "minor effect" represent approximately 54% of the total reports for the years 1985 through 1997. There were 732 reports with a "major" outcome (2.3% of the total reports) and 36 reports of deaths (0.1%). The mortality rate with exposures to cyclobenzaprine alone was 0.02% (3 of 16,996). The clinical outcome profile with cyclobenzaprine is notably different from the outcome profile with tricyclic antidepressants based on data from AAPCC. The mortality rate for all exposures (1985 to 1994) with 5 common antidepressants (amitriptyline, desipramine, doxepin, imipramine, nortriptyline) was 1.0% (1049 of 107,908).

The most common symptoms reported to AAPCC with single-agent cyclobenzaprine exposures related to the cardiovascular, gastrointestinal, and nervous systems. The proportion of patients who experienced tachycardia and hypertension were 9.5% and 1.5%, respectively, and for CNS symptoms, the proportion of patients who experienced drowsiness/lethargy was 31.5%, agitated/irritable, 5.2%, and confusion, 2.4%. Nausea and vomiting (1.1 and 2.1%, respectively) were observed as gastrointestinal side effects but it is not known the extent to which the use of an emetic in hospital emergency rooms may have contributed to the occurrence of these effects.

The potential for cyclobenzaprine to be a recreational and/or abused drug was assessed by examining WAES reports, the published literature, and data supplied by the Substances Abuse and Mental Health Services Administration, which monitors drug abuse through the Drug Abuse and Warning Network (DAWN). There are no published reports on the recreational use of cyclobenzaprine. Furthermore, there are no WAES reports that could be construed as evidence of drug abuse with cyclobenzaprine.

DAWN collects information about drug use occurrences that resulted in a medical crisis and emergency room (ER) evaluation. The total number of episodes of cyclobenzaprine abuse, as assessed in hospital emergency departments, varied somewhat from year to year with a peak number of episodes in 1996. For the years in which data were available (1988 to 1993), the proportion of drug abuse episodes assessed to be related to recreational use compared to the total ER drug abuse episodes was stable at approximately 0.6 to 1.9%. These data suggest that cyclobenzaprine is not frequently used for recreational purposes.