CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

17-821 / S-045

Trade Name: **Flexeril**

Generic Name: **Cyclobenzaprine HCL**

Sponsor: **McNeil Consumer and Specialty Pharamaceuticals**

Approval Date: **February 3, 2003**

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APPLICATION NUMBER:

17-821 / S-045

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-821 / S-045

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-821/S-045

McNeil Consumer and Specialty Pharmaceuticals
Attention: Susan Cousounis
Assistant Director
Regulatory Development
7050 Camp Hill Road
Fort Washington, PA 19034-2299

Dear Ms. Cousounis:

Please refer to your supplemental new drug application dated April 18, 2001, received April 19, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flexeril (cyclobenzaprine HCL) Tablets 5 mg.

We acknowledge our Approvable Letter dated February 13, 2002 and receipt of your submissions, dated August 2, 2002, October 8, 2002, January 9, 14, 28 and 30, 2003.

This supplemental new drug application provides for the use of Flexeril Tablets 5 mg for the relief of muscle spasm associated with acute, painful, musculoskeletal conditions.

We completed our review of this application as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 17-821/S-045. Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Nancy Halonen, Regulatory Project Manager, at (301) 827-2019.

Sincerely,

{See appended electronic signature page}

Lee S. Simon, M.D.
Director,
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550 Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure (attached labeling)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lee Simon
2/3/03 02:06:19 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-821 / S-045

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-821/S-045

Merck & Co., Inc.
Attention: Kenneth A. Kramer
Associate Manager Regulatory Affairs
BLA-20 P.O. Box 4
West Point, PA 19486

Dear Dr. Kramer:

Please refer to your supplemental new drug application dated April 18, 2001, received April 19, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flexeril (cyclobenzaprine HCl) Tablets.

We acknowledge receipt of your submission dated October 31, 2001.

In addition, we would like to acknowledge that this label will supercede supplemental applications S-034, S-035, S-036, S-038, S-042, S-043 and S-044.

This supplemental new drug application proposes the use of Flexeril 5mg three times a day as an adjunct for the relief of muscle spasm associated with acute, painful musculoskeletal conditions.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling.

We also ask that you revise the specification for the drug product to [redacted] products with appropriate acceptance criteria for total [redacted] and an acceptance criteria of NMT [redacted] for unspecified [redacted]

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   Present tabulations of the new safety data combined with the original NDA data.

   Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options

under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Carmen DeBellas, Chief, Project Manager, at 301-827-2090.

Sincerely,

{See appended electronic signature page}

Lee S. Simon
Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

9 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: ____

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/s/

Lee Simon
2/13/02 10:11:00 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

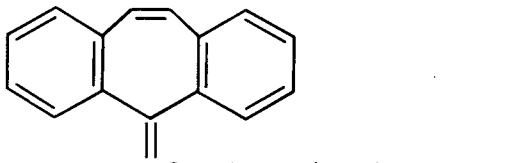
17-821 / S-045

LABELING

FLEXERIL®
(CYCLOBENZAPRINE HCl) Tablets

DESCRIPTION

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



FLEXERIL 5 mg (Cyclobenzaprine HCl) is supplied as a 5 mg tablet for oral administration. FLEXERIL 10 mg (Cyclobenzaprine HCl) is supplied as a 10 mg tablet for oral administration.

FLEXERIL tablets contain the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, starch, and titanium dioxide. FLEXERIL 5 mg tablets also contain Yellow D&C #10 Aluminum Lake HT, and Yellow FD&C #6 Aluminum Lake.

CLINICAL PHARMACOLOGY

Cyclobenzaprine HCl relieves skeletal muscle spasm of local origin without interfering with muscle function. It is ineffective in muscle spasm due to central nervous system disease.

Cyclobenzaprine reduced or abolished skeletal muscle hyperactivity in several animal models. Animal studies indicate that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. Such studies show that cyclobenzaprine acts primarily within the central nervous system at brain stem as opposed to spinal cord levels, although its action on the latter may contribute to its overall skeletal muscle relaxant activity. Evidence suggests that the net effect of cyclobenzaprine is a reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems.

Pharmacological studies in animals showed a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

Pharmacokinetics

Estimates of mean oral bioavailability of cyclobenzaprine range from 33% to 55%. Cyclobenzaprine exhibits linear pharmacokinetics over the dose range 2.5 mg to 10 mg, and is subject to enterohepatic

circulation. It is highly bound to plasma proteins. Drug accumulates when dosed three times a day, reaching steady-state within 3-4 days at plasma concentrations about four-fold higher than after a single dose. At steady state in healthy subjects receiving 10 mg t.i.d. (n=18), peak plasma concentration was 25.9 ng/mL (range, 12.8-46.1 ng/mL), and area under the concentration-time (AUC) curve over an 8-hour dosing interval was 177 ng.hr/mL (range, 80-319 ng.hr/mL).

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

The plasma concentration of cyclobenzaprine is generally higher in the elderly and in patients with hepatic impairment. (See PRECAUTIONS, Use in the Elderly and PRECAUTIONS, Impaired Hepatic Function.)

Elderly

In a pharmacokinetic study in elderly individuals (≥65yrs old), mean (n=10) steady- state cyclobenzaprine AUC values were approximately 1.7 fold (171.0 ng.hr/mL, range 96.1-255.3) higher than those seen in a group of eighteen younger adults (101.4 ng.hr/mL, range 36.1-182.9) from another study. Elderly male subjects had the highest observed mean increase, approximately 2.4 fold (198.3 ng.hr/mL, range 155.6-255.3 versus 83.2 ng.hr/mL, range 41.1-142.5 for younger males) while levels in elderly females were increased to a much lesser extent, approximately 1.2 fold (143.8 ng.hr/mL, range 96.1-196.3 versus 115.9 ng.hr/mL, range 36.1-182.9 for younger females).

In light of these findings, therapy with FLEXERIL in the elderly should be initiated with a 5 mg dose and titrated slowly upward.

Hepatic Impairment

In a pharmacokinetic study of sixteen subjects with hepatic impairment (15 mild, 1 moderate per Child-Pugh score), both AUC and C_{max} were approximately double the values seen in the healthy control group. Based on the findings, FLEXERIL should be used with caution in subjects with mild hepatic impairment starting with the 5 mg dose and titrating slowly upward. Due to the lack of data in subjects with more severe hepatic insufficiency, the use of FLEXERIL in subjects with moderate to severe impairment is not recommended.

No significant effect on plasma levels or bioavailability of FLEXERIL or aspirin was noted when single or multiple doses of the two drugs were administered concomitantly. Concomitant administration of FLEXERIL and naproxen or diflunisal was well tolerated with no reported unexpected adverse effects. However combination therapy of FLEXERIL with naproxen was associated with more side effects than therapy with naproxen alone, primarily in the form of drowsiness. No well-controlled studies have been performed to indicate that FLEXERIL enhances the clinical effect of aspirin or other analgesics, or whether analgesics enhance the clinical effect of FLEXERIL in acute musculoskeletal conditions.

Clinical Studies

Eight double-blind controlled clinical studies were performed in 642 patients comparing FLEXERIL 10 mg, diazepam**, and placebo. Muscle spasm, local pain and tenderness, limitation of motion, and restriction in activities of daily living were evaluated. In three of these studies there was a significantly greater improvement with FLEXERIL than with diazepam, while in the other studies the improvement following both treatments was comparable.

Although the frequency and severity of adverse reactions observed in patients treated with FLEXERIL were comparable to those observed in patients treated with diazepam, dry mouth was observed more frequently in patients treated with FLEXERIL and dizziness more frequently in those treated with diazepam. The incidence of drowsiness, the most frequent adverse reaction, was similar with both drugs.

The efficacy of FLEXERIL 5 mg was demonstrated in two seven-day, double-blind, controlled clinical trials enrolling 1405 patients. One study compared FLEXERIL 5 and 10 mg t.i.d. to placebo; and a second study compared FLEXERIL 5 and 2.5 mg t.i.d. to placebo. Primary endpoints for both trials were determined by patient-generated data and included global impression of change, medication helpfulness, and relief from starting backache. Each endpoint consisted of a score on a 5-point rating scale (from 0 or worst outcome to 4 or best outcome). Secondary endpoints included a physician's evaluation of the presence and extent of palpable muscle spasm.

Comparisons of FLEXERIL 5 mg and placebo groups in both trials established the statistically significant superiority of the 5 mg dose for all three primary endpoints at day 8 and, in the study comparing 5 and 10 mg, at day 3 or 4 as well. A similar effect was observed with FLEXERIL 10 mg (all endpoints). Physician-assessed secondary endpoints also showed that FLEXERIL 5 mg was associated with a greater reduction in palpable muscle spasm than placebo.

Analysis of the data from controlled studies shows that FLEXERIL produces clinical improvement whether or not sedation occurs.

**VALIUM® (diazepam, Roche)

Surveillance Program

A post-marketing surveillance program was carried out in 7607 patients with acute musculoskeletal disorders, and included 297 patients treated with FLEXERIL 10 mg for 30 days or longer. The overall effectiveness of FLEXERIL was similar to that observed in the double-blind controlled studies; the overall incidence of adverse effects was less (see ADVERSE REACTIONS).

INDICATIONS AND USAGE

FLEXERIL is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions.

Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, limitation of motion, and restriction in activities of daily living.

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

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

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation. Hyperpyretic crisis seizures, and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.

Acute recovery phase of myocardial infarction, and patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure.

Hyperthyroidism.

WARNINGS

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

Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke.

FLEXERIL may enhance the effects of alcohol, barbiturates, and other CNS depressants.

PRECAUTIONS

General

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

Impaired Hepatic Function

The plasma concentration of cyclobenzaprine is increased in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Hepatic Impairment).

These patients are generally more susceptible to drugs with potentially sedating effects, including cyclobenzaprine. FLEXERIL should be used with caution in subjects with mild hepatic impairment starting with a 5 mg dose and titrating slowly upward. Due to the lack of data in subjects with more severe hepatic insufficiency, the use of FLEXERIL in subjects with moderate to severe impairment is not recommended.

Information for Patients

FLEXERIL, especially when used with alcohol or other CNS depressants, may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. In the elderly, the frequency and severity of adverse events associated with the use of cyclobenzaprine, with or without concomitant medications, is increased. In elderly patients, FLEXERIL should be initiated with a 5 mg dose and titrated slowly upward.

Drug Interactions

FLEXERIL may have life-threatening interactions with MAO inhibitors. (See CONTRAINDICATIONS.)

FLEXERIL may enhance the effects of alcohol, barbiturates, and other CNS depressants.

Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds.

Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol.[†]

[†]ULTRAM® (tramadol HCl tablets, Ortho-McNeil Pharmaceutical)
ULTRACET® (tramadol HCl and acetaminophen tablets, Ortho-McNeil Pharmaceutical)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In rats treated with FLEXERIL for up to 67 weeks at doses of approximately 5 to 40 times the maximum recommended human dose, pale, sometimes enlarged, livers were noted and there was a dose-related hepatocyte vacuolation with lipidosis. In the higher dose groups this microscopic change was seen after 26 weeks and even earlier in rats which died prior to 26 weeks; at lower doses, the change was not seen until after 26 weeks.

Cyclobenzaprine did not affect the onset, incidence or distribution of neoplasia in an 81-week study in the mouse or in a 105-week study in the rat.

At oral doses of up to 10 times the human dose, cyclobenzaprine did not adversely affect the reproductive performance or fertility of male or female rats. Cyclobenzaprine did not demonstrate mutagenic activity in the male mouse at dose levels of up to 20 times the human dose.

Pregnancy

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness of FLEXERIL in pediatric patients below 15 years of age have not been established.

Use in the Elderly

The plasma concentration of cyclobenzaprine is increased in the elderly (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Elderly).* The elderly may also be more at risk for CNS adverse events such as hallucinations and confusion, cardiac events resulting in falls or other sequelae, drug-drug and drug-disease interactions. For these reasons, in the elderly, cyclobenzaprine should be used only if clearly needed. In such patients FLEXERIL should be initiated with a 5 mg dose and titrated slowly upward.

ADVERSE REACTIONS

Incidence of most common adverse reactions in the 2 double-blind[‡], placebo-controlled 5 mg studies (incidence of > 3% on FLEXERIL 5 mg):

	FLEXERIL 5 mg N=464	FLEXERIL 10 mg N=249	Placebo N=469
Drowsiness	29%	38%	10%
Dry Mouth	21%	32%	7%
Fatigue	6%	6%	3%
Headache	5%	5%	8%

Adverse reactions which were reported in 1% to 3% of the patients were: abdominal pain, acid regurgitation, constipation, diarrhea, dizziness, nausea, irritability, mental acuity decreased, nervousness, upper respiratory infection, and pharyngitis.

The following list of adverse reactions is based on the experience in 473 patients treated with FLEXERIL 10 mg in additional controlled clinical studies, 7607 patients in the post-marketing surveillance program, and reports received since the drug was marketed. The overall incidence of adverse reactions among patients in the surveillance program was less than the incidence in the controlled clinical studies.

The adverse reactions reported most frequently with FLEXERIL were drowsiness, dry mouth and dizziness. The incidence of these common adverse reactions was lower in the surveillance program than in the controlled clinical studies:

‡ ***Note: FLEXERIL 10 mg data are from one clinical trial. FLEXERIL 5 mg and placebo data are from two studies.***

	Clinical Studies With FLEXERIL 10 mg	*Surveillance Program With FLEXERIL 10 mg*
Drowsiness	39%	16%
Dry Mouth	27%	7%
Dizziness	11%	3%

Among the less frequent adverse reactions, there was no appreciable difference in incidence in controlled clinical studies or in the surveillance program. Adverse reactions which were reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion.

The following adverse reactions have been reported in post-marketing experience or with an incidence of less than 1% of patients in clinical trials with the 10 mg tablet:

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

Causal Relationship Unknown

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

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

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

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

MANIFESTATIONS

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

Other potential effects of overdosage include any of the symptoms listed under ADVERSE REACTIONS.

MANAGEMENT

General

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

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

Gastrointestinal Decontamination

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

Cardiovascular

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

CNS

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

PSYCHIATRIC FOLLOW-UP

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

PEDIATRIC MANAGEMENT

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

DOSAGE AND ADMINISTRATION

For most patients, the recommended dose of FLEXERIL is 5 mg three times a day. Based on individual patient response, the dose may be increased to 10 mg three times a day. Use of FLEXERIL for periods longer than two or three weeks is not recommended. (see INDICATIONS AND USAGE).

Less frequent dosing should be considered for hepatically impaired or elderly patients (see PRECAUTIONS, *Impaired Hepatic Function, and Use in the Elderly*).

HOW SUPPLIED

FLEXERIL tablets are available in 5 mg and 10 mg dosage strengths. The 5 mg tablets are yellow-orange, 5-sided D-shaped, film coated tablets, coded FLEXERIL on one side and without coding on the other. The 10 mg tablets are butterscotch yellow, 5-sided D-shaped, film coated tablets, coded MSD 931 on one side and FLEXERIL on the other. The two dosage strengths are supplied as follows:

5 mg	30 count carton (5 blister cards, each with 6 tablets)	NDC 50580-280
10 mg	100 count bottle	NDC 50580-874-1
	100 count unit dose package (each tablet individually sealed)	NDC 50580-874-2

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature].

Rx Only

For more information call **1-xxx-xxx-xxxx** or visit www.xxx.xxx.

Manufactured by
Merck & Co. Inc., West Point, PA 19486, USA.

Distributed and Marketed by
McNeil Consumer & Specialty Pharmaceuticals, Fort Washington, PA 19034

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[Identification number]

Edition: xx/xxx

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-821 / S-045

MEDICAL REVIEW(S)

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS -- HFD-550

Medical Officer Review of NDA Labeling Supplement

NDA 17-821
(Flexeril tablets (Cyclobenzaprine HCl)

Complete response to SLR-045 Approvable letter (February 13, 2002)

Submission date (letter):	August 02, 2002
Review completed:	January 31, 2003
Drug name:	Flexeril
Applicant	McNeil
Pharmacologic category:	Muscle relaxant
Proposed indications:	Relief of muscle spasm associated with acute, painful musculoskeletal conditions.
Dosage form and route:	5 and 10 mg oral tablet
Related reviews:	PK: Tapash Ghosh, Ph.D./Dennis Bashaw, Ph.D Chemistry: Vispi Bhavnagri, Ph.D. Clinical: Jim Witter, MD, Ph.D.

1.0 Background and Overview

Cyclobenzaprine HCl (Flexeril®) is a centrally acting muscle relaxant marketed in the US as a prescription drug since 1977 for the relief of muscle spasm associated with acute, painful musculoskeletal conditions.

In February, 2002, the FDA issued an Approvable letter to NDA 17-821 SRL 045 (efficacy supplement for the 5 mg dose). The current submission is a complete response to the Approvable letter. Additionally, the sponsor proposes the use of the name [redacted] instead of "FLEXERIL" and provides for marketing of a 5-mg tablet using a new manufacturing process.

2.0 Proposed labeling changes

The label by proposed by the sponsor in the August 3, 2002, submission is the one the FDA sent in February 2002, with minor changes:

[redacted]

In January 9, 2003 upon being advised by the Division that the name change had not been approved by the Nomenclature committee, the sponsor submitted an amendment stating that the name FLEXERIL would be retained.

3.0 Review

Most of the changes proposed by the sponsor (with exception of the name change) were acceptable to the Agency, with minor modifications. For detailed review of the PK and Chemistry changes see Dr. Bashaw and Dr. Bhavnagri's reviews.
Clinical: Changes regarding starting with the minimum possible dose and the addition of a bolded sentence referring patients to contact Poison Control are acceptable.

4.0 Conclusions and recommendations

The supplement should be Approved.
Agreed upon label is attached.

10 Page(s) Withheld

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✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical-_____

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/s/

Maria Villalba
2/4/03 09:27:45 AM
MEDICAL OFFICER

James Witter
2/5/03 12:11:51 PM
MEDICAL OFFICER
Concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-821 / S-045

CHEMISTRY REVIEW(S)

Chemistry Review #1	1. Division HFD-550	2. NDA Number 17-821
3. Name and Address of Applicant Merck & Co., Inc. Sumneytown Pike, P.O. Box 4, BL A-20 West Point, PA 19486	**4. Supplement Number:** 045(SE8) **Letter Date:**4/18/01 **Stamp Date:** 4/19/01 **Due Date :** 2/19/02	
5. Name of Drug Flexeril® Tablets	**6. Nonproprietary Name** Cyclobenzaprine Tablets	
7. Supplement Provides for: Approval of an additional 5 mg dose and associated labeling changes		**8. Amendment(s)** BC dated 10/28/01
9. Pharmacological Category Muscle Relaxant	**10. How Dispensed** Rx	**11. Related Documents** NDA 21-070
12. Dosage Form Tablets	**13. Potency(ies)** 5 mg (10 mg strength is approved)	
14. Chemical Name and Structure See USAN		

15. Comments

This is a PA supplement. The applicant submitted an NDA [redacted] use. The NDA was not approvable largely because of abuse potential if the [redacted]ıe 5 mg dose however showed sufficient efficacy. The company therefore has chosen to market the 5 mg tablets, for Rx use, and is seeking to gain approval of the 5 mg dose in this supplement.

In this supplement the applicant has addressed the deficiencies in [redacted] appears from the cover letter of this supplement that this product will be sold to [redacted] ıfter approval of this supplement and Merck will continue to act as an agent for this DP when dealing with the Agency.

The deficiencies, Merck's responses and the evaluation of the responses are given in the attached notes.

No EER was necessary since all the DS/DP facilities were acceptable for the 5 mg OTC or the 10 mg Rx NDA.

16. Conclusions and Recommendations Merck has still not answered one deficiency (# 8) satisfactorily. It is therefore recommended that the supplement be approvable.		
17. Name Vispi P. Bhavnagri, Ph.D., Review Chemist	**Signature**	**Date**
Concurrence John Smith, Ph.D., Chemistry Team Leader		

APPROVABLE

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Withheld Track Number: Chemistry- 1a

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/s/

Vispi Bhavnagri
2/20/02 03:23:24 PM
CHEMIST

John Smith
2/20/02 04:10:30 PM
CHEMIST

Chemistry Review #2	1. Division HFD-550	2. NDA Number 17-821
3. Name and Address of Applicant McNeil Consumer and Specialty Pharmaceuticals 7050 Camp Hill Rd. Ft. Washington, PA 19034-2299	**4. Supplement Number:** 045(SE8) **RS** **Letter Date:** 8/2/02 **Stamp Date:** 8/5/02 **Due Date :** 2/5/03	
5. Name of Drug Flexeril® Tablets	**6. Nonproprietary Name** Cyclobenzaprine Tablets	
7. Supplement Provides for: Approval of an additional 5 mg dose and associated labeling changes		**8. Amendment(s)** NC Dated 9/17/02 BL Dated 1/9/03 BC Dated 1/14/03
9. Pharmacological Category Muscle Relaxant	**10. How Dispensed** Rx	**11. Related Documents** NDA 21-070
12. Dosage Form Tablets	**13. Potency(ies)** 5 mg (10 mg strength is approved)	
14. Chemical Name and Structure See USAN		

15. Comments

This is a resubmission of an approvable PA supplement.

In this supplement the applicant has addressed one pending CMC deficiency and has submitted a number of labeling changes. The major changes are for other sections of the label. The CMC related label changes are minor in nature.

It appears from the cover letters of the resubmission and its amendments that this product is now sold to McNeil and not to ——— previously indicated by Merck.

All the facilities for the 5 mg dose in ——— However a warning letter was issued for one of the ——— consequently the OC made a withhold recommendations on 4/17/00 and 10/9/02. McNeil has chosen to withdraw ——— ——— since it is one of the many ——— for this application.

No fresh EER was necessary since all the DS/DP manufacturing facilities for the 5 mg and the 10 mg strengths are the same (see Attachment 1).

16. Conclusions and Recommendations

McNeil has now answered the one outstanding deficiency (deficiency # 8) satisfactorily. The CMC part of the label is also acceptable. Recommend approval.

17. Name	Signature	Date
Vispi P. Bhavnagri, Ph.D., Review Chemist		
Concurrence John Smith, Ph.D., Chemistry Team Leader		

APPROVAL

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Vispi Bhavnagri
1/30/03 04:24:22 PM
CHEMIST

John Smith
1/30/03 04:30:54 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-821 / S-045

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

Cyclobenzaprine 5 & 10mg Tablets
NDA 17-821 S-045
FLEXERIL Tablets
Reviewer: E.D. Bashaw, Pharm.D.

McNeil Consumer
Fort Washington, PA

Submission Date:
Aug. 2, 2002
Jan. 9 & 23, 2003

Review of Response to the 2/13/02 Approvable Letter

Background

Flexeril (cyclobenzaprine tablets) is an old product that was originally approved in the 1970's as an adjunct to rest and physical therapy in the treatment of acute muscle spasm. It was originally marketed by and continues to be made by Merck & Co. (West Point, Pa). McNeil Consumer now owns the product and is in the process of introducing a new tablet strength (5mg) for the purposes of [redacted] This supplement contains the sponsors response to an FDA approvable letter of 2/13/2002 in which both labeling revisions and additional requests for information were made. From a biopharmaceutic standpoint the only outstanding issue is final agreement on various labeling statements made by the sponsor.

Labeling

In their response to the 2/13/02 approvable letter, the sponsor has identified three areas in the proposed label, relating to pk, that they would like to suggest alternative labeling. Each of these areas will be presented in turn below, along with a discussion of the issue-where appropriate:

1.) Pharmacokinetics, first sentence, first paragraph, 2/13/02 version:

[redacted]

The sponsor would like to change the wording to read as follows:

Estimates of mean oral bioavailability of cyclobenzaprine range from 33% to 55%.

The new wording is acceptable to the Agency as it demonstrates the variability in bioavailability following oral dosing.

2.) Pharmacokinetics, sub-heading Elderly, first paragraph, should be changed to read as follows:

Elderly

In a pharmacokinetic study in elderly individuals (≥65yrs old), mean (n=10) steady-state cyclobenzaprine AUC values were approximately 1.7 fold (171.0 ng.hr/mL, range 96.1-255.3) higher than those seen in a group of eighteen younger adults (101.4 ng.hr/mL, range 36.1-182.9) from another study. Elderly male subjects had the highest observed mean increase, approximately 2.4 fold (198.3 ng.hr/mL, range 155.6-255.3 versus 83.2 ng.hr/mL, range 41.1-142.5 for younger males) while levels in elderly females were increased to a much lesser extent, approximately 1.2 fold (143.8 ng.hr/mL, range 96.1-196.3 versus 115.9 ng.hr/mL, range 36.1-182.9 for younger females).

In light of these findings, therapy with FLEXERIL in the elderly should be initiated with a 5 mg dose and titrated slowly upward

These changes reflect discussions held between the FDA and the sponsor during the review cycle and incorporate more descriptive language and data and are acceptable.

3.) Pharmacokinetics, sub-headings Elderly and Hepatic Impairment.

In both sections the prescriber is directed to use the lowest possible dose for both elderly subjects and subjects with mild hepatic insufficiency. As the 5mg tablet now represents the lowest approved dose, this change is also acceptable to the biopharmaceutics reviewer.

Recommendation

In this submission the sponsor has proposed a number of revisions to the package insert that was contained in the FDA's 2/13/02 approvable letter for cyclobenzaprine. From a clinical pharmacology/biopharmaceutic standpoint, the proposed changes that deal with pharmacokinetics/drug disposition are acceptable with the indicated modifications.

E. Dennis Bashaw, Pharm.D.
Team Leader, Pharmacokinetics
HFD-880

Secondary Review: Arzu Selen, Ph.D., Deputy Director, DPE-III_____

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/s/

Dennis Bashaw
1/31/03 01:12:07 PM
BIOPHARMACEUTICS

Arzu Selen
1/31/03 03:53:30 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-821 / S-045

PROPRIETARY NAME REVIEW(S)

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 26, 2002

NDA# 17-821/S-045

NAME OF DRUG: [redacted]
(Cyclobenzaprine Tablets)
5 mg and 10 mg

NDA HOLDER: McNeil Pharmaceuticals

I. INTRODUCTION:

This consult is written in response to a request from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550), for an assessment of the proposed proprietary names [redacted] A draft package insert was submitted for review and comment. The container labels and carton labeling were not submitted, and therefore have not been reviewed at this time.

This supplement is for the addition of a new strength of cyclobenzaprine 5mg. Cyclobenzaprine is currently marketed under the proprietary name Flexeril. The sponsor has requested to change the trade name of the currently approved product, Flexeril, to [redacted] because Flexeril is widely recognized, and has been associated with the 10 mg strength since approval in 1977, the sponsor is concerned that there could be potential confusion among doctors and pharmacists in writing and filling prescriptions for the new 5 mg dose. The sponsor believes that the names [redacted] which correspond to the [redacted] respectively, will enable healthcare professionals to easily distinguish the prescriptions. The sponsor has also indicated that they intend to retain ownership of the Flexeril trademark, and will use it in educational and promotional materials to educate the medical community of the change in the product name.

PRODUCT INFORMATION

[redacted] ntains the active ingredient cyclobenzaprine and is indicated for the treatment of skeletal muscle spasms. The recommended dose of [redacted] is 5 mg three times a day. Based on individual patient response, the dose may be increased to 10 mg three times a day, up to a maximum daily dose of 60 mg. The use of [redacted] or periods of more than two or three weeks is not recommended. [redacted] ill be available as [redacted] nd [redacted] corresponding to the correct strengths of 5 mg and 10 mg.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
[redacted]	**:lobenzaprine Tablets 5 mg and 10 mg**	**5 mg three times a day. Dose may be increased to 10 mg three times a day. Maximum dose is 60 mg per day. Less frequent dosing should be considered for hepatically impaired or elderly patients.**	
Floxin	Ofloxacin Tablets 200 mg, 300 mg, and 400 mg	Bronchitis, pneumonia: 400 mg every 12 hours for 10 days. Urethritis, cervicitis: 300 mg every 12 hours for 7 days. Gonorrhea: 400 mg every 12 hours for 10-14 days.	**S/A, LA
Flexon	Orphenadrine Citrate Solution 30 mg/mL	60 mg IV or IM. May repeat every 12 hours.	**S/A, L/A
Flarex	Fluorometholone Acetate Ophthalmic Suspension 0.1%	One to two drops in conjunctival sac(s) 2-4 times per day. May initiate with 2 drops every 2 hours during first 24-48 hours.	** S/A
Flextra DS	Acetaminophen and Phenyltoloxamine Citrate Tablets 500 mg/50 mg	1 tablet every 4 hours. Maximum daily dose is 5 tablets.	**S/A, L/A
Flextra-650	Acetaminophen and Phenyltoloxamine Citrate Tablets 650 mg/60 mg	½ to 1 tablet every 6 hours. Maximum daily dose is 4 tabs.	**SA, LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of [redacted] ith other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription fo [redacted] ee page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to [redacted], a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name [redacted] Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel expressed concern that [redacted] ppears to be half of a drug name, as it appears in several currently approved prescription, over the counter, and personal care products. Examples include: [redacted] here was also concern that using the word [redacted] ould be interpreted as a physical therapy range of motion physician order.

2. The Expert Panel also expressed concern with the use of the modifier [redacted] n conjunction with the proposed name. [redacted] The use of [redacted] not recommended because they can be confused with a [redacted] erefore increasing the risk of medication errors.

3. Four proprietary names were identified by the Expert Panel that were thought to have the potential for confusion with [redacted] hese products are listed in table 1 (see page 4), along with the usual dosage and available dosage forms.

4. DDMAC did not have concerns about the name [redacted] ith regard to promotional claims.

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[1]MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4]WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

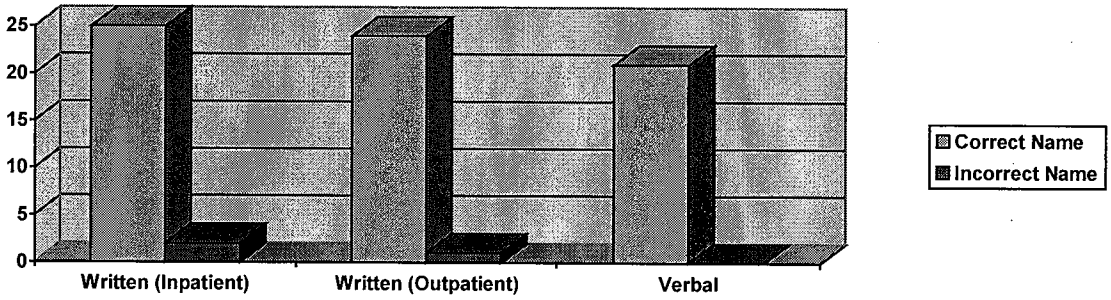
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: —/. 10 mg Sig: 1 po TID #30 Inpatient RX: — 10 mg. tid	— 10 mg, take 1 by mouth 3 times a day. Dispense #30.

2. Results:

The results are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	39	27 (67%)	25 (93%)	2 (7%)
Written Outpatient	35	25 (71%)	24 (96%)	1 (4%)
Verbal	32	21 (66%)	21 (100%)	0 (0%)
Total	106	73 (69%)	70 (96%)	3 (4%)



Among the verbal prescription study participants for — ll participants (100%) interpreted the name correctly.

Among the written prescription study participants for — of 52 (6%) participants interpreted the name incorrectly. It should be noted that in the written prescription studies, the three incorrect responses were cases when the participants wrote out the drug name as Flexeril.

C. AERS and DQRS DATABASE SEARCH

In order to determine the degree of name confusion with Flexeril and other approved drug products already on the U.S. market, we Searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with Flexeril. The Meddra Preferred Term (PT), "Medication Error" and the drug name "Flexeril%" and "cyclobenzaprine%" were used to perform the search. In addition, the Drug Quality Reporting System *(DQRS)* database was searched for similar reports. This search strategy retrieved a total of 15 reports. The reports involved cases of patients' experiencing adverse reactions to Flexeril, the medication dispensed with incorrect directions on the label, and instances of the incorrect medication being dispensed due to generic look-alike bottles and labels. Of the 15 reports reviewed, no account involved name confusion with Flexeril.

D. SAFETY EVALUATOR RISK ASSESSMENT:

1. Look-alike and Sound-alike Names

In reviewing the proprietary nam[redacted] ne primary concerns raised were related to four look-alike and/or sound-alike names: Floxin, Flexon, Flarex, and Flextra.

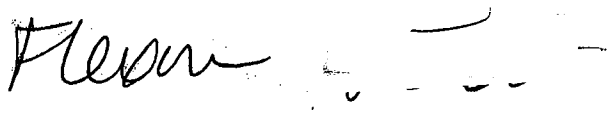
We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between [redacted] id Floxin, Flexon, Flarex, and Flextra DS. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size. Three participants interpreted the proposed name as Flexeril, which is the original proprietary name for this product.

Floxin is a quinolone antibiotic, indicated for the treatment of susceptible inflections, including acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, acute pelvic inflammatory disease (PID), cervical, acute uncomplicated gonorrhea, uncomplicated skin and skin structure, urinary tract infections, and prostatitis. Floxin is available in 200 mg, 300 mg, and 400 mg tablets. The DMETS Expert Panel expressed concern that the proposed nam[redacted] when used with the [redacted] can sound similar to Floxin as both words contain two syllables, and the beginning of each name differs by only one letter, ("flox" vs. [redacted] Also, the endings of the names are phonetically similar when pronounced, [redacted] Floxin and [redacted] lso share overlapping dosing intervals. Floxin is prescribed twice a day for anywhere from 7 to 14 days, depending on the condition being treated. Because less frequent dosing is appropriate in hepatically impaired and elderly patients, [redacted] an be taken twice a day for periods of no more than 2 to 3 weeks, depending on the response in these patients. Floxin and [redacted] n also look similar when scripted (see below), which could result in confusion between the two products. Furthermore, it is likely that these products will be stored near each other on pharmacy shelves, thus increasing the risk of confusion between the two products.

Floxin [redacted]

Flexon contains orphenadrine and is indicated as an adjunct therapy to rest and physical therapy for relief of discomfort associated with acute, painful musculoskeletal conditions. Flexon is available in a strength of 30 mg/mL, and is supplied in 2 mL ampules and 10 mL vials. The usual dose is 60 mg intravenously or intramuscularly, which may be repeated in 12 hours. The DMETS Expert Panel expressed concern that Flexon and the proposed nam[illegible] the [illegible] sound and look similar when scripted (see below). Both names consist of two syllables and have the same letters at the beginning of each name ([illegible]). Additionally, the [illegible] ' can look similar to the letters "on", as in the name Flexon. Furthermore, Flexon and the proposed name [illegible] so share an overlapping indication of muscle relaxation, therefore it is likely that the same type of physician will prescribe these two medications. The sound-alike and look-alike characteristics, in addition to the overlap in indication, increase the risk of confusion between these two products.

Flexon



Flarex contains fluorometholone acetate 0.1%, a prescription only ophthalmic steroid, indicated for the treatment of ocular inflammation. The DMETS Expert Panel expressed concern that Flarex and the proposed name [illegible] sound similar. Both names share the letter combinations "Fl" and [illegible]larex and [illegible] share overlapping dosing intervals of three times per day. Additionally, Flarex is supplied in either a 5 mL or 10 mL bottle. Despite the difference in dosage form, it is possible for an error to occur with Flarex and either [illegible]. If, for example, a prescription for Flarex were called in to a pharmacy as "Flarex 5 mL, one three times a day", it could potentially be misinterpreted as [illegible]ne three times a day". Should a patient receive [illegible]stead of Flarex 5, the patient would be at risk for experiencing side effects associated with [illegible]his includes drowsiness, dry mouth, dizziness, stomach upset, headache, nervousness, blurred vision, tachycardia, hypotension, and arrhythmias.

Flextra DS and Flextra-650 are prescription only combination products of acetaminophen and phenyltoloxamine. Both products are indicated for temporary relief of minor aches and pains associated with headache, backache, muscular ache, toothaches, menstrual pain, as well as for minor pain from arthritis, and to reduce fever. The Expert Panel expressed concern that Flextra and proposed name [illegible]nd and look similar, due to the identical letter combinat[illegible] at the beginning of each name. Also, the terminal letter combination "ra" in the name Flextra can look similar to the [illegible]hen scripted (see page 8). Although the dosing schedules for the medications differ, the products are taken orally, and will likely be prescribed by the same group of physicians. The products, however, differ in strength and dosing regimen. Flextra DS contains 500 mg of acetaminophen and 50 mg of phenyltoloxamine, and Flextra-650 contains 650 mg of acetaminophen and 60 mg of phenyltoloxamine, whereas [illegible] 5 mg and 10 mg of cyclobenzaprine, respectively. Additionally, [illegible] given up to three times per day, where as Flextra DS is given every four hours and Flextra-650 is given every six hours. These differences help minimize the risk of confusion between the drug products.

Flextra

2.

In regards to the proposed numerical modifiers DMETS discourages the use of numbers as a part of the proprietary name. The may be misinterpreted in the prescription to mean a quantity, especially since an expression of strength, such as is not utilized to clarify the suffix. Such an example includes Viokase 8, (ISR# 3863466-8, Dated 1/14/02), in which a physician wrote an inpatient hospital order "Viokase 8 tabs with meals TID". In this case, numerical suffix 8 was confused as the number of tablets needed per dose, rather than as the intended representation of the number of units of Viokase. In this particular case, the error was detected before the medication reached the patient, and the patient was not harmed.

III. COMMENTS TO BE PROVIDED TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name n addition, DMETS does not recommend the use of the DMETS believes that the creation of a new name will cause confusion among healthcare practitioners and patients. A search in AERS and DQRS databases revealed no reports of name confusion with the proprietary name "Flexeril". Therefore, DMETS recommends that the sponsor retain the original proprietary name "Flexeril" and utilize contrasting colors, boxing, or some other means to differentiate between the two strengths. In addition, the sponsor should educate the public on the addition of the new 5 mg strength to the existing 10 mg strength.

In reviewing the proprietary name e primary concerns raised were related to look-alike and sound-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion were Floxin, Flexon, and Flarex.

1. Look-alike and Sound-alike Names

We conducted prescription studies to simulate the prescription ordering process. Three participants interpreted the proposed name as Flexeril, which is the original proprietary name for this product.

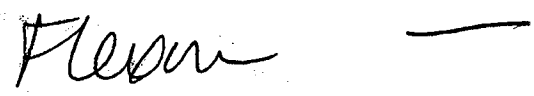
Floxin is a quinolone antibiotic, indicated for the treatment of susceptible inflections, including acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, acute pelvic inflammatory disease (PID), cervical, acute uncomplicated gonorrhea, uncomplicated skin and skin structure, urinary tract infections, and prostatitis. Floxin is available in 200 mg, 300 mg, and 400 mg tablets. The DMETS Expert Panel expressed concern that the proposed name hen used with the an sound similar to Floxin as both words contain two syllables, and the beginning of each name differs by only one letter, ("flox" vs. Also, the endings of the names are phonetically similar when pronounced, ("in" vs. Floxin and o share overlapping dosing intervals. Floxin is prescribed twice a day anywhere from 7 to 14 days depending on the condition being treated. Because less frequent dosing is appropriate in hepatically impaired and elderly patient n be taken twice a day for periods of no more than 2 to 3 weeks, depending on the response in these patients.

Floxin and [illegible] can also look similar when scripted (see page 9), which could result in confusion between the two products. Furthermore, it is likely that these products will be stored near each other on pharmacy shelves, thus increasing the risk of confusion between the two products.

Floxin

Flexon contains orphenadrine and is indicated as an adjunct therapy to rest and physical therapy for relief of discomfort associated with acute, painful musculoskeletal conditions. Flexon is available in a strength of 30 mg/mL, and is supplied in 2 mL ampules and 10 mL vials. The usual dose is 60 mg intravenously or intramuscularly, which may be repeated in 12 hours. The DMETS Expert Panel expressed concern that Flexon and the proposed name [illegible] .s the numerical modifier, sound and look similar when scripted (see below). Both names consist of two syllables and have the same letters at the beginning of each name (Additionally, the [illegible] can look similar to the letters "on", as in the name Flexon. Furthermore, Flexon and the proposed name so share an overlapping indication of muscle relaxation, therefore it is likely that the same type of physician will prescribe these two medications. The sound-alike and look-alike characteristics, in addition to the overlap in indication, increase the risk of confusion between these two products.

Flexon



Flarex contains fluorometholone acetate 0.1%, a prescription only ophthalmic steroid, indicated for the treatment of ocular inflammation. The DMETS Expert Panel expressed concern that Flarex and the proposed name, [illegible] y sound similar. Both names share the letter combination Flarex an [illegible] o share overlapping dosing intervals of three times per day. Additionally, Flarex is supplied in either a 5 mL or 10 mL bottle. Despite the difference in dosage form, it is possible for an error to occur with Flarex and If, for example, a prescription for Flarex were called in to a pharmacy as "Flarex 5 mL, one three times a day", it could potentially be misinterpreted as [illegible] e three times a day". Should a patient receive tead of Flarex 5, the patient would be at risk for experiencing side effects associated with his includes drowsiness, dry mouth, dizziness, stomach upset, headache, nervousness, blurred vision, tachycardia, hypotension, and arrhythmias.

Flextra DS and Flextra-650 are prescription only combination products of acetaminophen and phenyltoloxamine. Both products are indicated for temporary relief of minor aches and pains associated with headache, backache, muscular ache, toothaches, menstrual pain, as well as for minor pain from arthritis, and to reduce fever. The Expert Panel expressed concern that Flextra and proposed name, [illegible] sound and look similar, due to the identical letter combination [illegible] at the beginning of each name. Also, the terminal letter combination "ra" in the name Flextra can look similar to the numera' [illegible] when scripted (see page 10). Although the dosing schedules for the medications differ, the products are taken orally, and will likely be prescribed by the same group of physicians. The products, however, differ in strength and dosing regimen. Flextra DS contains 500 mg of acetaminophen and 50 mg of phenyltoloxamine, and Flextra-650 contains 650 mg of acetaminophen and 60 mg of phenyltoloxamine,

where? [redacted] ontain 5 mg and 10 mg of cyclobenzaprine, respectively. Additionally, [redacted] s given up to three times per day, where as Flextra DS is given every four hours and Flextra-650 is given every six hours. These differences help minimize the risk of confusion between the drug products.

Flextra

Flextra [redacted]

2. [redacted]

In regards to the proposed [redacted] METS discourages the use of numbers as a part of the proprietary name. The numerical modifier may be misinterpreted in the prescription to mean a quantity, especially since an expression of strength, such as "mg", is not utilized to clarify the suffix. Such an example includes Viokase 8, in which a physician wrote an inpatient hospital order "Viokase 8 tabs with meals TID". In this case, numerical suffix 8 was confused as the number of tablets needed per dose, rather than as the intended representation of the number of units of Viokase.

In review of the package insert, DMETS focused on safety issues relating to possible medication errors. DMETS has identified areas of possible improvement, which might minimize potential user error:

We noted that in the "How Supplied" section of the draft package insert, the sponsor indicated that the name "Flexeril" will be coded on one side of both the [redacted] ets. DMETS does not recommend the use of a drug name that is different from a drug product's approved name be used as a means of product identification.

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name [redacted] addition, DMETS does not recommend the use of the [redacted] conjunction with the proposed proprietary name.

B. DMETS recommends the labeling revisions as outlined in Section III of this review.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tia Harper-Velazquez
10/29/02 09:45:27 AM
PHARMACIST

Alina Mahmud
10/29/02 09:59:14 AM
PHARMACIST

Carol Holquist
10/29/02 11:55:06 AM
PHARMACIST

Jerry Phillips
10/30/02 08:12:44 AM
DIRECTOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-821 / S-045

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 17-821 SUPPL # 045

Trade Name Flexeril Generic Name cyclobenzaprine HCL
Applicant Name McNeil Consumer Healthcare
HFD- 550
Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/__/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

   If yes, what type(SE1, SE2, etc.)? SE8

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /_X__/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:
   The supplement required review of two efficacy studies.

d) Did the applicant request exclusivity?

YES /__X_/NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years exclusivity.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 17-821 Flexeril

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # [redacted] Study # 006

Investigation #2, Study # [redacted], Study # 008

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /X__/	NO /___/
Investigation #2	YES /X__/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the

NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X__/

Investigation #2 YES /___/ NO /X__/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of

the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # 7,246_ YES /_x__/	NO /___/ Explain:
Investigation #2	
IND # 7,246_ YES /x__/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /x___/

If yes, explain: _____

_____

_____

Nancy M. Halonen
Signature of Preparer
Title: Project Manager

January 16, 2003
Date

Lee S. Simon, M.D.
Signature of Office or Division Director

February 3, 2002
Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Nancy Halonen
2/4/03 06:22:55 AM
CSO

Carmen DeBellas
2/4/03 01:53:09 PM
CSO

Lee Simon
2/7/03 02:14:44 PM
MEDICAL OFFICER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: August 16, 2002	**DUE DATE:** December 2, 2002	**ODS CONSULT #:** 02-0175

TO: Lee Simon, M.D.
Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

THROUGH: Nancy Halonen
Project Manager
HFD-550

PRODUCT NAME: [redacted] (Cyclobenzaprine Tablets) 5 mg and 10 mg **NDA 17-821/S045**	**NDA SPONSOR:** McNeil Pharmaceuticals

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

SUMMARY: In response to a consult from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names [redacted] to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS does not recommend the use of the proprietary name [redacted]. Additionally, DMETS does not recommend the use of the [redacted] in conjunction with the proposed proprietary name. DMETS recommends revising the labeling as outlined in Section III of this review.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:

Associate Director, marketing Error Prevention
Office of Post marketing Drug Risk Assessment, HFD-400
(Rm. 15 B-03, PKLN Bldg.)

FROM:
Ms. Nancy Halonen
Project Manager, HFD-550

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
8-14-02		17-821		8-2-02

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Flexeril (cyclobenzaprine hydrochloride) Tablets	Yes	Anti-Inflammatory	12-2-02

NAME OF FIRM: McNeil Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*: Trade name change/review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
The Sponsor wishes to change the trade name from Flexeril® —
Please forward to Ms. Marci Le, Pharm D., HFD-550 point of contact

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Nancy Halonen	X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Sammie Beam
nulldate

Carmen DeBellas
9/4/02 10:20:43 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-821/S-045

PRIOR APPROVAL SUPPLEMENT

Merck & Company, Incorporated
Attention: Kenneth A. Kramer
Associate Manager Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, Pennsylvania 19486

Dear Mr. Kramer:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Flexeril (cyclobenzaprine HCL) 5mg tablet

NDA Number: 17-821

Supplement Number: S-045

Review Priority Classification: Standard (S)

Date of Supplement: April 18, 2001

Date of Receipt: April 19, 2001

This supplement proposes the following change: adding a 5 mg new dosage form three times daily as a starting dose for relief of muscle spasm associated with acute, painful musculoskeletal .

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 15, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be February 19, 2002 and the secondary user fee goal date will be April 19, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have requested [redacted]

We will make a determination whether to grant or deny a request for a [redacted] pediatric studies

during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If ——— not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
Attention: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call me at (301) 827-2536.

Sincerely,

{See appended electronic signature page}

Sharon Schmidt, M.S.
Project Manager
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Schmidt
6/15/01 06:09:47 PM