McNeil
Consumer & Specialty Pharmaceuticals

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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

NOV 0 5 2003

Comment to Docket No. 2003P-0461/CP1
Cyclobenzaprine Hydrochloride Tablets 7.5mg

Dear Sir or Madam:

Reference is made to the above referenced citizen petition requesting the Food and Drug Administration to find that a change in strength of Cyclobenzaprine Hydrochloride Tablets is suitable for submission in an abbreviated new drug application (ANDA). The petitioner, Anabolic Laboratories Inc. is seeking the addition of an intermediate strength of a 7.5 mg tablet that lies between the approved 5 mg and 10mg tablet versions.

McNeil Consumer & Specialty Pharmaceuticals (McNeil) is the holder of approved NDA 17-821 for Flexeril Tablets 5mg and 10mg. McNeil received approval "for the use of Flexeril [cyclobenzaprine hydrochloride] Tablets 5 mg for the relief of muscle spasm associated with acute, painful musculoskeletal conditions" on February 3, 2003. (see FDA approval letter for S-045, Attachment A). To support approval of this supplement the FDA required McNeil to conduct new clinical studies. At the time of approval of the supplement, those studies were deemed essential for approval and McNeil's 5 mg tablet product was awarded a 3-year period of Hatch-Waxman exclusivity which expires on February 3, 2006. (see excerpt from FDA's Electronic Orange Book Attachment B)

It was the approval of S-045 to NDA 17-821 that permitted labeling changes and documented that the new lower, 5 mg starting dose of cyclobenzaprine hydrochloride was effective. The clinical program referenced above supported the approval of the supplement.

It is recognized from past agency actions on ANDA suitability petitions that the FDA typically permits requests for intermediate strengths that lie between two already approved strengths if the approved labeling of the reference listed drug product clearly contemplates or supports such a dose. While McNeil does not argue with the agency's past precedent and has no specific objections to the approval of this petition, we would like to point out that because the petitioner does in referencing the 5 mg product as evidence of the efficacy of a lower starting dose in fact rely in part on the showing of efficacy associated with the approval of S-045. Therefore any decision to grant the petition for permission to submit an ANDA for a 7.5mg intermediate dose strength should also acknowledge that any ANDA submitted based on the petition if approved, would be subject to the exclusivity protections associated with the 5 mg Flexeril product and as such could not be approved prior to the expiration of the exclusivity period.

2003P-0461 C1

McNeil appreciates the opportunity to comment on this petition. Should you require addition information or clarification of our position, please do not hesitate to contact me directly at 215-273-7731.

Sincerely,

McNeil Consumer & Specialty Pharmaceuticals

Lynn Pawelski
Executive Director
Regulatory Affairs

Attachments:
FDA supplemental approval letter (17-821, S-045) dated February 3, 2003.
Excerpt from FDA's Electronic Orange Book demonstrating the exclusivity period

ATTACHMENT A

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}

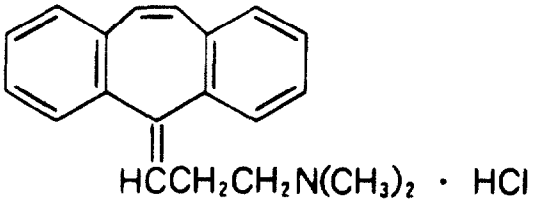
Lee S. Simon, M.D.
Director,
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550 Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure (attached labeling)

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*] cycloheptен-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

[McNeil Consumer & Specialty Pharmaceuticals LOGO]
[Identification number]

Edition: xx/xxx

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

ATTACHMENT B

Proprietary Name Search Results from "Rx" table for query on "Flexeril."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
017821	AB	Yes	CYCLOBENZAPRINE HYDROCHLORIDE	Tablet; Oral	10MG	FLEXERIL	MCNEIL CONS SPECLT
017821		No	CYCLOBENZAPRINE HYDROCHLORIDE	Tablet; Oral	5MG	FLEXERIL	MCNEIL CONS SPECLT

Thank you for searching the Electronic Orange Book

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Search results from the "Rx" table for query on "017821."

Active Ingredient:	CYCLOBENZAPRINE HYDROCHLORIDE
Dosage Form;Route:	Tablet; Oral
Proprietary Name	FLEXERIL
Applicant:	MCNEIL CONS SPECLT
Strength:	5MG
Application Number:	017821
Product Number:	001
Approval Date:	Approved prior to Jan 1, 1982
Reference Listed Drug:	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	CYCLOBENZAPRINE HYDROCHLORIDE
Dosage Form;Route:	Tablet; Oral
Proprietary Name	FLEXERIL
Applicant:	MCNEIL CONS SPECLT
Strength:	10MG
Application Number:	017821
Product Number:	002
Approval Date:	Approved prior to Jan 1, 1982
Reference Listed Drug:	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	Click Here

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Patent and Exclusivity Search Results from query on 017821 001.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
017821	001	D-78	FEB 03,2006

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Patent and Exclusivity Terms

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