

**THERABENZAPRINE-90 - cyclobenzaprine hydrochloride, .gamma.-aminobutyric acid
Physician Therapeutics LLC**

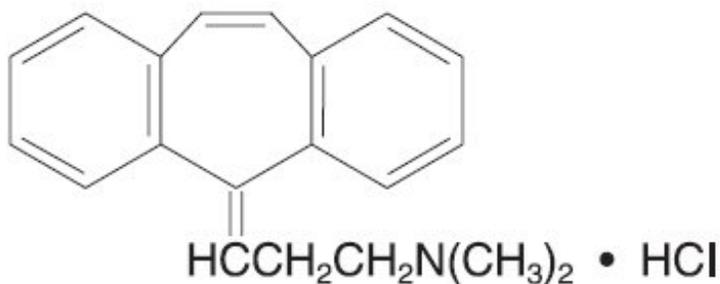
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Therabenzaprine-90

DESCRIPTION

Cyclobenzaprine hydrochloride is a white, crystalline tricyclic amine salt with the empirical formula C₂₀H₂₁N - HCl and a molecular weight of 311.9. It has a melting point of 217 degree C, and a pKa of 8.47 at 25 degree 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:



Cyclobenzaprine Hydrochloride Tablets, USP are supplied as 5 mg and 10 mg tablets for oral administration.

Each tablet contains the following inactive ingredients: croscarmellose sodium, FD and C Yellow #6, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide; 5 mg tablets also contain FD and C Red #40 and 10 mg tablets contain D and C Yellow #10 and polysorbate.

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 (≥ 65 yrs 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.-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 cyclobenzaprine hydrochloride tablets 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, cyclobenzaprine hydrochloride tablets 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 cyclobenzaprine hydrochloride tablets in subjects with moderate to severe impairment is not recommended.

No significant effect on plasma levels or bioavailability of cyclobenzaprine hydrochloride tablets or aspirin was noted when single or multiple doses of the two drugs were administered concomitantly. Concomitant administration of cyclobenzaprine hydrochloride tablets and naproxen or diflunisal was well tolerated with no reported unexpected adverse effects. However combination therapy of cyclobenzaprine hydrochloride tablets 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 cyclobenzaprine hydrochloride tablets enhance the clinical effect of aspirin or other analgesics, or whether analgesics enhance the clinical effect of cyclobenzaprine hydrochloride tablets in acute musculoskeletal conditions.

Clinical Studies

Eight double-blind controlled clinical studies were performed in 642 patients comparing cyclobenzaprine hydrochloride 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 cyclobenzaprine 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 cyclobenzaprine were comparable to those observed in patients treated with diazepam, dry mouth was

observed more frequently in patients treated with cyclobenzaprine 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 cyclobenzaprine hydrochloride tablets 5 mg was demonstrated in two seven-day, double-blind, controlled clinical trials enrolling 1405 patients. One study compared cyclobenzaprine hydrochloride tablets 5 and 10 mg t.i.d. to placebo; and a second study compared cyclobenzaprine hydrochloride tablets 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 cyclobenzaprine hydrochloride tablets 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 cyclobenzaprine hydrochloride tablets 10 mg (all endpoints). Physician-assessed secondary endpoints also showed that cyclobenzaprine hydrochloride tablets 5 mg was associated with a greater reduction in palpable muscle spasm than placebo.

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

Surveillance Program

A post-marketing surveillance program was carried out in 7607 patients with acute musculoskeletal disorders, and included 297 patients treated with cyclobenzaprine hydrochloride tablets 10 mg for 30 days or longer. The overall effectiveness of cyclobenzaprine 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

Cyclobenzaprine hydrochloride tablets are 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.

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

Cyclobenzaprine hydrochloride tablets have 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.

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

PRECAUTIONS

General

Because of its atropine-like action, cyclobenzaprine hydrochloride 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. Cyclobenzaprine hydrochloride tablets 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 cyclobenzaprine hydrochloride tablets in subjects with moderate to severe impairment is not recommended.

Information for Patients

Cyclobenzaprine hydrochloride tablets, 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, cyclobenzaprine hydrochloride tablets should be initiated with a 5 mg dose and titrated slowly upward.

Drug Interactions

Cyclobenzaprine may have life-threatening interactions with MAO inhibitors (see CONTRAINDICATIONS).

Cyclobenzaprine 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In rats treated with cyclobenzaprine hydrochloride 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 cyclobenzaprine. 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 cyclobenzaprine hydrochloride is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of cyclobenzaprine hydrochloride 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 cyclobenzaprine 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 greater than 3% on cyclobenzaprine hydrochloride tablets 5 mg):

	Cyclobenzaprine Hydrochloride Tablets 5 mg N=464	Cyclobenzaprine Hydrochloride Tablets 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 cyclobenzaprine hydrochloride tablets

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 cyclobenzaprine hydrochloride 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: Cyclobenzaprine hydrochloride tablets 10 mg data are from one clinical trial. Cyclobenzaprine hydrochloride tablets 5 mg and placebo data are from two studies

	Clinical Studies with Cyclobenzaprine Hydrochloride Tablets 10 mg	Surveillance Program with Cyclobenzaprine Hydrochloride Tablets 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 cyclobenzaprine hydrochloride 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 cyclobenzaprine hydrochloride 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 cyclobenzaprine hydrochloride. 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 LD50 of cyclobenzaprine hydrochloride 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 cyclobenzaprine hydrochloride 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 alkalization, 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 greater than 7.60 or a pCO₂ less than 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 cyclobenzaprine hydrochloride tablets 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 cyclobenzaprine hydrochloride tablets 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

Cyclobenzaprine Hydrochloride Tablets, USP 5 mg round, orange film-coated tablets, debossed "2631" on one side and debossed "V"

on the reverse side, supplied in bottles of 10, 100, 500 and 1000.

Cyclobenzaprine Hydrochloride Tablets, USP 10 mg round, yellow film-coated tablets, debossed "2632" on one side and debossed

"V" on the reverse side, supplied in bottles of 10, 100, 500, 1000 and 5000.

Store at 20 degree -25 degree C (68 degree -77 degree F) [see USP Controlled Room Temperature].

Manufactured for:

QUALITEST PHARMACEUTICALS

Huntsville, AL 35811

8181950

R5/08-R1

EACH TABLET CONTAINS:

Cyclobenzaprine
Hydrochloride, USP 5 mg

USUAL ADULT DOSAGE: One tablet (5 mg) three times a day. See accompanying product information,

DISPENSE in a well-closed container.

STORE at 20 degree - 25 degree C (68 degree - 77 degree F) [see USP Controlled Room Temperature].

NDC 0603-3078-21

CYCLOBENZAPRINE HYDROCHLORIDE TABLETS, USP 5 mg

Rx only 100 TABLETS

Qualitest

Manufactured for:

QUALITEST PHARMACEUTICALS HUNTSVILLE, AL 35811

Rev. 3/08 R1

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Theramine™ PRODUCT INFORMATION

Theramine (U.S. patent pending) capsules by oral administration. A specially formulated Medical Food product, consisting of a proprietary blend of amino acids and polyphenol ingredients in specific proportions, for the dietary management of the metabolic processes associated with pain disorders and inflammatory conditions. (PD) (IC). Must be administered under physician supervision.

Medical Foods

Medical Food products are often used in hospitals (e.g., for burn victims or kidney dialysis patients) and outside of a hospital setting under a physician's care for the dietary management of diseases in patients with particular medical or metabolic needs due to their disease or condition. Congress defined "Medical Food" in the Orphan Drug Act and Amendments of 1988 as "a food which is formulated to be consumed or administered enterally [or orally] under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Medical Foods are complex formulated products, requiring sophisticated and exacting technology. Theramine has been developed, manufactured, and labeled in accordance with both the statutory and the FDA regulatory definition of a Medical Food. Theramine must be used while the patient is under the ongoing care of a physician.

PAIN DISORDERS (PD) INFLAMMATORY CONDITIONS (IC)

PD and IC as a Metabolic Deficiency Disease

A critical component of the definition of a Medical Food is the requirement for a distinctive nutritional deficiency. FDA scientists have proposed a physiologic definition of a distinctive nutritional deficiency as follows: "the dietary management of patients with specific diseases requires, in some instances, the ability to meet nutritional requirements that differ substantially from the needs of healthy persons. For example, in establishing the recommended dietary allowances for general, healthy population, the Food and Nutrition Board of the Institute of Medicine National Academy of Sciences, recognized that different or distinctive physiologic requirements may exist for certain persons with "special nutritional needs arising from metabolic disorders, chronic diseases, injuries, premature birth,

other medical conditions and drug therapies. Thus, the distinctive nutritional needs associated with a disease reflects the total amount needed by a healthy person to support life or maintain homeostasis, adjusted for the distinctive changes in the nutritional needs of the patient as a result of the effects of the disease process on absorption, metabolism and excretion.” It was also proposed that in patients with certain disease states who respond to nutritional therapies, a physiologic deficiency of the nutrient is assumed to exist. For example, if a patient with pain disorders responds to a tryptophan formulation by decreasing perceived pain, a deficiency of tryptophan is assumed to exist. Patients with pain disorders and inflammatory conditions are known to have nutritional deficiencies of tryptophan, choline, arginine, GABA, flavonoids, and certain antioxidants. Patients with pain disorders and inflammatory conditions frequently exhibit reduced plasma levels of tryptophan and GABA and have been shown to respond to oral administration of GABA, arginine, tryptophan, or a 5-hydroxytryptophan formulation. Research has shown that tryptophan, arginine or GABA reduced diets result in a fall of circulating tryptophan, arginine, and/or GABA.

Patients with pain disorders frequently exhibit activation of the degradation pathways that increases the turnover of GABA, arginine and/or tryptophan leading to a reduced level of production of serotonin, GABA or nitric oxide for a given precursor blood level. Research has also shown that a genetic predisposition to accelerated degradation can lead to increased precursor requirements in certain patients with pain disorders and inflammatory conditions.

Choline is required to fully potentiate acetylcholine synthesis by brain neurons. A deficiency of choline leads to reduced acetylcholine production by the neurons. Flavonoids potentiate the production of acetylcholine by the neurons thereby reducing delta pain. Diets deficient in flavonoid rich foods and choline result in inadequate flavonoid concentrations, impeding acetylcholine production in certain patients with pain disorders and/or inflammatory conditions. Acetylcholine in pre-synaptic ganglia is necessary for the production of serotonin and nitric oxide in post-synaptic ganglia. Provision of tryptophan, arginine, GABA, choline and flavonoids with antioxidants, in specific proportions can restore the production of beneficial serotonin, nitric oxide, and acetylcholine, thereby reducing the perception of pain and reducing inflammation. L-Histidine is known to produce brain histamine that stimulates production of ACTH.

PRODUCT DESCRIPTION

Primary Ingredients Theramine consists of a proprietary blend of amino acids, cocoa, caffeine, cinnamon, and flavonoids in specific proportions. These ingredients fall into the category of “Generally Regarded as Safe” (GRAS) as defined by the Food and Drug Administration (FDA) (Sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act). A GRAS substance is distinguished from a food additive on the basis of the common knowledge about the safety of the substance for its intended use. The standard for an ingredient to achieve GRAS status requires not only technical demonstration of non-toxicity and safety, but also general recognition of safety through widespread usage and agreement of that safety by experts in the field. Many ingredients have been determined by the U.S. Food and Drug Administration (FDA) to be GRAS, and are listed as such by regulation, in Volume 21 Code of Federal Regulations (CFR) Sections 182, 184, and 186.

Amino Acids

Amino Acids are the building blocks of protein. All amino acids are GRAS listed as they have been ingested by humans for thousands of years. The doses of the amino acids in Theramine are equivalent to those found in the usual human diet. Patients with pain disorders may require an increased amount of certain amino acids that cannot be obtained from normal diet alone. Tryptophan, for example, is an obligatory amino acid. The body cannot make tryptophan and must obtain tryptophan from the diet. Tryptophan is needed to produce serotonin. Serotonin is required to reduce pain. Patients with pain disorders and inflammatory conditions have altered serotonin metabolism. Some patients with pain disorders and inflammatory conditions have a resistance to the use of tryptophan that is similar to the

mechanism found in insulin resistance. Patients with pain disorders and inflammatory conditions cannot acquire sufficient tryptophan from the diet to alter the perception of pain and the inflammatory process without ingesting a prohibitively large amount of calories, particularly calories from protein.

Flavonoids

Flavonoids are a group of phytochemical compounds found in all vascular plants including fruits and vegetables. They are a part of a larger class of compounds known as polyphenols. Many of the therapeutic or health benefits of colored fruits and vegetables, cocoa, red wine, and green tea are directly related to their flavonoid content. The specially formulated flavonoids found in Theramine cannot be obtained from conventional foods in the necessary proportions to elicit a therapeutic response.

Other Ingredients

Theramine contains the following inactive or other ingredients, as fillers, excipients, and colorings: magnesium stearate, microcrystalline cellulose, Maltodextrin NF, gelatin (as the capsule material).

Physical Description

Theramine is a yellow to light brown powder. Theramine contains L-Glutamine, L-Arginine, L-Histidine, and L-Serine, 5-Hydroxytryptophan as Griffonia Seed Extract, GABA, Choline Bitartrate, Cinnamon, Cocoa, Hydrolyzed Whey Protein, and Grape Seed Extract.

CLINICAL PHARMACOLOGY

Mechanism of Action

Theramine acts by restoring and maintaining the balance of the neurotransmitters; GABA, nitric oxide, serotonin, and acetylcholine that are associated with pain disorders and inflammatory conditions. Theramine stimulates the production ACTH to reduce inflammation.

Metabolism

The amino acids in Theramine are primarily absorbed by the stomach and small intestines. All cells metabolize the amino acids in Theramine. Circulating tryptophan, arginine and choline blood levels determine the production of serotonin, nitric oxide, and acetylcholine.

Excretion

Theramine is not an inhibitor of cytochrome P450 1A2, 2C9, 2C19, 2D6, or 3A4. These isoenzymes are principally responsible for 95% of all detoxification of drugs, with CYP3A4 being responsible for detoxification of roughly 50% of drugs. Amino acids do not appear to have an effect on drug metabolizing enzymes.

INDICATIONS FOR USE

Theramine is intended for the clinical dietary management of the metabolic processes of pain disorders and inflammatory conditions.

CLINICAL EXPERIENCE

Administration of Theramine has demonstrated significant reduction in symptoms of pain and inflammation in patients with acute and chronic pain when used for the dietary management of the metabolic processes associated with pain disorders and inflammatory conditions. Administration of Theramine results in the induction and maintenance of pain relief in patients with pain disorders and inflammatory conditions.

PRECAUTIONS AND CONTRAINDICATIONS

Theramine is contraindicated in an extremely small number of patients with hypersensitivity to any of the nutritional components of Theramine.

ADVERSE REACTIONS

Oral supplementation with L-tryptophan, L-arginine or choline at high doses up to 15 grams daily is generally well tolerated. The most common adverse reactions of higher doses — from 15 to 30 grams

daily — are nausea, abdominal cramps, and diarrhea. Some patients may experience these symptoms at lower doses. The total combined amount of amino acids in each Theramine capsule does not exceed 400 mg.

DRUG INTERACTIONS

Theramine does not directly influence the pharmacokinetics of prescription drugs. Clinical experience has shown that administration of Theramine may allow for lowering the dose of co-administered drugs under physician supervision.

OVERDOSE

There is a negligible risk of overdose with Theramine as the total dosage of amino acids in a one month supply (90 capsules) is less than 36 grams. Overdose symptoms may include diarrhea, weakness, and nausea.

POST-MARKETING SURVEILLANCE

Post-marketing surveillance has shown no serious adverse reactions. Reported cases of mild rash and itching may have been associated with allergies to Theramine flavonoid ingredients, including cinnamon, cocoa, and chocolate. These reactions were transient in nature and subsided within 24 hours.

DOSAGE AND ADMINISTRATION

Recommended Administration For the dietary management of the metabolic processes associated with pain disorders and inflammatory conditions. Take (2) capsules one to three times daily or as directed by physician. As with most amino acid formulations Theramine should be taken without food to increase the absorption of key ingredients.

How Supplied

Theramine is supplied in purple and white, size 0 capsules in bottles of 60 or 90 capsules.

Physician Supervision

Theramine is a Medical Food product available by prescription only and must be used while the patient is under ongoing physician supervision.

U.S. patent pending.

Manufactured by Arizona Nutritional Supplements, Inc. Chandler AZ 85225

Distributed by Physician Therapeutics LLC, Los Angeles, CA 90077. www.ptlcentral.com

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NDC: 68405-1008-02

Storage

Store at room temperature, 59-86OF (15-30OC) Protect from light and moisture. Theramine is supplied to physicians in a recyclable plastic bottle with a child-resistant cap.

PHYSICIAN THERAPEUTICS THERAMINE Medical Food Rx only 90 Capsules Directions for use: Must be administered under medical supervision. For adults only. As a Medical Food, take one (1) or two (2) capsules every four hours or as directed by your medical practitioner. For the dietary management of Myalgia. Contains no added sugar, starch, wheat, yeast, preservatives, artificial flavor. Storage: Keep tightly closed in a cool dry place 8-320 C (45-900 F), relative humidity, below 50%. Warning: Keep this product out of the reach of children. NDC# 68405-1008-03 Ingredients: Each serving (per 2 capsules) contains: Proprietary Amino Acid Blend Griffonia Seed Extract (5-HTP), Whey Protein Hydrolysate, L-Arginini, L-Histidine (as L-Histidine HCl), L-Glutamine, L-Serine, Gamma Amino Butyric Acid, Choline Bitartrate, Cocoa (6% Theobromine) (fruit), Grape Extract (95% Polyphenols) (seed), Cinnamon (bark) Other Ingredients: Gelatin, Silicon Dioxide, Tricalcium

phosphate, Vegetable Magnesium Stearate, Cellulose, FD and C Blue #1, FD and C red#3, titanium dioxide. Distributed by: Physician Therapeutics LLC, Los Angeles, CA 90077 www.ptlcentral.com
Patent Pending

For the Dietary Management of Pain and Inflammation.

The capsules twice daily or as directed by physician. See product label and insert.

Theramine Medical Food

Theramine Cyclobenzaprine 5 mg

A Convenience Packed Medical Food And Drug

Therabenzaprine-90

PHYSICIAN THERAPEUTICS

> Theramine 90 Capsules

> Cyclobenzaprine 10 mg 60 Tablets

No Refills Without Physician Authorization

Rx only

NDC# 68405-8058-36 of this co-pack

As prescribed by physician. See product label and product information insert.

Cyclobenzaprine 10 mg

Rx Drug



Directions for use:
Must be administered under medical supervision.
For adults only. As a Medical Food, take one (1) or two (2) capsules every four hours or as directed by your medical practitioner.
For the dietary management of Myalgia.
Contains no added sugar, starch, wheat, yeast, preservatives, artificial flavor.

Storage:
Keep tightly closed in a cool dry place 8-32°C (45-90°F), relative humidity, below 50%.

Warning: Keep this product out of the reach of children.
NDC# 68405-1008-03



PHYSICIAN THERAPEUTICS™

THERAMINE
Medical Food

Rx only
90 Capsules

Ingredients:

Each serving (per 2 capsules) contains:

Proprietary Amino Acid Blend

Griffonia Seed Extract (5-HTP),

Whey Protein Hydrolysate,

L-Arginine, L-Histidine (as

L-Histidine HCl), L-Glutamine,

L-Serine,

Gamma Amino Butyric Acid,

Choline Bitartrate,

Cocoa (6% Theobromine) (fruit),

Grape Extract (95% Polyphenols) (seed),

Cinnamon (bark)

Other Ingredients: Gelatin, Silicon Dioxide,

Tricalcium phosphate, Vegetable Magnesium

Stearate, Cellulose, FD&C Blue#1, FD&C red

#3, titanium dioxide.

Distributed by:

Physician Therapeutics LLC, Los Angeles, CA 90077

www.ptlcentral.com

Patent Pending

52959-0042-60

CAUTION: Federal law PROHIBITS the transfer of this drug to anyone other than the person to whom prescribed and prohibits dispensing without a prescription unless OTC. See insert for additional info. KEEP OUT OF REACH OF CHILDREN. Store in a cool dry place at 68 to 77 degrees F.

CYCLOBENZAPRINE HCL 10mg TAB.

Lot #: CYB103QT

#60

Mfg: QUALITEST

Exp: 05/12

Compare to: Flexeril

Mfg. NDC: 00603-3079-34



Take as directed by your Doctor or
See insert for usual dosage information



CYCLOBENZAPRINE HCL 10mg TAB.
52959-0042-60 Qty #60
05/12 Lot CYB103QT
Flexeril 00603-3079-34

CYCLOBENZAPRINE HCL 10mg TAB.
52959-0042-60 Qty #60
05/12 Lot CYB103QT
Flexeril 00603-3079-34

CYCLOBENZAPRINE HCL 10mg TAB.
52959-0042-60 Qty #60
05/12 Lot CYB103QT
Flexeril 00603-3079-34

CYCLOBENZAPRINE HCL 10mg TAB.
52959-0042-60 Qty #60
05/12 Lot CYB103QT
Flexeril 00603-3079-34

Repack: HJ Harkins Co., Inc., Norcross, GA 30444

A Convenience Packed Medical Food & Drug

Therabenzaprine-90™



- ▶ **Theramine™ 90 Capsules**
- ▶ **Cyclobenzaprine 10 mg 60 Tablets**

No Refills Without
Physician Authorization

Rx Only
NDC# 68405- 058-36
of this co-pack

THERABENZAPRINE-90

cyclobenzaprine hydrochloride, .gamma.-aminobutyric acid kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:68405-058
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Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68405-058-36	1 in 1 KIT		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 BOTTLE	60
Part 2	1 BOTTLE	90

Part 1 of 2**CYCLOBENZAPRINE HYDROCHLORIDE**

cyclobenzaprine hydrochloride tablet, film coated

Product Information

Item Code (Source)	NDC:52959-042(NDC:0603-3079)
Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CYCLOBENZAPRINE HYDROCHLORIDE (UNII: 0VE05JYS2P) (CYCLOBENZAPRINE - UNII:69O5WQ5TI)	CYCLOBENZAPRINE HYDROCHLORIDE	10 mg

Inactive Ingredients

Ingredient Name	Strength
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL (UNII: 3WJQ0SDW1A)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	

Product Characteristics

Color	yellow (YELLOW)	Score	no score
Shape	ROUND	Size	7mm
Flavor		Imprint Code	2632;V
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52959-042-60	60 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077797	02/15/2011	

Part 2 of 2

THERAMINE 90

.gamma.-aminobutyric acid capsule

Product Information

Route of Administration ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
.GAMMA.-AMINOBUTYRIC ACID (UNII: 2ACZ6IPC6I) (.GAMMA.-AMINOBUTYRIC ACID - UNII:2ACZ6IPC6I)	.GAMMA.-AMINOBUTYRIC ACID	100 mg

Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
MALTODEXTRIN (UNII: 7CVR7L4A2D)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics

Color	green (GREEN)	Score	no score
Shape	CAPSULE	Size	21mm
Flavor		Imprint Code	;
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		90 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Medical Food		02/15/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		02/16/2011	

Labeler - Physician Therapeutics LLC (931940964)

Establishment

Name	Address	ID/FEI	Business Operations
Vintage Pharmaceuticals		825839835	manufacture

Establishment

Name	Address	ID/FEI	Business Operations
H.J. Harkins Company, Inc.		147681894	repack

Establishment

Name	Address	ID/FEI	Business Operations
Targeted Medical Pharma Inc.		126962740	manufacture

Revised: 8/2011

Physician Therapeutics LLC