

CYCLOBENZAPRINE HCL ER- cyclobenzaprine hcl er capsule, extended release

Direct_Rx

Cyclobenzaprine HCL ER

Cyclobenzaprine hydrochloride extended-release capsules 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, and limitation of motion.

Limitations of Use:

Cyclobenzaprine hydrochloride extended-release capsules 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 extended-release capsules have not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.

The recommended adult dose for most patients is one (1) cyclobenzaprine hydrochloride 15 mg extended-release capsule taken once daily. Some patients may require up to 30 mg/day, given as one (1) cyclobenzaprine hydrochloride 30 mg extended-release capsule taken once daily or as two (2) cyclobenzaprine hydrochloride 15 mg extended-release capsules taken once daily.

It is recommended that doses be taken at approximately the same time each day. Use of cyclobenzaprine hydrochloride extended-release capsules for periods longer than two or three weeks is not recommended [SEE INDICATIONS AND USAGE (1)].

Instruct patients to swallow cyclobenzaprine hydrochloride extended-release capsules intact. Alternatively, the contents of the cyclobenzaprine hydrochloride extended-release capsule may be sprinkled over applesauce and then swallowed. This method is appropriate only for patients able to reliably swallow the applesauce without chewing. Other foods have not been tested and should not be substituted for applesauce.

Instruct the patient to:

Sprinkle the contents of the capsule onto a tablespoon of applesauce and consume immediately without chewing.

Rinse the mouth to ensure all of the contents have been swallowed.

Discard any unused portion of the cyclobenzaprine hydrochloride extended-release capsules after the contents have been sprinkled on applesauce.

Extended-release capsules in the following strengths:

15 mg: Capsules are orange opaque body and orange opaque cap with "B15" in blue ink on cap.

30 mg: Capsules are dark blue opaque body and standard red opaque cap with "B30" in white ink on cap.

Hypersensitivity to any component of this product. These adverse reactions may

manifest as an anaphylactic reaction, urticaria, facial and/or tongue swelling, or pruritus. Discontinue cyclobenzaprine hydrochloride extended-release capsules if a hypersensitivity reaction is suspected.

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.

During the acute recovery phase of myocardial infarction, and in patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure. Hyperthyroidism.

5.1 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with cyclobenzaprine when used in combination with other drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. The concomitant use of cyclobenzaprine hydrochloride extended-release with MAO inhibitors is contraindicated [SEE CONTRAINDICATIONS (4)]. Serotonin syndrome symptoms may include mental status changes (e.g., confusion, agitation, hallucinations), autonomic instability (e.g., diaphoresis, tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., tremor, ataxia, hyperreflexia, clonus, muscle rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Treatment with cyclobenzaprine hydrochloride extended-release and any concomitant serotonergic agents should be discontinued immediately if the above reactions occur and supportive symptomatic treatment should be initiated. If concomitant treatment with cyclobenzaprine hydrochloride extended-release and other serotonergic drugs is clinically warranted, careful observation is advised, particularly during treatment initiation or dose increases.

5.2 Tricyclic Antidepressant-like Effects

Cyclobenzaprine is structurally related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke [SEE CONTRAINDICATIONS (4)]. Cyclobenzaprine hydrochloride extended-release may enhance the effects of alcohol, barbiturates, and other CNS depressants.

Some of the more serious central nervous system (CNS) reactions noted with the tricyclic antidepressants have occurred in short-term studies of cyclobenzaprine for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm. If clinically significant CNS symptoms develop, consider discontinuation of cyclobenzaprine hydrochloride extended-release.

5.3 Use in the Elderly

As a result of a 40% increase in cyclobenzaprine plasma levels and a 56% increase in plasma half-life following administration of cyclobenzaprine hydrochloride extended-release in elderly subjects as compared to young adults, use of cyclobenzaprine hydrochloride extended-release is not recommended in the elderly [SEE CLINICAL PHARMACOLOGY (12.3)].

5.4 Use in Patients with Hepatic Impairment

As a result of two-fold higher cyclobenzaprine plasma levels in subjects with mild hepatic impairment, as compared to healthy subjects, following administration of immediate-release cyclobenzaprine and because there is limited dosing flexibility with cyclobenzaprine hydrochloride extended-release, use of cyclobenzaprine hydrochloride extended-release is not recommended in patients with mild, moderate, or severe hepatic impairment [SEE CLINICAL PHARMACOLOGY (12.3)].

5.5 Atropine-like Action

Because of its atropine-like action, cyclobenzaprine hydrochloride extended-release 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.

The following clinically significant reactions are described in greater detail, in other sections.

Serotonin Syndrome [see WARNINGS AND PRECAUTIONS (5.1)]

Adverse Cardiovascular Effects [see WARNINGS AND PRECAUTIONS (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to cyclobenzaprine hydrochloride extended-release in 253 patients in 2 clinical trials. Cyclobenzaprine hydrochloride extended-release was studied in two double-blind, parallel-group, placebo-controlled, active-controlled trials of identical design [see CLINICAL STUDIES (14)]. The study population was composed of patients with muscle spasms associated with acute painful musculoskeletal conditions. Patients received 15 mg or 30 mg of cyclobenzaprine hydrochloride extended-release capsules taken orally once daily, cyclobenzaprine immediate-release (IR) 10 mg three times a day, or placebo for 14 days.

The most common adverse reactions (incidence $\geq 3\%$ in any treatment group and greater than placebo) were dry mouth, dizziness, fatigue, constipation, nausea, dyspepsia, and somnolence (see Table 1).

Table 1: Incidence of the Most Common Adverse Reactions Occurring in $\geq 3\%$ of Patients in any Treatment Group* and Greater Than Placebo in the Two Phase 3, Double-Blind Cyclobenzaprine Hydrochloride Extended-Release Trials

Placebo

Cyclobenzaprine Hydrochloride Extended-Release Capsules
15 mg

Cyclobenzaprine Hydrochloride Extended-Release Capsules
30 mg

N=128

N=127

N=126

Dry mouth

2%

6%

14%

Dizziness

2%

3%

6%

Fatigue

2%

3%

3%

Constipation

0%

1%

3%

Somnolence

0%

1%

2%

Nausea

1%

3%

3%

Dyspepsia

1%

0%

4%

*Cyclobenzaprine hydrochloride extended-release capsules, 15 mg QD, Cyclobenzaprine hydrochloride extended-release capsules, 30 mg QD, or cyclobenzaprine IR tablets TID

6.2 Postmarketing Experience

The following adverse reactions have been reported in clinical studies or postmarketing experience with cyclobenzaprine hydrochloride extended-release, cyclobenzaprine IR, or tricyclic drugs. Because some of these reactions are reported voluntarily from a

population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In a postmarketing surveillance program of cyclobenzaprine IR, the adverse reactions reported most frequently were drowsiness, dry mouth, and dizziness and adverse reactions 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 postmarketing experience (cyclobenzaprine hydrochloride extended-release or cyclobenzaprine IR), in clinical studies of cyclobenzaprine IR (incidence <1%), or in postmarketing experience with other tricyclic drugs:

Body as a Whole: Syncope; malaise; chest pain; edema.

Cardiovascular: Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension; hypertension; myocardial infarction; heart block; stroke.

Digestive: Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice, and cholestasis; paralytic ileus, tongue discoloration; stomatitis; parotid swelling.

Endocrine: Inappropriate ADH syndrome.

Hematologic and Lymphatic: Purpura; bone marrow depression; leukopenia; eosinophilia; thrombocytopenia.

Hypersensitivity: Anaphylaxis; angioedema; pruritus; facial edema; urticaria; rash.

Metabolic, Nutritional, and Immune: Elevation and lowering of blood sugar levels; weight gain or loss.

Musculoskeletal: Local weakness; myalgia.

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; serotonin syndrome; neuroleptic malignant syndrome; decreased or increased libido; abnormal gait; delusions; aggressive behavior; paranoia; peripheral neuropathy; Bell's palsy; alteration in EEG patterns; extrapyramidal symptoms.

Respiratory: Dyspnea.

Skin: Sweating; photosensitization; alopecia.

Special Senses: Ageusia; tinnitus.

Urogenital: Urinary frequency and/or retention; impaired urination; dilatation of urinary tract; impotence; testicular swelling; gynecomastia; breast enlargement; galactorrhea.

Based on its structural similarity to tricyclic antidepressants, cyclobenzaprine hydrochloride extended-release may have life-threatening interactions with MAO inhibitors [SEE CONTRAINDICATIONS (4)], may enhance the effects of alcohol, barbiturates, and other CNS depressants, may enhance the seizure risk in patients taking tramadol, or may block the antihypertensive action of guanethidine and similarly acting compounds.

Postmarketing cases of serotonin syndrome have been reported during combined use of cyclobenzaprine and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil, or MAO inhibitors [SEE WARNINGS AND PRECAUTIONS (5.1)].

8.1 Pregnancy

Risk Summary

Available data from case reports with cyclobenzaprine hydrochloride extended-release use in pregnancy have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In rats, decreased pup body weight and survival was noted at cyclobenzaprine doses ≥ 10 mg/kg/day (approximately ≥ 3 times the maximum recommended human dose (MRHD) of 30 mg/day), when administered orally during pregnancy and lactation (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

No adverse embryofetal effects were reported following oral administration of cyclobenzaprine during organogenesis to mice and rabbits at maternal doses up to 20 mg/kg/day (approximately 3 and 15 times the MRHD, respectively, on a mg/m² basis). Maternal toxicity characterized by decreased body weight gain was observed only in mice at the highest tested dose of 20 mg/kg/day.

Decreased pup body weight and survival were reported in a prenatal and postnatal study where pregnant rats were treated orally with cyclobenzaprine during pregnancy and lactation with maternal doses of 10 and 20 mg/kg/day (approximately 3 and 6 times the MRHD on a mg/m² basis). Maternal toxicity, characterized by a decreased body weight gain, was observed only at the highest tested dose of 20 mg/kg/day.

8.2 Lactation

Risk Summary

There are no data on the presence of cyclobenzaprine in either human or animal milk, the effects on a breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for cyclobenzaprine hydrochloride extended-release and any potential adverse effects on the breastfed child from cyclobenzaprine hydrochloride extended-release or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of cyclobenzaprine hydrochloride extended-release have not been studied in pediatric patients.

8.5 Geriatric Use

Clinical studies of cyclobenzaprine hydrochloride extended-release did not include sufficient numbers of patients aged 65 and over to determine the safety and efficacy of

cyclobenzaprine hydrochloride extended-release in the elderly population. The plasma concentration and half-life of cyclobenzaprine are substantially increased in the elderly when compared to the general patient population. Accordingly, use of cyclobenzaprine hydrochloride extended-release is not recommended in the elderly [SEE WARNINGS AND PRECAUTIONS (5.3) and CLINICAL PHARMACOLOGY (12.3)].

8.6 Hepatic Impairment

The use of cyclobenzaprine hydrochloride extended-release is not recommended in patients with mild, moderate, or severe hepatic impairment [SEE WARNINGS AND PRECAUTIONS (5.4) and CLINICAL PHARMACOLOGY (12.3)].

9.3 Dependence

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when cyclobenzaprine hydrochloride extended-release 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.

10.1 Manifestations

Although rare, deaths may occur from overdosage with cyclobenzaprine hydrochloride extended-release. 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 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 (6).

10.2 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 extended-release 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 pCO₂ <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 overdosage are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

Cyclobenzaprine hydrochloride is a skeletal muscle relaxant which relieves muscle spasm of local origin without interfering with muscle function. The active ingredient in cyclobenzaprine hydrochloride extended-release capsules is cyclobenzaprine hydrochloride, USP. Cyclobenzaprine hydrochloride (HCl) 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°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 hydrochloride is designated chemically as 3-(5H-dibenzo[a,d] cyclohepten-5-ylidene)-N,N-dimethyl-1-propanamine hydrochloride, and has the following structural formula:

[Structural Formula]

Cyclobenzaprine hydrochloride extended-release capsules for oral administration are supplied in 15 mg and 30 mg strengths. Cyclobenzaprine hydrochloride extended-release capsules contain the following inactive ingredients: diethyl phthalate NF, ethylcellulose NF (Ethocel Standard 10 Premium), gelatin, Opadry® Clear YS-1-7006, sugar spheres NF (20 to 25 mesh), and titanium dioxide. Cyclobenzaprine hydrochloride 15 mg extended-release capsules also contain D&C yellow #10, FD&C green #3, and FD&C red #40. Cyclobenzaprine hydrochloride 30 mg extended-release capsules also contain FD&C blue #1, FD&C blue #2, FD&C red #40, and FD&C yellow #6.

12.1 Mechanism of Action

Cyclobenzaprine relieves skeletal muscle spasm of local origin without interfering with muscle function. Cyclobenzaprine has not been shown to be effective in muscle spasm due to central nervous system disease. In animal models, cyclobenzaprine reduced or abolished skeletal muscle hyperactivity. 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 the brain stem as opposed to the spinal cord level, although an overlapping 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 demonstrated 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.

12.3 Pharmacokinetics

Absorption

Following single-dose administration of cyclobenzaprine hydrochloride extended-release capsules, 15 mg and 30 mg in healthy adult subjects ($n=15$), C_{max} , AUC_{0-168h} and $AUC_{0-\infty}$ increased in an approximately dose-proportional manner from 15 mg to 30 mg. The time to peak plasma cyclobenzaprine concentration (T_{max}) was 7 to 8 hours for both doses of cyclobenzaprine hydrochloride extended-release capsules.

A food effect study conducted in healthy adult subjects ($n=15$) utilizing a single dose of cyclobenzaprine hydrochloride extended-release capsules, 30 mg demonstrated a statistically significant increase in bioavailability when cyclobenzaprine hydrochloride extended-release capsules, 30 mg was given with food relative to the fasted state. There was a 35% increase in peak plasma cyclobenzaprine concentration (C_{max}) and a 20% increase in exposure (AUC_{0-168h} and $AUC_{0-\infty}$) in the presence of food. No effect, however, was noted in T_{max} or the shape of the mean plasma cyclobenzaprine concentration versus time profile. Cyclobenzaprine in plasma was first detectable in both the fed and fasted states at 1.5 hours.

When the contents of cyclobenzaprine hydrochloride extended-release capsules were administered by sprinkling on applesauce, it was found to be bioequivalent to the same dose when administered as an intact capsule.

In a multiple-dose study utilizing cyclobenzaprine hydrochloride extended-release capsules, 30 mg administered once daily for 7 days in a group of healthy adult subjects ($n=35$), a 2.5-fold accumulation of plasma cyclobenzaprine levels was noted at steady-state.

Metabolism and Excretion

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 has an elimination half-life of 32 hours (range 8 to 37 hours; $n=18$); plasma clearance is 0.7 L/min following single-dose administration of cyclobenzaprine hydrochloride extended-release capsules.

Special Populations

Elderly

Although there were no notable differences in C_{max} or T_{max}, cyclobenzaprine plasma AUC is increased by 40% and the plasma half-life of cyclobenzaprine is prolonged in elderly subjects greater than 65 years of age (50 hours) after dosing with cyclobenzaprine hydrochloride extended-release capsules compared to younger subjects 18 to 45 years of age (32 hours). Pharmacokinetic characteristics of cyclobenzaprine following multiple-dose administration of cyclobenzaprine hydrochloride extended-release capsules in the elderly were not evaluated.

Hepatic Impairment

In a pharmacokinetic study of immediate-release cyclobenzaprine in 16 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. The pharmacokinetics of cyclobenzaprine in subjects with severe hepatic impairment is not known.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies were conducted in CD-1 mice and Sprague-Dawley rats with oral cyclobenzaprine to evaluate its carcinogenic potential. In an 81-week carcinogenicity study, metastatic hemangiosarcoma was seen in 3 of 21 male mice at 10 mg/kg/day (approximately 2 times the maximum recommended human dose (MRHD) of 30 mg/day on a mg/m² basis). In a 105-week carcinogenicity study, malignant astrocytoma was seen in 3 of 50 male rats at 10 mg/kg/day (approximately 3 times the MRHD on a mg/m² basis). There were no tumor findings in female mice or rats.

Mutagenesis

Cyclobenzaprine hydrochloride was not mutagenic or clastogenic in the following assays: an in vitro Ames bacterial mutation assay, in vitro Chinese hamster ovary (CHO) cell chromosomal aberration test, and in vivo mouse bone marrow micronucleus assay.

Impairment of Fertility

Cyclobenzaprine hydrochloride, when administered 70 and 14 days prior to mating to male and female rats, respectively, had no effects on fertility or reproductive performance at oral doses up to 20 mg/kg/day (approximately 6.5 times the MRHD on a mg/m² basis).

13.2 Animal Toxicology and/or Pharmacology

In a 67-week study with rats that received cyclobenzaprine at oral doses of 10, 20, or 40 mg/kg/day (3 to 15 times the MRHD on mg/m² basis), there were findings in the liver consisting of midzonal vacuolation with lipidosis for males and midzonal and centrilobular hepatocytic enlargement for females. In addition, there were findings of centrilobular coagulative necrosis. In the higher dose groups, these microscopic changes were seen after 26 weeks and even earlier in rats that died prior to 26 weeks; at lower doses, these changes were not seen until after 26 weeks.

In a 26-week study with Cynomolgus monkeys that received cyclobenzaprine at oral doses of 2.5, 5, 10, or 20 mg/kg/day, one monkey at 20 mg/kg/day (15 times the MRHD

on mg/m² basis) was euthanized in week 17. Morbidity for this animal was attributed to findings of chronic pancreatitis, cholecystitis, cholangitis, and focal liver necrosis.

Efficacy was assessed in two double-blind, parallel-group, active-controlled, placebo-controlled studies of identical design of cyclobenzaprine hydrochloride extended-release capsules, 15 mg and 30 mg taken once daily, between 6:00 and 7:00 PM, cyclobenzaprine 10 mg three times a day, or placebo for 14 days in patients with muscle spasms associated with acute painful musculoskeletal conditions.

There were significant differences in the primary efficacy analysis, the patient's rating of medication helpfulness, between the cyclobenzaprine hydrochloride extended-release capsules, 15 mg group and the placebo group at Days 4 and 14 in one study and between the cyclobenzaprine hydrochloride extended-release capsules, 30 mg group and the placebo group at Day 4 in the second study.

Table 2: Patients' Rating of Medication Helpfulness - Study 1*

Day 4

Day 14

Number of Patients (%)

Number of Patients (%)

Placebo
(N = 64)

Cyclobenzaprine Hydrochloride Extended-Release Capsules
30 mg
(N = 64)

Placebo
(N = 64)

Cyclobenzaprine Hydrochloride Extended-Release Capsules
30 mg
(N = 64)

Excellent

1 (2%)

3 (5%)

12 (19%)

15 (23%)

Very Good

5 (8%)

13 (20%)

9 (14%)

19 (30%)

Good

15 (23%)

22 (34%)

10 (16%)

15 (23%)

Fair

24 (38%)

20 (31%)

16 (25%)

10 (16%)

Poor

10 (16%)

5 (8%)

9 (14%)

4 (6%)

Missing

9 (14%)

1 (2%)

8 (13%)

1 (2%)

*Percentages are rounded to the nearest whole percent.

Table 3: Patients' Rating of Medication Helpfulness - Study 2*

Day 4

Day 14

Number of Patients (%)

Number of Patients (%)

Placebo

(N = 64)

Cyclobenzaprine Hydrochloride Extended-Release Capsules

15 mg

(N = 63)

Placebo

(N = 64)

Cyclobenzaprine Hydrochloride Extended-Release Capsules

15 mg

(N = 63)

Excellent

1 (2%)

2 (3%)

10 (16%)

13 (21%)

Very Good

10 (16%)

12 (19%)

12 (19%)

21 (33%)

Good

14 (22%)

21 (33%)

13 (20%)

9 (14%)

Fair

16 (25%)

17 (27%)

14 (22%)

10 (16%)

Poor

19 (30%)

6 (10%)

12 (19%)

5 (8%)

Missing

4 (6%)

5 (8%)

3 (5%)

5 (8%)

*Percentages are rounded to the nearest whole percent.

In addition, one of the two studies demonstrated significant differences between the cyclobenzaprine hydrochloride extended-release capsules, 30 mg group and the placebo

group in terms of patient-rated relief from local pain due to muscle spasm at Day 4 and Day 8, in patient-rated restriction of movement at Day 4 and Day 8, and in patient-rated global impression of change at Day 4, Day 8, and Day 14.

In both studies, there were no significant treatment differences between the cyclobenzaprine hydrochloride extended-release treatment groups and the placebo group in physician's global assessment, patient-rated restriction in activities of daily living, or quality of nighttime sleep.

16.1 How Supplied

Cyclobenzaprine hydrochloride extended-release capsules are available in 15 mg and 30 mg strengths, packaged in bottles of 60 capsules.

Cyclobenzaprine Hydrochloride Extended-Release Capsules, 15 mg (NDC 0115-1436-13) are orange opaque body and orange opaque cap with "B15" in blue ink on cap.

Cyclobenzaprine Hydrochloride Extended-Release Capsules, 30 mg (NDC 0115-1437-13) are dark blue opaque body and standard red opaque cap with "B30" in white ink on cap.

16.2 Storage and Handling

Dispense in a tight, light-resistant container as defined in the USP/NF.

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

See FDA-approved patient labeling (Patient Information).

Instruct patients to swallow cyclobenzaprine hydrochloride extended-release capsules intact or to sprinkle capsule contents on a tablespoon of applesauce and swallow immediately without chewing.

Advise patients to stop taking cyclobenzaprine hydrochloride extended-release capsules and to notify their physician right away if they experience symptoms of an allergic reaction, such as difficulty breathing, hives, swelling of face or tongue, or itching.

Advise patients that cyclobenzaprine hydrochloride extended-release capsules should not be taken with MAO inhibitors or within 14 days after their discontinuation.

Caution patients about the risk of serotonin syndrome with concomitant use of cyclobenzaprine hydrochloride extended-release and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. Advise patients of the signs and symptoms of serotonin syndrome [SEE WARNINGS AND PRECAUTIONS (5.1)] and instruct patients to seek medical care immediately if they experience these symptoms.

Advise patients to stop taking cyclobenzaprine hydrochloride extended-release capsules and to notify their physician right away if they experience arrhythmias or tachycardia.

Advise patients that cyclobenzaprine hydrochloride extended-release capsules may enhance the impairment effects of alcohol. These effects may also be seen if cyclobenzaprine hydrochloride extended-release capsules are taken with other CNS depressants.

Caution patients about operating an automobile or other hazardous machinery until it is reasonably certain that cyclobenzaprine hydrochloride extended-release capsules therapy will not adversely affect their ability to engage in such activities.

Advise patients to take cyclobenzaprine hydrochloride extended-release capsules at approximately the same time each day.

Manufactured By:
Adare Pharmaceuticals, Inc.
Vandalia, OH 45377

Distributed by:
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

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CYCLOBENZAPRINE HCL ER

cyclobenzaprine hcl er capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:72189-389(NDC:0115-1436)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CYCLOBENZAPRINE HYDROCHLORIDE (UNII: 0VE05JYS2P) (CYCLOBENZAPRINE - UNII:69O5WQQ5TI)	CYCLOBENZAPRINE HYDROCHLORIDE	15 mg

Inactive Ingredients

Ingredient Name	Strength
ETHYLCELLULOSE (10 MPA.S) (UNII: 3DYK7UYZ62)	
GELATIN (UNII: 2G86QN327L)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
FD&C GREEN NO. 3 (UNII: 3P3ONR601S)	
DIETHYL PHTHALATE (UNII: UF064M00AF)	

POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)

D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)

Product Characteristics

Color	orange (Orange Opaque Body/Orange Opaque Cap)	Score	no score
Shape	CAPSULE	Size	14mm
Flavor		Imprint Code	B15
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72189-389-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	11/09/2022	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021777	11/09/2022	

Labeler - Direct_Rx (079254320)

Registrant - Direct_Rx (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
Direct_Rx		079254320	repack(72189-389)

Revised: 11/2022

Direct_Rx