CYCLOBENZAPRINE HYDROCHLORIDE TABLETS, USP

Rx Only

DESCRIPTION
Cyclobenzaprine hydrochloride is a white, crystalline tricyclic amine salt with the empirical formula \( \text{C}_{19}\text{H}_{22}\text{N}_{2}\text{O} \cdot \text{HCl} \) and a molecular weight of 315.3. It has a melting point of 317°C, and a pK\text{a} of 8.47 at 25°C. It is soluble in water and alcohol, sparingly soluble in chloroform, and insoluble in hydrocarbons. If aqueous solutions are made alkaline, the free base separates. Cyclobenzaprine hydrochloride is designated chemically as 3-(3-diethylamino)phenyl)-N\text{a}

Each 5 mg Cyclobenzaprine hydrochloride tablet for oral administration contains 5 mg Cyclobenzaprine hydrochloride. Each 10 mg Cyclobenzaprine hydrochloride tablet for oral administration contains 10 mg Cyclobenzaprine hydrochloride.

Each tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate, camphor wax, titanium dioxide, polyethylene glycol, and iron oxide yellow.

In addition, 5 mg tablets also contain polyvinyl alcohol, talc, lactose, and FD&C yellow #6; sunset yellow FFD aluminum lake, FD&C yellow #6 aluminum lake, methyl paraben, potassium sorbate, propylene glycol, propyl paraben, sodium citrate, and xanthan gum.

CLINICAL PHARMACOLOGY
Cyclobenzaprine hydrochloride relieves skeletal muscle spasm of local origin without interfering with muscular function. It is ineffective in muscle spasms due to central nervous system disease.

Cyclobenzaprine hydrochloride is a mixed agonist-antagonist at muscarinic acetylcholine receptor sites of the central nervous system. 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 (\( \gamma \)) and alpha (\( \alpha \)) motor neurons.

Pharmacological studies in animals showed a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants in animals. 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 (\( \gamma \)) and alpha (\( \alpha \)) motor neurons.

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 accumulation occurs upon dosing twice a day. Steady-state plasma concentrations are achieved in 3 to 4 days at plasma concentrations about four-fold higher than after a single dose. At steady-state, mean plasma concentrations were 29.5 ng/mL (range, 12.8-46.1 ng/mL) in elderly males and 27.0 ng/mL (range, 8.3-59.5 ng/mL) in elderly females. 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 and older), mean (\( \pm \) SD) steady-state cyclobenzaprine AUC\text{\textregistered} values were approximately 1.7 fold (171.9 ng.hour/mL, range 96.3-253.2) higher than those seen in a group of eighteen younger adults (101.4 ng.hour/mL, range 61.9-182.7) from another study. Elderly male subjects dosed for 10 days showed a mean increase, approximately 2.4 fold (193.8 ng.hour/mL, range 135.6-253.5 versus 83.2 ng.hour/mL, range 41.1-142.5 for younger males) while levels in elderly females increased were much less, to a modest extent, approximately 1.2 fold (143.8 ng.hour/mL, range 96.3-191.6 versus 83.2 ng.hour/mL, range 41.1-142.5 for younger females). In light of these findings, therapy with Cyclobenzaprine hydrochloride tablets, USP in the elderly should be initiated with a 5 mg dose and titrated slowly upward.

Hepatic Impairment
In a pharmacokinetic study in subjects with hepatic impairment (15 mild, 1 moderate per Child-Pugh score), both AUC and C\text{max} were approximately double the values seen in the healthy control group. Based on the findings, Cyclobenzaprine hydrochloride tablets, USP 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, USP, in subjects with moderate to severe impairment is not recommended.

No significant effect on plasma levels or bioavailability of Cyclobenzaprine hydrochloride tablets, USP or aspirin was noted when single or multiple doses of the two drugs were administered concomitantly. Concomitant administration of Cyclobenzaprine hydrochloride tablets, USP and naproxen or diflunisal was well tolerated with no reported unusual adverse effects. However, concomitant therapy of Cyclobenzaprine hydrochloride tablets, USP and naproxen was associated with more side effects than therapy with naproxen alone, primarily due to the nature of the dosing regimen. No well-controlled studies have been performed to indicate that Cyclobenzaprine hydrochloride tablets, USP enhance the clinical effect of aspirin or other analgesics, or that Cyclobenzaprine hydrochloride tablets, USP may enhance the effects of alcohol, barbiturates, and other CNS depressants.

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PRECAUTIONS
General
Because of its atropine-like action, Cyclobenzaprine hydrochloride tablets, USP 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.

Drug Interactions
Cyclobenzaprine hydrochloride tablets, USP interact with other CNS depressants, including those given concomitantly. These principles may apply in other clinical situations requiring the use of CNS depressants. Infusion of anesthetic agents may enhance the clinical effect of Cyclobenzaprine hydrochloride tablets, USP. There is evidence that concomitant use of CNS depressant medications increases the potential for adverse drug interactions and toxicity. Allergic sensitivity to one component of this product, concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation, hypertension or seizures, and deaths have occurred in patients receiving cyclobenzaprine hydrochloride tablets (see W AR N IN G S, below, and ADVE R SE  R E ACTION S).

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

CONTRAINDICATIONS
Hypersensitivity to any component of this product. Agmatism of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation, hypertension or seizures, and deaths have occurred in patients receiving cyclobenzaprine hydrochloride tablets (see W AR N IN G S, below, and ADVE R SE  R E ACTION S).

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TRANSIENTS
Triacylglycerol levels were observed to rise in patients taking cyclobenzaprine hydrochloride tablets, USP or with concomitant medications that increase triacylglycerol levels (e.g., corticosteroids, nonsteroidal anti-inflammatory drugs, and oral contraceptives).

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of Cyclobenzaprine hydrochloride tablets, USP was evaluated in two 2-year studies in male and female rats at oral dose levels of 50 and 150 mg/kg/day. There was no evidence of carcinogenic activity in these studies. There was no evidence of mutagenicity or clastogenicity in Cyclobenzaprine hydrochloride tablets, USP (see W AR N IN G S, below, and ADVE R SE  R E ACTION S).

Cyclobenzaprine hydrochloride tablets, USP, like other tricyclic antidepressants, may enhance the effects of alcohol, barbiturates, and other CNS depressants.

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Although rare, deaths may occur from overdosage with Cyclobenzaprine hydrochloride tablets. USP. 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.

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 administer oxygen. 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 overdose include any of the symptoms listed under ADVERSE REACTIONS.

MANAGEMENT

General
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