PRODUCT MONOGRAPH

AVA-CYCLOBENZAPRINE

Cyclobenzaprine Hydrochloride Tablets USP

10 mg

Skeletal Muscle Relaxant

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Cyclobenzprine Hydrochloride Tablets USP

10 mg

THERAPEUTIC CLASSIFICATION

Skeletal Muscle Relaxant

ACTIONS AND CLINICAL PHARMACOLOGY

Cyclobenzaprine hydrochloride relieves skeletal muscle spasm of local origin without interfering with muscle function. It is not effective in muscle spasm due to central nervous system disease.

Controlled clinical studies show that cyclobenzaprine hydrochloride improves the signs and symptoms of skeletal muscle spasm.

Cyclobenzaprine hydrochloride is well absorbed in man after oral administration, but there is a large intersubject variation in plasma levels. After oral or intravenous doses (10 mg) of ^{14}C-labelled cyclobenzaprine hydrochloride to human subjects, plasma levels of radioactivity were comparable. In addition, the excretion of radioactivity was similar after both routes (38 to 51 percent in the urine; 14 to 15 percent in the feces), suggesting that oral absorption is almost complete. The half-life varies from one to three days. No effect on plasma levels or bioavailability was noted in 14 human subjects, when cyclobenzaprine hydrochloride and multiple doses of acetylsalicylic acid was coadministered.

Cyclobenzaprine hydrochloride is extensively metabolized by man. In the study with ^{14}C-labelled drug, about 1 percent of the dose was excreted in the urine as unchanged cyclobenzaprine hydrochloride. The metabolites (probably glucuronides) were excreted as water soluble

conjugates. After oral or intravenous administration of 40 mg of unlabelled cyclobenzaprine hydrochloride to two subjects, only 0.2 to 1.5 percent of the dose was excreted as unchanged drug in the urine within 24 hours.

A single-dose (20 mg), double-blinded, randomized, two-way crossover bioavailability study was conducted in 16 healthy male volunteers to evaluate the relative bioavailability of Ava-Cyclobenzaprine 10 mg tablets manufactured by Apotex Inc. and Flexeril® 10 mg tablets manufactured by Frosst, Division of Merck Frosst Canada Inc. Fifteen subjects completed the study. The following mean (±SD) pharmacokinetic indices were found:

Parameter	AVA-CYCLOBENZAPRINE	Flexeril®
AUC_{0-T} (ng•hr/mL)	327 ± 177	342 ± 147
$AUC_{0-\infty}$ (ng•hr/mL)	377 ± 204	404 ± 174
C_{max} (ng/mL)	17.7 ± 7.64	18.1 ± 6.15
T_{max} (hr)	4.07 ± 1.49	4.47 ± 1.77
K_{el} (hr^{-1})	0.0388 ± 0.0157	0.0342 ± 0.0156
$t_{1/2}$ (hr)	21.6 ± 11.4	29.2 ± 27.2

INDICATIONS AND CLINICAL USE

AVA-CYCLOBENZAPRINE (cyclobenzaprine hydrochloride) is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions.

AVA-CYCLOBENZAPRINE should be used only for short periods (up to two to 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 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 the drug. Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation. Acute recovery phase of myocardial infarction, and patients with arrhythmias, heart block or conduction disturbances, congestive heart failure. Hyperthyroidism.

WARNINGS

AVA-CYCLOBENZAPRINE (cyclobenzaprine hydrochloride) is not recommended for periods longer than two or three weeks (see INDICATIONS AND CLINICAL USE).

AVA-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 more serious central nervous system reactions noted with the tricyclic antidepressants have occured (see WARNINGS below, and ADVERSE REACTIONS).

AVA-CYCLOBENZAPRINE may interact with monoamine oxidase (MAO) inhibitors. Hyperpyretic crises, severe convulsions, and death have occurred in patients receiving tricyclic antidepressants and MAO inhibitors.

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

AVA-CYCLOBENZAPRINE may enhance the effects of alcohol, barbiturates, and other CNS depressants.

PRECAUTIONS

AVA-CYCLOBENZAPRINE (cyclobenzaprine hydrochloride) may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Because of its atropine-like action, AVA-CYCLOBENZAPRINE 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.

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

Use in Pregnancy: The safe use of AVA-CYCLOBENZAPRINE in pregnant women has not been established. Therefore, it should not be administered to women of childbearing potential unless, in the opinion of the treating physician, the anticipated benefits outweigh the possible hazards to the fetus.

Use in Nursing Mothers: Because it is likely that cyclobenzaprine is excreted in milk, AVA-CYCLOBENZAPRINE should not be given to nursing mothers.

Use in Children: Safety and effectiveness of AVA-CYCLOBENZAPRINE in children below the age of 15 have not been established.

ADVERSE REACTIONS

The following adverse reactions have been reported with cyclobenzaprine hydrochloride tablets:

Most frequent: Drowsiness (39%), dry mouth (27%), dizziness (11%).

Less frequent: Increased heart rate (and several cases of tachycardia), weakness, fatigue, dyspepsia, nausea, paresthesia, unpleasant taste, blurred vision, and insomnia.

Rare: Sweating, myalgia, dyspnea, abdominal pain, constipation, coated tongue, tremors, dysarthria, euphoria, nervousness, disorientation, confusion, headache, urinary retention, decreased bladder tonus, ataxia, depressed mood, hallucinations, and allergic reaction including rash, urticaria, and edema of the face and tongue.

The listing which follows includes other adverse reactions which have been reported with tricyclic compounds, but not with cyclobenzaprine hydrochloride when used in short-term studies in muscle spasm of peripheral origin. Some of these reactions were noted, however, when cyclobenzaprine hydrochloride was studied for other indications, usually in higher dosage. Pharmacologic similarities among the tricyclic drugs require that each of the reactions be considered when cyclobenzaprine hydrochloride is administered.

Cardiovascular: Hypotension, hypertension, palpitation, myocardial infarction, arrhythmias, heart block, stroke.

CNS and Neuromuscular: Confusional states, disturbed concentration, delusions, excitement, anxiety, restlessness, nightmares, numbness and tingling of the extremities, peripheral neuropathy, incoordination, seizures, alteration in EEG patterns, extrapyramidal symptoms, tinnitus, syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Anticholinergic: Disturbance of accommodation, paralytic ileus, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue.

Hematologic: Bone marrow depression including agranulocytosis, leukopenia, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Epigastric distress, vomiting, anorexia, stomatitis, diarrhea, parotid swelling, black tongue. Rarely hepatitis (including altered liver function and jaundice).

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement and galactorrhea in the female. Increased or decreased libido, elevation and lowering of blood sugar levels.

Other: Weight gain or loss, urinary frequency, mydriasis, jaundice, alopecia.

Withdrawal Symptoms: Abrupt cessation of treatment after prolonged administration may produce nausea, headache and malaise. These are not indicative of addiction.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Manifestations: High doses may cause temporary confusion, disturbed concentration, transient visual hallucinations, agitation, hyperactive reflexes, muscle rigidity, vomiting, or hyperpyrexia, in addition to anything listed under ADVERSE REACTIONS. Based on the known pharmacologic actions of the drug, overdosage may cause drowsiness, hypothermia, tachycardia and other cardiac rhythm abnormalities such as bundle branch block, ECG evidence of impaired conduction, and congestive heart failure. Other manifestations may be dilated pupils, convulsions, severe hypotension, stupor, and coma.

Treatment: Treatment is symptomatic and supportive. Empty the stomach as quickly as possible by emesis, followed by gastric lavage. After gastric lavage, activated charcoal may be administered. Twenty to 30 g of the activated charcoal may be given after every four to six hours during the first 24 to 48 hours after ingestion. An ECG should be taken and close monitoring of cardiac function must be instituted if there is any evidence of dysrhythmia. Maintenance of an open airway, adequate fluid intake, and regulation of body temperature are necessary.

The slow intravenous administration of 1 to 3 mg of physostigmine salicylate is reported to reverse symptoms of poisoning by atropine and other drugs with anticholinergic activity. Physostigmine may be helpful in the treatment of cyclobenzaprine overdose. Because physostigmine is rapidly metabolized, its dosage should be repeated as often as required when life threatening signs such as arrhythmias, convulsions, and deep coma recur or persist.

Standard medical measures should be used to manage circulatory shock and metabolic acidosis. Cardiac arrhythmias may be treated with neostigmine, pyridostigmine, or propranolol. When signs of cardiac failure occur, the use of a short-acting digitalis preparation should be considered. Close monitoring of cardiac function for not less than five days is advisable.

Anticonvulsants may be given to control seizures.

Dialysis is probably of no value because of low plasma concentrations of the drug.

Since overdosage is often deliberate, patients may attempt suicide by other means during recovery phase. Deaths by deliberate or accidental overdosage have occurred with this class of drugs.

DOSAGE AND ADMINISTRATION

The usual dosage of AVA-CYCLOBENZAPRINE (cyclobenzaprine hydrochloride) is 10 mg three times a day, with range of 20 to 40 mg a day in divided doses. Dosage should not exceed 60 mg a day. Use of AVA-CYCLOBENZAPRINE is not indicated or recommended for periods longer than two or three weeks.

PHARMACEUTICAL INFORMATION

Drug Substance

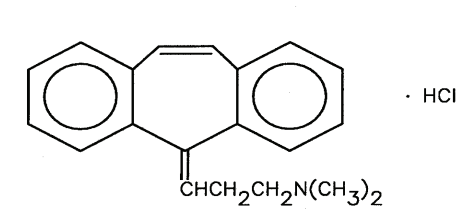
Proper/Common Name: Cyclobenzaprine hydrochloride

Chemical Name(s):

1) 1-Propanamine, 3-(5*H*-dibenzo-[*a,d*] cyclohepten-5-ylidene)-*N,N*-dimethyl-, hydrochloride

2.) *N,N*-Dimethyl-5H-dibenzo [*a,d*]cycloheptene-Δ^5, □-propylamine hydrochloride

Structural Formula:



Molecular Formula: $C_{20}H_{21}N \bullet HCl$

Molecular Weight: 311.85

Description: Cyclobenzaprine hydrochloride is a white to off-white, odourless, crystalline powder. It is freely soluble in water, alcohol, and methanol; sparingly soluble in isopropyl alcohol; slightly soluble in chloroform and methylene chloride; and practically insoluble in hydrocarbon solvents.

Cyclobenzaprine hydrochloride has a melting range between 215° and 219°, and a pKa of 8.47 at 25°C.

Composition

Each tablet contains 10 mg cyclobenzaprine hydrochloride as well as the following non-medicinal ingredients: colloidal silicon dioxide, lactose anhydrous, magnesium stearate, microcrystalline cellulose, starch, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, yellow ferric oxide and purified water.

Stability and Storage Recommendations

Preserve in well-closed containers at room temperature (15-30°C).

AVAILABILITY OF DOSAGE FORMS

AVA-CYCLOBENZAPRINE 10 mg tablets: each yellow, biconvex, film-coated, D-shaped tablet, engraved APO over 10 on one side, contains cyclobenzaprine hydrochloride 10 mg. Available in bottles of 100 tablets.

PHARMACOLOGY

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.

Cyclobenzaprine hydrochloride has skeletal muscle spasmolytic activity in a number of experimental situations, including tetanus toxin hyperactivity in rabbits, supraspinal rigidity and ischemic cord (spinal) rigidity in cats, and muscle spasm in mice.

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 and alpha motor systems.

Studies in several species of laboratory test animals showed that cyclobenzaprine hydrochloride also possesses psychotropic activity (evidenced by tetrabenazine and reserpine antagonism in mice and rats, potentiation of norepinephrine pressor response in anesthetized dogs, typical

ataraxic drug taming action in monkeys), significant anticholinergic and antihistaminic activity, weak adrenergic blocking and antiserotonin activity, and minor local anesthetic action. In dogs with Heidenhain gastric pouches, cyclobenzaprine did not stimulate gastric secretion.

Following either oral or intravenous doses of ^{14}C-labelled drug, peak plasma levels of radioactivity appeared in half an hour in rats, in two hours in dogs, and in two to four hours in monkeys. Radioactivity was excreted mainly in the feces in rats (59 percent of the dose vs 13 percent in the urine), mainly in the urine in dogs (55 percent vs 28 percent in the feces), and mostly in the urine in monkeys (81 percent vs 14 percent in the feces). Rats excreted 25 percent of an intravenous dose in the bile in six hours. Urinary radioactivity was present almost entirely as water-soluble conjugates, but some species differences were observed in preliminary extraction experiments. The excretion pattern was similar after oral and intravenous doses, suggesting that the drug is extensively absorbed. In rats, all tissues except red blood cells contained higher levels of radioactivity than did plasma two hours after an intravenous dose of labelled drug. Levels were particularly high in small intestine, lung, kidney, and liver. After 48 hours all levels had declined, but activity persisted in liver, kidney and red blood cells.

TOXICOLOGY

Acute Toxicity

Oral LD_{50} values were approximately 338 mg/kg in mice and 425 mg/kg in rats. Signs of drug effects were similar in both species and included ataxia, decreased respiratory rate, sedation, flaccid hind legs, loss of ear flick reflex, loss of righting reflex with swimming movements, and intermittent clonic convulsions. Deaths occurred 30 minutes to seven days following administration and was preceded by weight loss and lethargy. Dogs given single oral doses of 180 mg/kg or more by gavage developed ptyalism, emesis, tremors, convulsions, and increased

respiratory rate, and died within an hour. When the same dose was given in a capsule, dogs developed similar physical signs, followed by sedation, but recovered after three days, suggesting that the oral dosage form may influence the toxicity. The drug was more toxic to infant and weanling rats than to young adults.

Subacute and Chronic Toxicity: Signs of drug effect in subacute and chronic toxicity studies in rats, dogs, and monkey were primarily related to the pharmacologic activity of the compound.

Dose (mg/kg/day	Duration	Physical Signs	Postmortem Findings
RATS			
5 mg	56 weeks	Ptyalism	Low incidence of midzonal hepatocytic vacuolation with lipidosis
10 mg	67 weeks	Ptyalism, decreased activity, cromorhinorrhea, rales, frequent micturition, flaccidity, resistance to dosing, irritability	Midzonal hepatocytic vacuolation with lipidosis, enlarged hepatocytes, centrilobular necrosis
20 or 40 mg	67 weeks	Depressed body wt. Gain, increased mortality	Same as above, more frequent in males
60 mg	2 weeks	Decreased physical activity and growth rate	No postmorten examination
120 or 240 mg	2-8 doses	Severe wt. Loss, collapse, convulsions, death	No postmortem examination
DOGS			
2 mg	53 weeks	Minimal ptyalism, vomiting, dry nose, dry gums	No treatment-related changes
4 or 8 mg	53 weeks	Same as above but more pronounced	Small foci of gastric mucosal necrosis, hemorrhage or inflammation in 3/16 dogs
10 mg	28 weeks	Slight weight loss, slightly prominent P & T waves in ECG recordings	Small focus of unilateral renal papillary edema in 1 of 4 dogs
60 or 120 mg	28 weeks	Tachycardia, sedation, ataxia, convulsions, death	No postmortem examination

MONKEYS			
2.5 mg	26 weeks	Non observed	No treatment-related changes
5 or 10 mg	26 weeks	Sleepiness (rare)	No treatment-related changes
20 mg	26 weeks	General debilitation (1/6 monkeys), sleepiness	Chronic pancreatitis, cholecystitis, cholangitis, focal peritonitis (1/6 monkeys)

Teratogenicity: Studies in mice and rabbits did not reveal any evidence of embryo lethality or teratogenicity at oral doses of 5, 10, or 20 mg/kg/day. In rats, doses of 5 mg or 10 mg/kg/day did not adversely affect the reproduction performance or fertility of males or females, or the growth and survival of their offspring. At doses of 20 mg/kg/day there was decrease in litter size, decrease in size and survival of the pups, and reduced weight gain by mothers.

Carcinogenicity: Cyclobenzaprine hydrochloride did not have any effect on the onset, incidence or distribution of neoplasms when given in oral doses of 2, 5, and 10 mg/kg/day to mice for 81 weeks or to rats for 105 weeks.

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