PRODUCT MONOGRAPH

[Pr]CYCLOBENZAPRINE

(Cyclobenzaprine Hydrochloride Tablets USP)

10 mg

Skeletal Muscle Relaxant

SORRES PHARMA INC.
6111 Royalmount Ave.,
Montreal, Quebec
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Date of Preparation:
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Control #: 137552

PRODUCT MONOGRAPH

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(Cyclobenzaprine Hydrochloride Tablets USP)

10 mg

THERAPEUTIC CLASSIFICATION

Skeletal - Muscle Relaxant

ACTION AND CLINICAL PHARMACOLOGY

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

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

Cyclobenzaprine hydrochloride is well absorbed in man. 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 in man. In the study with ^{14}C-labelled drug, about 4 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 20 mg (2 tablets) dose, comparative two-way cross-over bioavailability study was performed using normal human volunteers on Cyclobenzaprine 10mg tablets versus FLEXRIL 10 mg tablets (Merck Frosst, Canada Inc.).

The summary of the results are as follows:

Summary Table of the Comparative Bioavailability Data of
Cyclobenzaprine 10 mg Tablets (Sorres Pharma Inc., Canada Lot# 640895) versus
Flexeril 10 mg Tablets (Merck-Frosst Canada Inc., Lot# T 0887)
20 mg (2 x 10 mg tablets) oral administration in the fasting state

Measured Data

	Geometric Mean Arithmetic Mean (C.V.%)		**Ratio of Means (%) (90% Confidence Limits)**
Parameter	**Test**	**Reference**	
AUC_{0-72h} (ng●h/mL)	231.03 247.45 (40.6)	233.80 247.09 (35.1)	98.8 (93.0 - 105.0)
AUC_T (ng●h/mL)	239.80 261.40 (46.3)	241.29 259.44 (41.2)	99.4 (93.2 - 106.0)
AUC_∞ (ng●h/mL)	267.12 287.02 (42.3)	269.08 286.87 (38.5)	99.3 (93.7 - 105.1)
C_{max} (ng/mL)	12.88 13.61 (37.0)	12.96 13.56 (29.9)	99.4 (92.2 - 107.1)
T_{max} (h)	4.04 (0.81)	4.04 (0.78)	---
$T1/2_{el}$ (h)	23.66 (6.26)	24.71 (5.97)	---

For the T_{max} and $T1/2_{el}$ parameters these are the arithmetic means with standard deviation in parenthesis.

INDICATIONS AND CLINICAL USE

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

CYCLOBENZAPRINE 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 has not been found effective in the treatment of spasticity associated with cerebral palsy.

CONTRAINDICATIONS

Hypersensitivity to the drug CYCLOBENZAPRINE. Concomitant use of monoamine oxidase inhibitors or within 14 days after their discontinuation. Acute recovery phase of myocardial infarction, and patients with arhythmias, heart block or conduction disturbances, or congestive heart failure. Hyperthyroidism.

WARNINGS

Use of CYCLOBENZAPRINE for periods longer than two or three weeks is not recommended (see INDICATIONS).

Cyclobenzaprine hydrochloride 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).

Cyclobenzaprine hydrochloride may interact with monoamine oxidase (MAO) inhibitors. Hyperpyretic crises, severe convulsions, and deaths 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.

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

PRECAUTIONS

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, 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 cyclobenzaprine hydrochloride 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 hydrochloride is excreted in milk, it should not be given to nursing mothers.

Use in Children: Safety and effectiveness of cyclobenzaprine hydrochloride in children below the age of 15 have not been established.

ADVERSE REACTIONS

The following adverse reactions have been reported with cyclobenzaprine hydrochloride:

Most frequent: Drowsiness (40%), dry mouth (28%), dizziness (11%).

Less frequent: Increased heart rate (and several cases or 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-terms 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.

Anticholinerpiic: 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, diturbed 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 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 one to three 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 ofter deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdosage have occurred with this class of drugs.

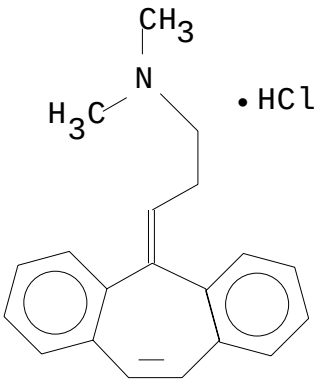
DOSAGE AND ADMINISTRATION

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

PHARMACEUTICAL INFORMATION

Chemical Name: 3-(5H-Dibenzo[a,d] cyclohepten-5-ylidene)-N,N-dimethyl-1-propanamine hydrochloride.
N,N-dimethyl-5H dibenzo[a,d]cyclohepten-Δ 5,γ-propylamine hydrochloride.

Structural Formula:



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

Molecular Weight: 311.9

Description: A white or off-white odourless crystalline powder. M.p. 215˚ to 219˚ with a range of not more than 2˚C. Freely soluble in water, alcohol, and methyl alcohol; sparingly soluble in isopropyl alcohol; slightly soluble in chloroform and methylene chloride; practically insoluble in hydrocarbous.

Composition:
Nonmedicinal Ingredients:
Each 10 mg tablet contains: Colloidal Silicon Dioxide, Hydroxypropyl Cellulose, Lactose, Magnesium Stearate, Pregelatinized Starch, Synthetic Yellow Iron Oxide, Purified Water.

Stability and Storage Recommendations:

Store at room temperature between 15˚ - 30˚C in tightly sealed containers. Protect from heat.

AVAILABILITY OF DOSAGE FORMS

CYCLOBENZAPRINE (cyclobenzaprine hydrochloride) 10 mg Tablets, are butterscotch yellow, film-coated D-shape tablets debossed "pms" on one side and "111" on the other side. They are supplied in bottles of 100 and 500 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 (μ) and alpha (α) 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.

Pharmacokenitics

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-solube 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 250-338 mg/kg in mice and 425 mg/kg in rats. Intravenous LD_{50} values were 35 - 36 mg/kg in mice. Signs of drug effects were similar in both species and included ataxia, decreased respiratory rate, sedation, flaccid hind legs, loss of the ear flick reflex, loss of righting reflex with swimming movements, and intermittent clonic convulsions. Death 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 monkeys were primarily related to the pharmacologic activity of the compound.

Dose mg/kg/day	Duration	Physical Signs	Postmortem Findings
Rats 5 mg	56 wks	ptyalism	low incidence of midzonal hepatocytic vacuolation with lipidosis.
10 mg	67 wks	ptyalism, decreased activity, chromorhinorrhea, rales, frequent micturition, flaccidity, resistance to dosing, irritability	midzonal hepatocytic vacuolation with lipidosis, enlarged hepatocytes, centrilobular necrosis
20 or 40 mg	67 wks	depressed body weight gain, increased mortality	same as above. More frequent in males
60 mg	2 wks	decreased physical activity, decreased growth rate	no postmortem examinations
120 mg or 240 mg	2 to 8 doses	severe weight loss, collapse, convulsions, death	no postmortem examinations
Dogs 2 mg	53 wks	minimal ptyalism, vomiting, dry nose, dry gums	no treatment related changes
4 or 8 mg	53 wks	same as above but more pronounced	small foci of gastric mucosal necrosis, hemorrhage, or inflammation in three of 16 dogs
10 mg	28 wks	slight weight loss, slightly prominint P and T waves in ECC recordings	small focus of unilateral renal papillary edema in one of four dogs
60 or 120 mg	6 to 8 doses	tachycardia, sedation, ataxia, convulsions, death	no postmortem examinations
Monkeys 2.5 mg	26 wks	non observed	no treatment related changes
5 or 10 mg	26 wks	sleepiness (rare	no treatment related changes
20 mg	26 wks	general debilitation (1 or 6 monkeys), sleepiness	chronic pancreatitis, cholecystitis, cholangitis, focal peritonitis (1 of 6 monkeys)

Teratogenicity

Studies in mice and rabbits did not reveal any evidence of embryo lethality or teratogenicity at oral doses of five, ten, or 20 mg/kg/day. In rats, doses of five mg or ten mg/kg/day did not adversely affect the reproductive performance on 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 of mothers.

Carcinogenicity

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

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