PRODUCT MONOGRAPH

RIVA-CYCLOBENZAPRINE

(Cyclobenzaprine Hydrochloride tablet USP)

10 mg Tablets

Skeletal Muscle Relaxant

Laboratoire Riva Inc.
660 Boul. Industriel
Blainville, Quebec, Canada
J7C 3V4

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(Cyclobenzaprine Hydrochloride tablet USP)

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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 not effective in muscle spasm caused by central nervous system disease.

Cyclobenzaprine hydrochloride has been shown to improve the signs and symptoms of skeletal muscle spasm in controlled clinical studies.

In man, cyclobenzaprine hydrochloride is well absorbed. Plasma levels of radioactivity were comparable following the administration of oral or intravenous doses (10 mg) of ^{14}C-labelled cyclobenzaprine hydrochloride to human subjects. Similar excretion of radioactivity was also found after both routes (38 to 51% in the urine and 14 to 15% in the faeces) which suggested almost complete absorption orally. The half-life varies from 1 to 3 days. In 14 human subjects, coadministration of cyclobenzaprine hydrochloride and multiple doses of acetylsalicylic acid had no effect on plasma levels or bioavailability.

In man, the metabolism of cyclobenzaprine hydrochloride is extensive. Approximately 1.8% of the dose was excreted in the urine as unchanged cyclobenzaprine hydrochloride in the study with ^{14}C-labelled drug. The metabolites, probably glucuronides, were excreted as water-soluble conjugates. In 2 subjects, only 0.2 to 1.5% of the dose was excreted within 24 hours as unchanged drug in the urine following the administration of oral or intravenous doses of 40 mg of unlabelled cyclobenzaprine hydrochloride.

A comparative bioavailability study was performed between RIVA-CYCLOBENZAPRINE 10 mg Tablets and FLEXERIL® 10 mg Tablets in 30 normal volunteers. The pharmacokinetic data are tabulated below:

	Geometric Mean Arithmetic Mean (C.V.)		
	RIVA-CYCLOBENZAPRINE (2 x 10 mg)	FLEXERIL® (2 x 10 mg)	Percentage of FLEXERIL®
AUC_T (ng•h/mL)	281.5 303.2 (38)	295.9 315.7 (38)	95
AUC_I (ng•h/mL)	340.4 366.0 (37)	354.2 373.3 (34)	96
C_{max} (ng/mL)	14.214.9 14.7 (27)	95 15.5 (28)	
T_{max}* (h)	4.57 (0.86)	4.33 (0.92)	
$T_{1/2}$* (h)	30.4 (13.3)	30.4 (12.8)	

*These are the arithmetic means (standard deviation).

INDICATIONS AND CLINICAL USE

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

Adequate evidence for the prolonged use of RIVA-CYCLOBENZAPRINE 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, the drug should be used only for short periods of up to 2 or 3 weeks.

Cyclobenzaprine hydrochloride has not been proven effective in treating spasticity associated with cerebral or spinal cord disease, or in children with cerebral palsy.

CONTRAINDICATIONS

RIVA-CYCLOBENZAPRINE (cyclobenzaprine hydrochloride) is contraindicated in patients who have exhibited hypersensitivity to the drug, in patients with arrhythmias, heart block or conduction disturbances, congestive heart failure or during the acute recovery phase of myocardial infarction, in patients with hyperthyroidism and during the concomitant use of monoamine oxidase inhibitors (or within 14 days after their discontinuation).

WARNINGS

RIVA-CYCLOBENZAPRINE (cyclobenzaprine hydrochloride) should not be used for periods longer than 2 or 3 weeks (see INDICATIONS).

Cyclobenzaprine hydrochloride is closely related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. Some of the more serious reactions of the central nervous system that have been noted with the tricyclic antidepressants have occurred with cyclobenzaprine hydrochloride in short term studies for indications other than muscle spasm related to acute musculoskeletal conditions (and usually at somewhat higher than recommended doses for skeletal muscle spasm) (see WARNINGS below, and ADVERSE REACTIONS).

Interactions may occur between RIVA-CYCLOBENZAPRINE and monoamine oxidase (MAO) inhibitors. In patients receiving tricyclic antidepressants and MAO inhibitors, hyperpyretic crises, severe convulsions and death have occurred.

Arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke have been produced by tricyclic antidepressants.

The effects of alcohol, barbiturates and other CNS depressants may be enhanced by RIVA-CYCLOBENZAPRINE.

PRECAUTIONS

Mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle may be impaired by RIVA-CYCLOBENZAPRINE (cyclobenzaprine hydrochloride).

Caution should be exercised when using RIVA-CYCLOBENZAPRINE in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure and in patients taking anticholinergic medication due to the drugs atropine-like action.

The antihypertensive action of guanethidine and similarly acting compounds may be blocked by tricyclic antidepressants.

Use in Pregnancy:

The safety of RIVA-CYCLOBENZAPRINE administration in pregnant women has yet to be established. Therefore, it should not be used in women who are, or may become pregnant, unless, in the opinion of a physician, the potential risk to the foetus is outweighed by the expected benefits for the mother.

Use in Lactation:

RIVA-CYCLOBENZAPRINE is not recommended for use in nursing mothers since it is likely that the drug is excreted in milk.

Use in Children:

Safety and effectiveness of RIVA-CYCLOBENZAPRINE have not been established in children below the age of 15.

ADVERSE REACTIONS

The following adverse reactions have been reported with cyclobenzaprine hydrochloride:

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, insomnia.

Rare: Sweating, myalgia, dyspnea, abdominal pain, constipation, tongue discoloration, tremors, dysarthria, nervousness, disorientation, confusion, headache, urinary retention, ataxia, depressed mood, hallucinations, allergic reaction (including rash, urticaria and oedema of the face and tongue).

The following adverse reactions have not been reported with cyclobenzaprine hydrochloride when used for muscle spasm of peripheral origin in short term studies but have been reported with tricyclic compounds. However, when cyclobenzaprine hydrochloride was studied for other indications, and usually at a higher dosage, some of these reactions were noted. Each of the reactions should be considered when cyclobenzaprine hydrochloride is administered due to pharmacological similarities among the tricyclic drugs.

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 the urinary tract.

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

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

Gastrointestinal: Epigastric distress, vomiting, anorexia, stomatitis, diarrhoea, 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: Nausea, headache and malaise may be caused by the abrupt cessation of treatment after prolonged administration; however, these are not indicative of addiction.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Manifestations:

Temporary confusion, disturbed concentration, transient visual hallucinations, agitation, hyperactive reflexes, muscle rigidity, vomiting, hyperpyrexia and anything listed under ADVERSE REACTIONS may be caused by high doses of cyclobenzaprine hydrochloride. Drowsiness, hypothermia, tachycardia and other cardiac rhythm abnormalities such as bundle branch block, ECG evidence of impaired conduction and congestive heart failure may be caused by overdose, on the basis of the known pharmacological actions of the drug. Dilated pupils, convulsions, severe hypotension, stupor and coma may be other manifestations.

Treatment:

Treatment is symptomatic and supportive. The stomach should be emptied as quickly as possible by emesis, followed by gastric lavage. Activated charcoal may be administered following gastric lavage. If there is any evidence of dysrhythmia, an ECG should be taken and cardiac function must be carefully monitored. An open airway must be maintained and it is necessary to regulate body temperature and provide adequate fluid intake.

It may be helpful to use physostigmine for treating cyclobenzaprine overdose. When life-threatening signs such as arrhythmias, convulsions and deep coma recur or persist, the dosage of physostigmine should be repeated as often as required due to its rapid metabolism.

Circulatory shock and metabolic acidosis should be managed by standard medical measures. Phenytoin, lidocaine or propranolol may be used to treat cardiac

arrhythmias. A short acting digitalis preparation should be considered for use when signs of cardiac failure occur. It is advisable to closely monitor cardiac function.

Seizures may be controlled by anticonvulsants.

Due to the low plasma concentrations of cyclobenzaprine hydrochloride, dialysis is probably of no value.

During the recovery phase, patients may attempt suicide by other means, since overdose is often deliberate.

DOSAGE AND ADMINISTRATION

The usual dosage of RIVA-CYCLOBENZAPRINE (cyclobenzaprine hydrochloride) is 10 mg 3 times a day, with a range of 20 to 40 mg/day in divided doses. Dosage should not exceed 60 mg/day. Use of RIVA-CYCLOBENZAPRINE is not indicated or recommended for periods longer than 2 or 3 weeks.

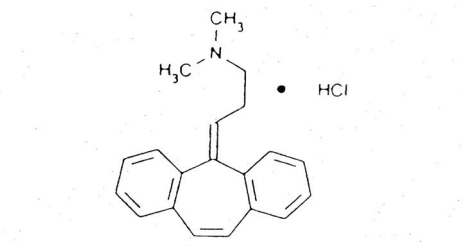
PHARMACEUTICAL INFORMATION

Trade Name: RIVA-CYCLOBENZAPRINE

Proper Name: Cyclobenzaprine Hydrochloride

Chemical Name: 1–propanamine,3–(5H–dibenzo[a,d]cyclohepten–5–ylidine)–N,N–dimethyl–,hydrochloride

Structural Formula:



Molecular Formula: $C_{20}H_{21}N \cdot HCl$ Molecular Weight: 311.85

Description: Cyclobenzaprine is a centrally acting skeletal muscle relaxant that is structurally and pharmacologically related to the tricyclic antidepressants. It occurs as a white to off–white, odourless, crystalline powder and is freely soluble in water, alcohol and methanol; sparingly soluble in isopropanol; slightly soluble in chloroform and methylene chloride and insoluble in hydrocarbons. The drug has a pK_a of 8.47.

STORAGE AND STABILITY:

RIVA-CYCLOBENZAPRINE tablets should be stored in well–closed containers at a temperature less than 30°C, preferably at 15 to 30°C. Unit dose strips should be stored between 15–25°C and protected from high humidity.

DOSAGE FORMS, PACKAGING AND COMPOSITION

RIVA-CYCLOBENZAPRINE 10 mg:Yellow, film-coated, biconvex, "D" shaped tablet, engraved “R 10” on one siudeand plain on the other.Available in bottles of 100 and 500 tablets.

Composition :

RIVA-CYCLOBENZAPRINE contains cyclobenzaprine HCL equivalent to 10 mg of cyclobenzaprine per tablet. Non-medicinal ingredients: Corn starch, Hydroxypropyl cellulose, Hypromellose, Lactose, Magnesium stearate, Polyethylene glycol, Polysorbate, Silicone dioxide, colloidal, Titanium dioxide and Yellow iron oxide.

PHARMACOLOGY

The effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, norepinephrine potentiation, potent peripheral and central anticholinergic effects and sedation have been found to be similar in pharmacological studies in animals. A slight to moderate increase in heart rate was produced by cyclobenzaprine in animals.

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

Cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle as indicated by animal studies. Such studies have demonstrated that cyclobenzaprine acts mainly within the central nervous system at brain stem rather than spinal cord levels; although, its action on the latter may contribute to its overall skeletal muscle relaxant activity. Evidence has suggested that reduced tonic somatic motor activity, influencing both gamma ($\sum\gamma$) and alpha ($\sum\alpha$) motor systems, is the net effect of cyclobenzaprine.

Cyclobenzaprine hydrochloride has also been shown to possess psychotropic activity (evidenced by tetrabenazine and reserpine antagonism in mice and rats, potentiation of norepinephrine pressor response in dogs and typical ataraxic drug taming action in monkeys), significant anticholinergic and antihistaminic activity, weak adrenergic blocking and antiserotonin activity and minor local anaesthetic action in studies in several species of laboratory test animals.

Plasma levels of radioactivity reached a maximum in 1/2 hour in rats, 2 hours in dogs and 2 to 4 hours in monkeys after either oral or intravenous doses of ^{14}C-labelled drug. Excretion of radioactivity occurred primarily in the faeces in rats (59% of the dose vs. 13% in the urine), primarily in the urine in dogs (55% vs. 29% in the faeces) and primarily in the urine in monkeys (75% vs. 9% in the faeces). Twenty-five percent of an intravenous dose was excreted in the bile of rats in 6 hours. Although preliminary extraction experiments demonstrated some species differences, radioactivity in the urine was present almost entirely as water-soluble conjugates. Extensive absorption was suggested by the similar excretion pattern following oral and intravenous doses. Two hours following an intravenous dose of labelled drug in rats, all tissues contained higher levels of radioactivity than did plasma, except red blood cells. Particularly high levels were observed in small intestine, lung, kidney and liver. All levels had declined after 48 hours, 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. Both species exhibited similar signs of drug effects including ataxia, decreased respiratory rate, sedation, flaccid hind legs, loss of the ear flick reflex, loss of the righting reflex

with swimming movements and intermittent clonic convulsions. Weight loss and lethargy preceded death which occurred 30 minutes to 7 days following administration. The drug was more toxic to infant and weaning rats than to young adults. Ptyalism, emesis, tremors, convulsions and increased respiratory rate developed and death occurred within 1 hour following single oral doses of 180 mg/kg or more by gavage in dogs.

Chronic Toxicity:

Signs of drug effect were mainly related to the pharmacological activity of the compound in chronic toxicity studies in rats, dogs and monkeys.

RATS

Dose (mg/kg/day)	Duration	Physical Signs	Post-mortem Findings
5 mg	56 weeks	Ptyalism.	Low incidence of midzonal hepatocytic vacuolation with lipidosis.
10 mg	67 weeks	Ptyalism, decreased activity, chromorhinorrhea, frequent micturition, flaccidity, resistance to dosing, irritability.	Midzonal hepatocytic vacuolation with lipidosis, enlarged hepatocytes, centrilobular necrosis.
20 or 40 mg	67 weeks	Depressed body weight gain, increased mortality.	Same as above. More frequent in males.
60 mg	2 weeks	Decreased physical activity, decreased growth rate.	No post-mortem examinations.
120 or 240 mg	2 to 8 doses	Severe weight loss, collapse, convulsions, death.	No post-mortem examinations.

DOGS

Dose (mg/kg/day)	Duration	Physical Signs	Post-mortem Findings
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, haemorrhage or inflammation in 3 of 16 dogs.
10 mg	28 weeks	Slight weight loss, slightly prominent P and T waves in ECG recordings.	Small focus of unilateral renal papillary oedema in 1 of 4 dogs.
60 or 120 mg	6 to 8 doses	Tachycardia, sedation, ataxia, convulsions,	No post-mortem examinations.

death.

MONKEYS

Dose (mg/kg/day)	Duration	Physical Signs	Post-mortem Findings
2.5 mg	26 weeks	None observed.	No treatment related changes.
5 or 10 mg	26 weeks	Sleepiness (rare).	No treatment related changes.
20 mg	26 weeks	General debilitation (1 of 6 monkeys), sleepiness.	Chronic pancreatitis, cholecystitis, cholangitis, focal peritonitis (1 of 6 monkeys).

Carcinogenicity:

Following oral doses of 2, 5 and 10 mg/kg/day to mice for 81 weeks or to rats for 105 weeks, the onset, incidence and distribution of neoplasms was not affected by cyclobenzaprine hydrochloride.

Reproduction and Teratology:

No evidence of embryo lethality or teratogenicity was revealed following oral doses of 5, 10 or 20 mg/kg/day in studies in mice and rabbits. The reproductive performance and fertility of males and females, and the growth and survival of their offspring were not adversely affected by doses of 5 or 10 mg/kg/day in rats. Litter size, size and survival of the pups, and weight gain of the mothers were decreased by doses of 20 mg/kg/day.

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