PRODUCT MONOGRAPH

Q-CYCLOBENZAPRINE
(Cyclobenzaprine Hydrochloride Tablets, USP)

10 mg Tablets

Skeletal Muscle Relaxant

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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 ineffective in muscle spasm due to disease of the central nervous system.

In controlled clinical studies, cyclobenzaprine hydrochloride has been shown to improve the signs and symptoms of skeletal muscle spasm.

In man, cyclobenzaprine hydrochloride is well absorbed. Plasma levels of radioactivity were comparable after oral or intravenous doses (10 mg) of ^{14}C-labelled cyclobenzaprine hydrochloride to human subjects. The excretion of radioactivity was found to be similar for both routes (38 to 51 percent in the urine; 14 to 15 percent in the feces), which would suggest that oral absorption is almost complete. The half-life varies from 1 to 3 days. In 14 human subjects, no effect on plasma levels or bioavailability was noted when cyclobenzaprine hydrochloride and multiple doses of acetylsalicylic acid were coadministered.

In man, the metabolism of cyclobenzaprine hydrochloride is extensive. In the study with ^{14}C-labelled drug, approximately 4 percent of the dose was excreted as unchanged cyclobenzaprine hydrochloride in the urine. The metabolites, probably glucuronides, were excreted as water-soluble conjugates. Following oral or intravenous administration of 40 mg of unlabelled cyclobenzaprine hydrochloride to 2 subjects, only 0.2 to 1.5 percent of the dose was excreted in the urine as unchanged drug within 24 hours.

A comparative bioavailability study was performed between Q-CYCLOBENZAPRINE (cyclobenzaprine hydrochloride) TABLETS 10 mg and the 10 mg strength of the Canadian reference product. Twenty-two healthy male volunteers participated in the study. The pharmacokinetic data for both formulations is tabulated below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA
CYCLOBENZAPRINE HYDROCHLORIDE
(2 x 10 mg Tablets)
From measured data

	GEOMETRIC MEAN ARITHMETIC MEAN (CV%)		
	Q-CYCLOBENZAPRINE	*Flexeril®**	% RATIO OF GEOMETRIC MEANS
AUC_T (ng.h/mL)	275.3 301.8 (46.9)	273.6 295.8 (43.9)	102 ---
AUC_I (ng.h/mL)	329.3 361.0 (48.6)	331.8 362.0 (51.1)	99 ---
C_{MAX} (ng/mL)	15.4 16.6 (39.0)	15.4 16.3 (34.9)	100 ---
T_{MAX} (h)	--- 4.8 (23.7)	--- 4.6 (28.2)	--- ---
$T_{½}$ (h)	--- 25.1 (29.1)	--- 26.3 (37.7)	--- ---

The T_{MAX} and $T_{½}$ parameters are expressed as the arithmetic means (CV%) only.
***** Flexeril® Tablets 10 mg, Merck Frosst Canada Inc., were purchased in Canada.

INDICATIONS AND CLINICAL USE

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

Q-CYCLOBENZAPRINE should be used for short periods of time only (up to 2 or 3 weeks), due to the fact that adequate evidence of effectiveness for more prolonged use is unavailable, and because muscle spasm associated with acute, painful musculoskeletal conditions is usually of short duration and specific therapy for longer periods is seldom warranted.

Cyclobenzaprine hydrochloride has been found to be ineffective in children with cerebral palsy, or in the treatment of spasticity associated with cerebral or spinal cord disease.

CONTRAINDICATIONS

Q-CYCLOBENZAPRINE(cyclobenzaprine hydrochloride) is contraindicated in patients who exhibit 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

Use of cyclobenzaprine hydrochloride in not recommended for periods longer than 2 or 3 weeks (see INDICATIONS).

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

Monoamine oxidase (MAO) inhibitors may interact with Q-CYCLOBENZAPRINE. Hyperpyretic crises, severe convulsions, and death have occurred in patients administered

tricyclic antidepressants and MAO inhibitors.

It has been reported that arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke have been produced by tricyclic antidepressants.

Enhancement of the effects of alcohol, barbiturates, and other CNS depressants may be produced by Q-CYCLOBENZAPRINE.

PRECAUTIONS

Impairment of mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle may occur as a result of the administration of Q-CYCLOBENZAPRINE (cyclobenzaprine hydrochloride).

Due to its atropine-like action, Q-CYCLOBENZAPRINE should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intra ocular pressure, and in patients taking anticholinergic medications.

Blockage of the antihypertensive action of guanethidine and similarly acting compounds may result from the administration of tricyclic antidepressants.

Use in Pregnancy: The safety of Q-CYCLOBENZAPRINE use in pregnant women has not yet been established. Therefore, it should not be given to women of childbearing potential unless the treating physician believes the anticipated benefits outweigh the possible hazards to the fetus.

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

Use in Children: The safety and effectiveness of Q-CYCLOBENZAPRINE in children below the age of 15 has not yet been established.

ADVERSE REACTIONS

The following adverse reactions have been reported with the use of cyclobenzaprine hydrochloride:

Most frequent: Drowsiness (40%), dry mouth (28%), 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, 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 following list includes other adverse reactions reported with tricyclic compounds, but not with cyclobenzaprine hydrochloride when it is used in short-term studies for muscle spasm of peripheral origin. However, some of these reactions were noted when cyclobenzaprine hydrochloride was studied, (usually at a greater dosage) for other indications. Due to the

pharmacologic similarities among the tricyclic drugs, each of the reactions should 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 the 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 reduction of blood sugar levels.

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

Withdrawal symptoms: Nausea, headache, and malaise may be produced by the abrupt cessation of treatment after prolonged use. However, these are not indicative of addiction.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Manifestations: In addition to the conditions listed under ADVERSE REACTIONS, high doses may result in temporary confusion, disturbed concentration, transient visual hallucinations, agitation, hyperactive reflexes, muscle rigidity, vomiting, or hyperpyrexia. On the basis of 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 the dilation of pupils, convulsions, severe hypotension, stupor, and coma.

Treatment: Treatment of overdosage is symptomatic and supportive. The stomach must be emptied as quickly as possible by emesis, followed by gastric lavage and the administration of activated charcoal. Twenty to 30 g of the activated charcoal may be administered every 4 to 6 hours during the first 24 to 48 hours after ingestion. If there is any evidence of dysrhythmia, an ECG should be taken and close monitoring of cardiac function must be instituted. It is necessary

to maintain an open airway, adequate intake of fluids, and regulation of body temperature.

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

Standard medical measures should be implemented for the management of circulatory shock and metabolic acidosis. Neostigmine, pyridostigmine, or propranolol may be used to treat cardiac arrhythmias. The use of a short-acting digitalis preparation should be considered when signs of cardiac failure occur. Close monitoring of cardiac function is advised for not less than 5 days.

Anticonvulsants may be administered to control seizures.
As a result of low plasma concentrations of the drug, dialysis is probably of no value.

Since overdosage is frequently deliberate, patients may attempt suicide by other means during the recovery phase. With this class of drugs, death by deliberate or accidental overdosage has occurred.

DOSAGE AND ADMINISTRATION

The usual dosage of Q-CYCLOBENZAPRINE (cyclobenzaprine hydrochloride) is 10 mg 3 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 Q-CYCLOBENZAPRINE is not indicated or recommended for periods longer than 2 or 3 weeks.

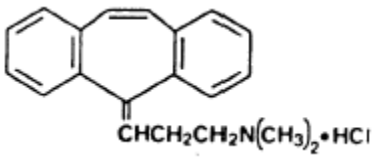
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Cyclobenzaprine Hydrochloride

Chemical Name: 1-Propanamide, 3-(5*H*-dibenzo [*a*,*d*] cyclohepten-5-ylidene)-*N*,*N*-dimethyl-, hydrochloride

Structural Formula:



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

Molecular Weight: 311.85

Physical Form: Cyclobenzaprine is structurally and pharmacologically related to the tricyclic antidepressants. It is a white or off-white, odourless, crystalline powder.

Solubility: Freely soluble in water, alcohol and methanol; sparingly soluble in isopropanol; slightly soluble in chloroform and methylene chloride; practically insoluble in hydrocarbons.

pKa and pH values: The pKa for the ionization at the amine group is reported as 8.47. The pH of a 1% solution in water is between 4.05-6.05.

Melting point: Between 215^{o}C to 219^{o}C.

COMPOSITION

The non-medicinal ingredients include lactose, magnesium stearate, pregelatinized starch, hydroxypropyl methylcellulose, polydextrose, polyethylene glycol, synthetic yellow iron oxide, titanium dioxide and triacetin.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature between 15^{o}C and 30^{o}C.

AVAILABILITY OF DOSAGE FORMS

Q-CYCLOBENZAPRINE (cyclobenzaprine hydrochloride) is available as yellow, shield-shaped, film-coated tablets with "CZ10" on one side and "G" on the other, containing 10 mg of cyclobenzaprine hydrochloride. They are available in bottles of 100 and 500.

PHARMACOLOGY

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 has been shown from pharmacological studies in animals. Cyclobenzaprine resulted in a slight to moderate increase in heart rate in animals.

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

Animal studies have indicated that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. Rather, these studies have shown that cyclobenzaprine acts primarily within the central nervous system at the brain stem, as opposed to spinal cord levels, although its action on the latter may contribute to its overall skeletal muscle relaxant activity. The evidence suggests that the net effect of cyclobenzaprine is a lowering of tonic somatic motor activity, which influences both gamma (γ) and alpha (α) motor systems.

From studies in several species of laboratory test animals, cyclobenzaprine hydrochloride has been shown to possess psychotropic activity (as 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. Cyclobenzaprine did not stimulate gastric secretion in dogs with Heidenhain gastric pouches.

Peak plasma levels of radioactivity appeared in half an hour in rats, in 2 hours in dogs, and in 2 to 4 hours in monkeys, following either oral or intravenous doses of ^{14}C-labelled drug. Radioactivity was excreted mainly in rats feces (59 percent of the dose vs 13 percent in the urine), mainly in dog urine (55 percent vs 28 percent in the feces), and mostly in monkey urine (81 percent vs 14 percent in the feces). Twenty five percent of an intravenous dose was excreted by rats in the bile in 6 hours. Although some species differences were observed in preliminary extraction experiments, urinary radioactivity was present almost primarily as water-soluble conjugates. The similarity of excretion pattern after oral and intravenous doses suggests extensive absorption of the drug. Two hours after an intravenous dose of labelled drug in rats, all tissues except the red blood cells contained higher levels of radioactivity than did plasma. Particularly high levels were found in the small intestine, lung, kidney, and liver. After 48 hours, all levels had decreased, however activity persisted in the 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 similarities in the signs of drug effects which 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. Preceding death, which occurred 30 minutes to 7 days following administration, weight loss and lethargy were evident. Dogs which were administered single oral doses of 180 mg/kg or more by gavage developed ptyalism, emesis, tremors, convulsions, and increased respiratory rate, and death occurred within an hour. When the same dose was administered in a capsule, dogs developed similar physical signs, followed by sedation, but recovery occurred after 3 days, suggesting that the oral dosage form may influence the toxicity. The drug was found to be 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 were primarily related to the pharmacologic activity of the compound, as evidenced from studies in rats, dogs, and monkeys.

RATS

Dose (mg/kg/day)	**Duration**	**Physical Signs**	**Postmortem Findings**
5 mg	56 wks	Ptyalism	Low incidence of midzonal hepatocytic vacuolation with lipidosis.
10 mg	67 wks	Ptyalism, decreased hepatocytic activity, chromorhinorrhea, rales frequent micturition, flaccidity, resistance to dosing, irritability.	Midzonal 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 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 Findings	Postmortem
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 3 of 16 dogs.
10 mg	28 wks	Slight weight loss, slight prominent P and T waves in ECG recordings.	Small focus of unilateral renal papillary edema in 1 of 4 dogs.
60 or 120 mg	6 to 8 doses	Tachycardia, sedation, ataxia, convulsions, death.	No postmortem examinations.

MONKEYS

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

Teratogenicity:

At oral doses of 5, 10, or 20 mg/kg/day, studies in mice and rabbits did not reveal any evidence of embryo lethality or teratogenicity. Doses of 5 mg or 10 mg/kg/day in rats did not adversely affect the reproductive performance and fertility of males and females, or the growth and survival of their offspring. Doses of 20 mg/kg/day resulted in decreased litter size, a decrease in size and survival of the pups, and a reduction in the weight gain of mothers.

Carcinogenicity:

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

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