

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

<sup>Pr</sup>**AURO-CYCLOBENZAPRINE**

cyclobenzaprine hydrochloride tablets

Tablets, 10 mg, Oral

USP

Skeletal Muscle Relaxant

**Auro Pharma Inc.**  
3700 Steeles Avenue West, Suite # 402  
Woodbridge, Ontario, L4L 8K8  
CANADA

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## RECENT MAJOR LABEL CHANGES

N/A

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Sections or subsections that are not applicable at the time of authorization are not listed.

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## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **1 INDICATIONS**

AURO-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 hydrochloride has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease, or in children with cerebral palsy.

#### **1.1 Pediatrics**

**Pediatrics (< 15 years of age):** The safety and effectiveness of cyclobenzaprine hydrochloride in children below 15 years of age have not been established.

#### **1.2 Geriatrics**

**Geriatrics (>65 years of age):** Evidence from clinical studies suggests that use in the geriatric population is associated with differences in safety or effectiveness (see [4.2 Recommended Dose and Dosage Adjustment](#), [7.1.4 Geriatrics](#) and [10.3 Pharmacokinetics](#)).

### **2 CONTRAINDICATIONS**

AURO-CYCLOBENZAPRINE is contraindicated:

- In patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).
- In patients with hyperthyroidism
- In the acute recovery phase of myocardial infarction,
- In patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure.
- With concomitant use of monoamine oxidase (MAO) inhibitors, or within 14 days after their discontinuation (see [9 DRUG INTERACTIONS](#)).

### **4 DOSAGE AND ADMINISTRATION**

#### 4.1 Dosing Considerations

Cyclobenzaprine hydrochloride is not recommended for periods longer than two or three weeks (see [1 INDICATIONS](#)).

#### 4.2 Recommended Dose and Dosage Adjustment

The usual dosage of 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.

#### Hepatic Insufficiency

The plasma concentration of cyclobenzaprine is generally higher in patients with hepatic impairment (see [10.3 Pharmacokinetics](#)). Patients with hepatic impairment are generally more susceptible to drugs with potentially sedating effects, including cyclobenzaprine.

Cyclobenzaprine is not recommended in those with moderate to severe impairment.

Cyclobenzaprine should be used with caution and reduced dosing (e.g. less frequent) in patients with mild hepatic impairment.

#### Geriatrics (> 65 years of age)

The plasma concentration of cyclobenzaprine is increased in the elderly (see [10.3 Pharmacokinetics](#)). In elderly patients cyclobenzaprine should be initiated with a reduced dose (e.g. reduced dose frequency) and titrated slowly upward (see [7.1.4 Geriatrics](#); [10.3 Pharmacokinetics](#)).

### 5 OVERDOSAGE

Signs and symptoms of toxicity may develop rapidly after cyclobenzaprine overdose; hospital monitoring is required as soon as possible. Monitor patients for an extended period after ingestion as delayed absorption may occur due to the anticholinergic effects of cyclobenzaprine.

**Manifestations:** Based on the known pharmacologic actions of the drug, overdosage may cause drowsiness, agitation, tachycardia and other cardiac rhythm abnormalities such as bundle branch block, ECG evidence of impaired conduction, and congestive heart failure. Other manifestations of high doses may be dilated pupils, severe hypotension, temporary confusion, disturbed concentration, transient visual hallucinations, stupor, coma, hyperactive reflexes, muscle rigidity, convulsions, vomiting, or hyperpyrexia, in addition to anything listed under [8.1 Adverse Reaction Overview](#).

Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of cyclobenzaprine toxicity.

**Treatment:** There are no specific antidotes. Treatment is symptomatic and supportive. Obtain

an ECG, and initiate cardiac monitoring and observation for signs of hypotension, CNS or respiratory depression, or seizures.

Maintain an open airway, adequate fluid intake, and regulation of body temperature. Standard medical measures should be used to manage circulatory shock and metabolic acidosis.

*Gastrointestinal decontamination / Elimination:* If early in therapy, empty the stomach as quickly as possible. The suitability of emesis, gastric lavage and activated charcoal for gastric decontamination depends upon the time since ingestion and upon the patient being asymptomatic, conscious and cooperative. These processes should be considered early in therapy, before absorption is complete. Absorption may be delayed due to the anticholinergic effects of cyclobenzaprine. Gastric decontamination should not delay hospitalization.

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

*Cardiovascular:* An ECG should be taken and cardiac function closely monitored if there is any evidence of dysrhythmia. Close monitoring of cardiac function for not less than five days is advisable.

Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate therapy/hyperventilation should be instituted for patients with dysrhythmias and/or QRS widening. Many antiarrhythmics are contraindicated; consult a poison control centre for current approaches to refractory dysrhythmia.

*CNS:* In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Anticonvulsants (e.g. benzodiazepines) may be given to control seizures. Consult a poison control centre if considering the use of physostigmine to treat life-threatening symptoms of cyclobenzaprine overdose that have been unresponsive to other therapies.

*Psychiatric Follow-up:* Since overdosage is often 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.

For management of a suspected drug overdose, contact your regional poison control center
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## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
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Oral	Tablets , 10 mg	Croscarmellose Sodium USNF, Hypromellose USP, Iron oxide yellow USNF, Lactose Monohydrate USNF, Magnesium Stearate USNF, Macrogol USNF , Pregelatinized Starch USNF & titanium dioxide USP
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**Description:** Tablets are butterscotch yellow, biconvex, 5-sided D-shaped film-coated tablets, debossed with 'D' and '32' on one side and plain on other side

**Packaging:** HDPE bottles of 100's, 500's & 1000's count

## 7 WARNINGS AND PRECAUTIONS

### General

#### Tricyclic Antidepressant-like Effects

Cyclobenzaprine is structurally related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke (see [2 CONTRAINDICATIONS](#)). Some of the more serious central nervous system (CNS) reactions noted with the tricyclic antidepressants have occurred in short-term studies of cyclobenzaprine for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm. (see also [8.1 Adverse Reaction Overview](#)).

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.

#### Carcinogenesis and Mutagenesis

See [16 NON-CLINICAL TOXICOLOGY](#).

#### Driving and Operating Machinery

Cyclobenzaprine may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. These effects may be enhanced in the presence of alcohol, barbiturates, and other CNS depressants (see [9.4 Drug-Drug Interactions](#)).

#### Neurologic

##### Serotonin Toxicity:

Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with cyclobenzaprine when used with other drugs (See [9 DRUG INTERACTIONS](#)).

Serotonin toxicity is characterized by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature  $>38^{\circ}\text{C}$  and ocular clonus or inducible clonus.

The concomitant use of cyclobenzaprine with MAO inhibitors is contraindicated. If concomitant treatment with cyclobenzaprine and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see [2 CONTRAINDICATIONS AND 9 DRUG INTERACTIONS](#)). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Patients should be cautioned about the risk of serotonin toxicity with the concomitant use of cyclobenzaprine and other serotonergic drugs. Patients should be advised of the signs and symptoms of serotonin toxicity, and be instructed to seek medical care immediately if they experience these symptoms.

### **Ophthalmologic**

**Angle-Closure Glaucoma:** Due to their atropine-like action, tricyclic antidepressants and other antidepressants can cause mydriasis which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Caution should be used when cyclobenzaprine is prescribed for patients with untreated narrow angles. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients should be advised to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

## **7.1 Special Populations**

**7.1.1 Pregnant Women:** The safety of cyclobenzaprine administration in pregnant women has yet to be established. A clinical report showed that cyclobenzaprine use during late pregnancy should be considered a potential cause of early ductal closure. Cyclobenzaprine should not be used in women who are, or may become pregnant, unless the possible risk to the fetus is outweighed by the expected benefits for the mother.

**7.1.2 Breast-feeding:** Because it is likely that cyclobenzaprine is excreted in milk, cyclobenzaprine hydrochloride should not be given to nursing mothers.

**7.1.3 Pediatrics (< 15 years of age):** The safety and effectiveness of cyclobenzaprine in children below 15 years of age have not been established.

**7.1.4 Geriatrics (> 65 years of age):** The plasma concentration of cyclobenzaprine is increased



in the elderly (see 10.3 Pharmacokinetics). The elderly may also be more at risk for CNS adverse events such as hallucinations and confusion, cardiac events resulting in falls or other sequelae, drug-drug and drug-disease interactions. For these reasons, in the elderly, cyclobenzaprine should be used only if clearly needed. (See [4.2 Recommended Dose and Dosage Adjustment](#)).

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

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, convulsions and abnormal liver function (hepatitis, jaundice and cholestasis).

**Rare:** Serotonin toxicity, 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.

## 9 DRUG INTERACTIONS

### 9.1 Serious Drug Interactions

#### Serious Drug Interactions

- MAO inhibitors such as phenelzine, tranylcypromine, the antibiotic linezolid and the thiazine dye methylthioninium chloride (methylene blue) See [9.4 Drug-Drug Interactions](#)

### 9.4 Drug-Drug Interactions

*The drugs listed here are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).*

#### Serotonergic drugs

Post-marketing cases of serotonin toxicity have been reported during combined use of cyclobenzaprine and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. (See [7 WARNINGS AND PRECAUTIONS, Neurologic](#))

#### MAO inhibitors

The concomitant use of cyclobenzaprine with MAO inhibitors, or within 14 days after their discontinuation, is contraindicated (see [2 CONTRAINDICATIONS](#)). Hyperpyretic crisis, severe seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.

#### Tramadol

Based on its structural similarity to tricyclic antidepressants, cyclobenzaprine hydrochloride may enhance the seizure risk in patients taking tramadol.

#### Guanethidine

Based on its structural similarity to tricyclic antidepressants, cyclobenzaprine hydrochloride

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

#### CNS depressants

Based on its structural similarity to tricyclic antidepressants, cyclobenzaprine hydrochloride may enhance the effects of alcohol, barbiturates, and other CNS depressants, including the level of psychomotor impairment (See [7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery](#)).

#### Acetylsalicylic acid

In 14 human subjects, the co-administration of cyclobenzaprine hydrochloride and multiple doses of acetylsalicylic acid had no effect on cyclobenzaprine plasma levels or bioavailability.

## **10 CLINICAL PHARMACOLOGY**

### **10.1 Mechanism of Action**

Cyclobenzaprine relieves skeletal muscle spasm of local origin without interfering with muscle function. The mechanism by which cyclobenzaprine exerts its therapeutic effects is unknown.

### **10.2 Pharmacodynamics**

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

Pharmacological studies in animals demonstrated 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.

### **10.3 Pharmacokinetics**

Cyclobenzaprine hydrochloride is well absorbed in man after oral administration, but there is a large inter subject variation in plasma levels. After oral or intravenous doses (10 mg) of <sup>14</sup>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 - 51 % in the urine; 14 - 15 % in the feces), suggesting that oral absorption is almost complete. The half-life varies from one to three days.

Cyclobenzaprine hydrochloride is extensively metabolized in man. In the study with <sup>14</sup>C-labelled drug, about 1 % 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 % of the dose was excreted as unchanged drug in the urine within 24 hours.

Cytochromes P-450 3A4, 1A2, and, to a lesser extent, 2D6, mediate N-demethylation, one of the oxidative pathways for cyclobenzaprine. Cyclobenzaprine is eliminated quite slowly, with an effective half-life of 18 hours (range 8-37 hours; n=18); plasma clearance is 0.7 L/min.

The plasma concentration of cyclobenzaprine is generally higher in the elderly and in patients with hepatic impairment.

### **Special Populations and Conditions**

**Geriatrics:** In a pharmacokinetic study in elderly individuals ( $\geq 65$  years of age), mean (n=10) steady-state cyclobenzaprine AUC values were approximately 1.7 fold (171.0 ng•hr/mL, range 96.1-255.3) higher than those seen in a group of eighteen younger adults (101.4 ng•hr/mL, range 36.1-182.9) from another study. Elderly male subjects had the highest observed mean increase, approximately 2.4 fold (198.3 ng•hr/mL, range 155.6-255.3 versus 83.2 ng•hr/mL, range 41.1-142.5 for younger males) while levels in elderly females were increased to a much lesser extent, approximately 1.2 fold (143.8 ng•hr/mL, range 96.1-196.3 versus 115.9 ng•hr/mL, range 36.1-182.9 for younger females).

In light of these findings, cyclobenzaprine therapy in the elderly should be initiated with lower (e.g. less frequent) dosing and titrated slowly upward.

**Hepatic Insufficiency:** In a pharmacokinetic study of sixteen subjects with hepatic impairment (15 mild, 1 moderate per Child-Pugh score), both AUC and  $C_{max}$  were approximately double the values seen in the healthy control group. Based on the findings, cyclobenzaprine should be used with caution in subjects with mild hepatic impairment; reduced (e.g. less frequent) daily doses should be considered. Due to the lack of data in subjects with more severe hepatic insufficiency, the use of cyclobenzaprine in subjects with moderate to severe impairment is not recommended.

### **11 STORAGE, STABILITY AND DISPOSAL**

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

### **12 SPECIAL HANDLING INSTRUCTIONS**

Not applicable

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

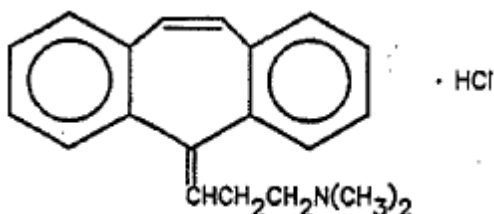
**Proper Name:** cyclobenzaprine hydrochloride

**Chemical Names:** 1) 1-Propanamine, 3-5H-dibenzo-[a,d] cyclohepten- 5- ylidene)-N,N-dimethyl-, hydrochloride  
2) N,N-Dimethyl-5H-dibenzo [a,d]cycloheptene-Δ5, γ-propylamine hydrochloride

**Molecular Formula:** C<sub>20</sub>H<sub>21</sub>N • HCl

**Molecular Weight:** 311.85

#### Structural Formula:



#### Physicochemical properties:

**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; practically insoluble in hydrocarbon solvents.

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

### 14 CLINICAL TRIALS

#### 14.2 Comparative Bioavailability Studies

##### Comparative Bioavailability data for Cyclobenzaprine hydrochloride 10 mg Tablets

An Open Label, Randomized, Two Treatment, Two Sequence, Two Period, Cross-Over, Single-

Dose Comparative Oral Bioavailability Study of AURO-CYCLOBENZAPRINE Tablets 10 mg (Test) of Aurobindo Pharma Ltd., India and APO-CYCLOBENZAPRINE Tablets 10 mg (Reference) of Apotex Inc., Canada in 48 Healthy, Adult, Male, Human Subjects under fasting conditions.

<b>Cyclobenzaprine Hydrochloride Tablets (1 x 10 mg) From measured data</b>				
<b>Geometric Mean Arithmetic Mean (CV %)</b>				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
<b>AUC<sub>0-72</sub> (hr.ng/mL)</b>	156.18 166.35 (34.96)	155.65 170.22 (40.99)	100.34	93.94–107.18
<b>AUC<sub>i</sub> (hr.ng/mL)</b>	192.39 212.54 (45.62)	187.31 211.04 (49.95)	102.71	95.62-110.33
<b>C<sub>max</sub> (ng/mL)</b>	7.32 7.80 (36.88)	7.48 8.12 (39.58)	97.87	90.24-106.13
<b>T<sub>max</sub>‡ (h)</b>	4.00 (2.00-7.50)	4.50 (2.00-8.00)		
<b>T<sub>½</sub>§ (h)</b>	32.36 (43.78)	31.17 (53.44)		

\*AURO-CYCLOBENZAPRINE 10 mg Tablets, manufactured by Aurobindo Pharma Ltd, India for Auro Pharma Inc.

†APO-CYCLOBENZAPRINE 10 mg Tablets, Apotex Canada Inc. were purchased in Canada

‡ Expressed as the Median (Range) instead of Arithmetic Mean (%CV)

§ Expressed as arithmetic mean (%CV) only

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

### Detailed pharmacology

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 <sup>14</sup>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 % of the dose vs 13 % in the urine), mainly in the urine in dogs (55 % vs 29 % in the feces), and mostly in the urine in monkeys (75% vs 9% in the feces). Rats excreted 25 % 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**

### **General Toxicology**

**Acute Toxicity:** Oral LD<sub>50</sub> values were approximately 338 mg/kg in mice and 425 mg/kg in rats (27 and 68 times the MRHD on mg/m<sup>2</sup> basis, respectively). 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 (97 times the MRHD on mg/m<sup>2</sup> basis) or more by gavage developed ptialism, 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. In a 67-week study with rats that received cyclobenzaprine at oral doses of 10 to 40 mg/kg/day

(1.6 to 6.5 times the MRHD on mg/m<sup>2</sup> basis), there were findings in the liver consisting of midzonal vacuolation with lipidosis for males and midzonal and centrilobular hepatocytic enlargement for females. In addition, there were findings of centrilobular coagulative necrosis. In the higher dose groups, these microscopic changes were seen after 26 weeks and even earlier in rats that died prior to 26 weeks; at lower doses, these changes were not seen until after 26 weeks.

In a 26-week study with Cynomolgus monkeys that received cyclobenzaprine at oral of doses of 2.5, 5, 10, or 20 mg/kg/day, one monkey at 20 mg/kg/day (6.4 times the MRHD on mg/m<sup>2</sup> basis) was euthanized in week 17. Morbidity for this animal was attributed to findings of chronic pancreatitis, cholecystitis, cholangitis, and focal liver necrosis.

Dose (mg/kg/day)*	Duration	Physical Signs	Postmortem Findings
<b>RATS</b>			
5 mg	56 weeks	ptyalism	low incidence of midzonal hepatocytic vacuolation with lipidosis.
10 mg	67 weeks	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 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 postmortem examinations
120 or 240 mg	2 - 8 doses	severe wt. loss, collapse, convulsions, death	no postmortem examinations
<b>DOGS</b>			
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 doses	tachycardia, sedation, ataxia, convulsions, death	no postmortem examination
<b>MONKEYS</b>			
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 (1/6 monkeys), sleepiness	chronic pancreatitis, cholecystitis, cholangitis, focal peritonitis (1/6 monkeys)

\* Based on a Maximum Recommended Human Dose of 60 mg/day (1.0 mg/kg/day) , on a



mg/m<sup>2</sup> basis:

- 10 mg/kg/day in mice is 0.8 times, and 20 mg/kg/day is 1.6 times the MRHD;
- 10 mg/kg/day in rats is 1.6 times, and 40 mg/kg/day is 6.4 times the MRHD;
- 10 mg/kg/day in dogs is 5.4 times, and 120 mg/kg/day is 65 times the MRHD;
- 10 mg/kg/day in monkeys and rabbits is 3.2 times, and 20 mg/kg/d is 6.4 times the MRHD.

### **Carcinogenicity**

Cyclobenzaprine hydrochloride did not have any effect on the onset, incidence or distribution of neoplasms when given in oral doses up to 10 mg/kg/day to mice for 81 weeks or to rats for 105 weeks (1 and 1.6 times the MRHD on a mg/m<sup>2</sup> basis, respectively).

### **Reproductive and Developmental Toxicology**

Studies in mice and rabbits did not reveal any evidence of embryo lethality or teratogenicity at oral doses up to 20 mg/kg/day. (respectively, 1.6 and 6.4 times the MRHD on a mg/m<sup>2</sup> basis)

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 (3.2 times the MRHD on a mg/m<sup>2</sup> basis) there was decrease in litter size, decrease in size and survival of the pups, and reduced weight gain of mothers.

## **17 SUPPORTING PRODUCT MONOGRAPHS**

1 <sup>Pr</sup>Teva-Cyclobenzaprine (Tablets, 10 mg) Submission Control: 250699, Product Monograph, Teva Canada Limited. Aug 26, 2021

2 <sup>Pr</sup>Flexeril (tablet, 10 mg), Product Monograph, Frosst Division of Merck Frosst Canada Inc. (MAR 08, 1988)

## **PATIENT MEDICATION INFORMATION**

### **READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

#### **AURO-CYCLOBENZAPRINE**

##### **Cyclobenzaprine hydrochloride tablets**

Read this carefully before you start taking AURO-CYCLOBENZAPRINE and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about AURO-CYCLOBENZAPRINE.

##### **What is AURO-CYCLOBENZAPRINE used for?**

AURO-CYCLOBENZAPRINE is used in adults and children (age 15 and older) to treat muscle spasm due to acute, painful musculoskeletal conditions. AURO-CYCLOBENZAPRINE is for use in combination with rest and physical therapy.

##### **How does AURO-CYCLOBENZAPRINE work?**

AURO-CYCLOBENZAPRINE relieves skeletal muscle spasm without interfering with muscle function. The way that AURO-CYCLOBENZAPRINE works is not known.

##### **What are the ingredients in AURO-CYCLOBENZAPRINE?**

Medicinal ingredients: Cyclobenzaprine hydrochloride.

Non-medicinal ingredients: Croscarmellose Sodium USNF, Hypromellose USP, Iron oxide yellow USNF, Lactose Monohydrate USNF, Magnesium Stearate USNF, Macrogol USNF, Pregelatinized Starch USNF & titanium dioxide USP.

##### **AURO-CYCLOBENZAPRINE comes in the following dosage forms:**

Tablets; 10 mg

##### **Do not use AURO-CYCLOBENZAPRINE if:**

- you are allergic to cyclobenzaprine hydrochloride or to any other ingredient in AURO-CYCLOBENZAPRINE.
- you have an overactive thyroid (hyperthyroidism).
- you recently had a heart attack.
- you have heart problems or heart failure .
- you have any problems with your heart rhythm.
- you are using a type of medication called a monoamine oxidase (MAO) inhibitor, or have taken them in the past 14 days. Ask your healthcare professional if you are unsure.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AURO-CYCLOBENZAPRINE. Talk about any health conditions or problems you may have, including if you:**

- have a history of eye problems including glaucoma
- have liver problems
- have trouble emptying your bladder (urinary retention)
- are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed.

**Other warnings you should know about:**

**Driving and using machines:** Do not drive, operate machinery, or do other dangerous activities until you know how AURO-CYCLOBENZAPRINE affects you.

**Serotonin Toxicity:** if you take AURO-CYCLOBENZAPRINE with other drugs that act on a chemical in the brain called serotonin, there is a risk that you may develop a rare but potentially life-threatening condition called Serotonin Toxicity. If you experience any of the following symptoms while taking AURO-CYCLOBENZAPRINE and another drug, get immediate medical help:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness and coma.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with AURO-CYCLOBENZAPRINE:**

#### **Serious Drug Interactions**

**Do not take AURO-CYCLOBENZAPRINE if you are taking or have recently taken (in the last 14 days) any of the following drugs as you may have serious side effects:**

- MAO Inhibitors such as phenelzine, tranylcypromine, linezolid, methylene blue
- alcohol, barbiturates and other medications that cause sedation or depress your central nervous system
- tricyclic antidepressants such as amitriptyline, doxepin, imipramine, nortriptyline
- medicines to treat depression, mood, anxiety, psychotic or thought disorders
- a pain medicine called tramadol or meperidine
- medicines that prevent nerve impulses (anticholinergic medicines)
- a medicine to help quit smoking called bupropion

- a blood pressure medicine called verapamil

**How to take AURO-CYCLOBENZAPRINE:**

- AURO-CYCLOBENZAPRINE is for short term use (no longer than 2 or 3 weeks)
- Take exactly as directed by your healthcare professional

**Usual dose:**

The usual dose is 1 tablet (10 mg) three times a day; but dosing can range from 2 to 4 tablets a day in divided doses. The maximum dose is 6 tablets (60 mg) a day.

**Overdose:**

Signs of an overdose may include:

- temporary confusion, disturbed concentration, hallucinations, agitation;
- overactive reflexes, stiff muscles;
- fast heartbeat, severe low blood pressure;
- high fever or hypothermia;
- vomiting;
- drowsiness, dilated pupils, convulsions, stupor, and coma.

If you think you, or a person you are caring for, have taken too much AURO-CYCLOBENZAPRINE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

Talk to your healthcare professional if you miss a dose.

**What are possible side effects from using AURO-CYCLOBENZAPRINE?**

These are not all the possible side effects you may have when taking AURO-CYCLOBENZAPRINE. If you experience any side effects not listed here, tell your healthcare professional.

- drowsiness
- dry mouth
- dizziness
- fatigue
- constipation
- nausea
- upset stomach

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>COMMON</b>			
<b>Tachycardia</b> (abnormally fast heartbeat): dizziness, light headedness, shortness of breath, racing heart			√
<b>RARE</b>			
<b>Allergic Reaction:</b> difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat.			√
<b>Acute Angle-closure Glaucoma:</b> blurred vision, halos around lights, eye pain and redness, nausea and vomiting, severe headache			√
<b>Serotonin Toxicity:</b> agitation, hallucinations, confusion, or other changes in mental status; coordination problems, stiff muscles, uncontrolled muscle spasms, or muscle twitching (overactive reflexes); restlessness, shivering, racing or fast heartbeat, high or low blood pressure, sweating or fever, nausea, vomiting, or diarrhea			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

### Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/healthcanada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice*

**Storage:**

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

Keep out of reach and sight of children.

**If you want more information about AURO-CYCLOBENZAPRINE:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this document by visiting the Health Canada website :  
<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's Website  
<http://www.auropharma.ca>, or by calling 1-855-648-6681.

This leaflet was prepared by Auro pharma Inc.

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