PRODUCT MONOGRAPH

[Pr]AG-Cyclobenzaprine
Cyclobenzaprine Hydrochloride Tablets, USP
10 mg

Skeletal Muscle Relaxant

ANGITA PHARMA INC.
1310 rue Nobel
Boucherville, Québec
J4B 5H3

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-Medicinal Ingredients
Oral	10 mg Tablets	Colloidal Silicon Dioxide, Hydroxypropyl Cellulose, Lactose monohydrate, Magnesium Stearate, partially pregelatinized maize Starch, titanium dioxide, polyethylene glycol, iron oxide yellow, carnauba wax, iron oxide red, hypromellose and FD&C Yellow #6 Aluminum Lake.

INDICATIONS AND CLINICAL USE

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

AG-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.

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 DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics, Elderly).

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

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

- Concomitant use of monoamine oxidase (MAO) inhibitors, or within 14 days after their discontinuation (see DRUG INTERACTIONS).

- Acute recovery phase of myocardial infarction, and patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure.

- Hyperthyroidism

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 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 ADVERSE REACTIONS).

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 TOXICOLOGY – Carcinogenicity.

Neurologic

Serotonin Syndrome
The development of a potentially life-threatening serotonin syndrome has been reported with cyclobenzaprine when used in combination with other drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. Serotonin syndrome symptoms may include mental status changes (e.g., confusion, agitation, hallucinations), autonomic instability (e.g., diaphoresis, tachycardia, labile blood pressure, hyperthermia), neuromuscular

abnormalities (e.g., tremor, ataxia, hyperreflexia, clonus, muscle rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Treatment with cyclobenzaprine and any concomitant serotonergic agents should be discontinued immediately if the above reactions occur and supportive symptomatic treatment should be initiated. If concomitant treatment with cyclobenzaprine and other serotonergic drugs is clinically warranted, careful observation is advised, particularly during treatment initiation or dosage increases. The concomitant use of cyclobenzaprine with MAO inhibitors is contraindicated (see CONTRAINDICATIONS).

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of cyclobenzaprine and other serotonergic drugs. Patients should be advised of the signs and symptoms of serotonin syndrome, 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.

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

Cyclobenzaprine, especially when used with alcohol or other CNS depressants, may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Special Populations

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.

Nursing Women
Because it is likely that cyclobenzaprine is excreted in milk, cyclobenzaprine hydrochloride should not be given to nursing mothers.

Pediatrics (< 18 years of age)
The safety and effectiveness of cyclobenzaprine in children below 15 years of age have not been

established.

Geriatrics (> 65 years of age)
The plasma concentration of cyclobenzaprine is increased in the elderly (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Elderly). 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. In such patients cyclobenzaprine should be initiated with a reduced dose (e.g. reduced dose frequency) and titrated slowly upward. (See DOSAGE AND ADMINISTRATION - Special Population, and ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics, Elderly).

Patients with Impaired Hepatic Function
The plasma concentration of cyclobenzaprine is generally higher in patients with hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). These patients are generally more susceptible to drugs with potentially sedating effects, including cyclobenzaprine. Cyclobenzaprine should be used with caution in patients with mild hepatic impairment and is not recommended in those with moderate to severe impairment (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

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

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

Less frequent: Increased heart rate (and several cases or tachycardia), weakness, fatigue, dyspepsia, nausea, paresthesia, unpleasant taste, blurred vision, and insomnia, convulsions and abnormal liver function (hepatitis, jaundice and cholestasis).

Rare: Serotonin syndrome, 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.

DRUG INTERACTIONS

Serious Drug Interactions

- Cyclobenzaprine may have life-threatening interactions with MAO inhibitors (see also CONTRAINDICATIONS).
- Postmarketing cases of serotonin syndrome have been reported during combined use of cyclobenzaprine and other serotonergic drugs (see also WARNINGS AND PRECAUTIONS).

Drug-Drug Interactions

Postmarketing cases of serotonin syndrome have been reported during combined use of cyclobenzaprine and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. (See WARNINGS AND PRECAUTIONS)

Cyclobenzaprine should not be used concomitantly with MAO inhibitors or within 14 days after their discontinuation (see CONTRAINDICATIONS). Hyperpyretic crisis, severe seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic

antidepressants) concomitantly with MAO inhibitor drugs.

Based on its structural similarity to tricyclic antidepressants, cyclobenzaprine hydrochloride may enhance the effects of alcohol, barbiturates, and other CNS depressants, may enhance the seizure risk in patients taking tramadol, or may block the antihypertensive action of guanethidine and similarly acting compounds.

Drug-Lifestyle Interactions

Cyclobenzaprine, especially when used with alcohol or other CNS depressants, may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

- Reduced (e.g. less frequent) dosing should be considered for patients who are elderly (>65 years of age) or have mild hepatic impairment (see WARNINGS AND PRECAUTIONS - Special Populations, and ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics – Special Populations and Conditions).

Recommended Dose
The usual dosage of AG-Cyclobenzaprine (cyclobenzaprine hydrochloride) 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.

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 ADVERSE REACTIONS.

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 Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

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

Mechanism of Action

Cyclobenzaprine relieves skeletal muscle spasm of local origin without interfering with muscle function. Cyclobenzaprine has not been shown to be effective in muscle spasm due to central nervous system disease.

Pharmacodynamics

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.

Pharmacokinetics

Cyclobenzaprine hydrochloride is well absorbed in man after oral administration, but there is a large intersubject variation in plasma levels. After oral or intravenous doses (10 mg) of 14C-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. 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.

Cyclobenzaprine hydrochloride is extensively metabolized in man. In the study with 14C-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 (≥65yrs old), 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 41.1142.5 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 Cmax 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.

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition
Each 10 mg tablet contains: Colloidal Silicon Dioxide, Hydroxypropyl Cellulose, Lactose monohydrate, Magnesium Stearate, Partially pregelatinized maize Starch, titanium dioxide, polyethylene glycol, iron oxide yellow, carnauba wax, iron oxide red, Hypromellose and FD&C Yellow #6 Aluminum Lake.

AG-Cyclobenzaprine (cyclobenzaprine hydrochloride) 10 mg Tablets, are butterscotch yellow, film-coated D-shape tablet debossed "10" on one side and "C" on the other side.

Packaging
They are supplied in bottles of 100 and 500 tablets.

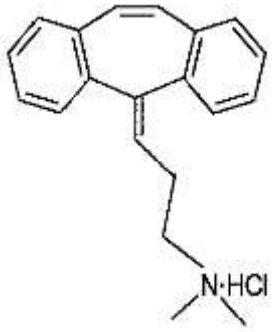
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

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: $C_{20}H_{21}N$•HCl

Molecular Weight: 311.85 g/mol

Physicochemical Properties:

Description: A white to off-white crystalline powder.

Melting Point: 217±3ºC.

Solubility: Freely soluble in water, methanol and ethanol; sparingly soluble in isopropyl alcohol; slightly soluble in chloroform and Dichloromethane; insoluble in hydrocarbons.

CLINICAL TRIALS

Comparative Bioavailability Study

A randomized, single-dose, blinded, standard 2-way crossover comparative bioavailability study was conducted under fasting conditions on healthy male volunteers (N=28). The rate and extent of absorption of cyclobenzaprine were measured following a single oral dose (1x 10 mg) of Cyclobenzaprine Hydrochloride 10 mg Tablet and pms-Cyclobenzaprine ® (cyclobenzaprine hydrochloride) 10 mg Tablet (Pharmascience Inc., Canada). The results from measured data in 27 subjects are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Cyclobenzaprine (1 x 10 mg cyclobenzaprine hydrochloride) From measured data Geometric mean Arithmetic Mean (CV%)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval 90%**
AUC_{0-72} (ng*hr/mL)	168.72 181.25 (37.17)	171.66 185.27 (39.45)	98.28	91.55 - 105.52
AUC_I (ng*hr/mL)	198.03 215.39 (41.68)	204.26 225.30 (46.54)	96.95	90.18 - 104.23
C_{max} (ng/mL)	7.77 8.39 (38.88)	7.78 8.44 (40.69)	99.91	92.39 - 108.04
T_{max} § (h)	4.50 (3.50-7.00)	4.50 (3.00-8.02)		
$T_{½}$ € (h)	27.58 (30.04)	27.30 (28.72)		

*Cyclobenzaprine hydrochloride 10 mg Tablet.
†pms-CYCLOBENZAPRINE® (cyclobenzaprine hydrochloride) 10 mg Tablet (Pharmascience Inc., Canada).
§ Expressed as the median (range) only.
€ Expressed as the arithmetic mean (CV%) only.

DETAILED PHARMACOLOGY

Non-clinical

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.

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% of the dose vs 13%t 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

Non-clinical

Acute Toxicity
Oral LD_{50} values were approximately 338 mg/kg in mice and 425 mg/kg in rats (27 and 69 times the MRHD on mg/m^2 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^2 basis) 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.

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^2 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^2 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	Post-mortem 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 post-mortem examinations
120 mg or 240 mg	2 to 8 doses	severe weight loss, collapse, convulsions, death	no post-mortem 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 prominent P and T waves in ECC 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 post-mortem 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 (1/6 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/m2 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.

Carcinogenesis, Teratogenicity, Impairment of Fertility

Cyclobenzaprine hydrochloride did not have any effect on the onset, incidence or distribution of neoplasms when given in oral doses of 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^2 basis, respectively).

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^2 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^2 basis) there was decrease in litter size, decrease in size and survival of the pups, and reduced weight gain of mothers.

REFERENCES

1. Product Monograph for FLEXERIL®, Frosst Division of Merck Frosst Canada Inc. Kirkland, Quebec, March 8, 1988.

2. Product Monograph for pms-CYCLOBENZAPRINE, Pharmascience Inc.,Montreal, Quebec. Date of revision:July 4, 2017, Submission Control No.:205173.

3. Product Monograph for JAMP-CYCLOBENZAPRINE, JAMP Pharma Corporation. Date of revision: December 21, 2018, Submission Control No.: 209945.

PART III: CONSUMER INFORMATION

[Pr]AG-Cyclobenzaprine
Cyclobenzaprine Hydrochloride Tablets, USP
10 mg

This leaflet is part III of a three-part "Product Monograph" and is a summary designed specifically for you to read. It will NOT tell you everything about AG-Cyclobenzaprine. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
AG-Cyclobenzaprine (cyclobenzaprine hydrochloride) is a prescription medication used along with rest and physical therapy for relief of muscle spasm due to acute, painful musculoskeletal conditions.

What it does:
AG-Cyclobenzaprine relieves skeletal muscle spasm without interfering with muscle function. Your doctor may choose to use this medication for other conditions not listed here. If you're unsure why you are taking this medication, contact your doctor.

When it should not be used:
AG-Cyclobenzaprine should not be used by anyone who:

- is hypersensitive or allergic to the drug cyclobenzaprine or any ingredients of the medication (See section titled What the nonmedicinal ingredients are).
- is taking antidepressants known as monoamine oxidase (MAO) inhibitors, or has taken them in the past 14 days.
- recently had a heart attack.
- has heart rhythm problems (arrhythmias)
- has heart failure.
- has an overactive thyroid gland (hyperthyroidism).

AG-Cyclobenzaprine tablets should not be used for more than two or three weeks.

It is not known if it is safe or effective in children below 15 years of age.

What the medicinal ingredient is:
Cyclobenzaprine Hydrochloride

What the non-medicinal ingredients are:
Colloidal Silicon Dioxide, Hydroxypropyl Cellulose, Lactose monohydrate, Magnesium Stearate, Partially pregelatinized maize Starch, titanium dioxide, polyethylene glycol, iron oxide yellow, carnauba wax, iron oxide red, hypromellose and FD&C Yellow #6 Aluminum Lake.

What dosage forms it comes in:
AG-Cyclobenzaprine comes as a tablet containing 10 mg of cyclobenzaprine hydrochloride.

WARNINGS AND PRECAUTIONS

BEFORE you use AG-Cyclobenzaprine talk to your doctor or pharmacist if you:

- have a history of eye problems including glaucoma
- have heart problems or have had a heart attack
- have liver problems
- have trouble emptying your bladder (urinary retention)
- are pregnant or plan to become pregnant. It is not known if this drug will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if this drug passes into your breast milk. You and your healthcare provider should decide if you will take this drug or breastfeed.

Do not drive, operate machinery, or do other dangerous activities until you know how AG-Cyclobenzaprine affects you.

You should not drink alcohol until you know how AG-Cyclobenzaprine affects you. Taking this medication with alcohol or other medicines that depress your central nervous system can slow your thinking and physical response times.

AG-Cyclobenzaprine may affect the way other medicines work, and other medicines may affect how this drug works. Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. It is especially important to tell your doctor if you are taking a medication listed under Interactions with this Medication.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with AG-Cyclobenzaprine include:

- alcohol, barbiturates and other medications that cause sedation
- MAO inhibitors (e.g., phenelzine, tranylcypromine) tricyclic antidepressants (e.g., amitriptyline, doxepin, imipramine, nortriptyline)

- medicines to treat depression, mood, anxiety, psychotic or thought disorders
- a pain medicine called tramadol or meperidine
- barbiturates or other medicines that depress your central nervous system (CNS depressants)
- a medicine that prevents nerve impulses (anticholinergic medicines)
- a medicine to help quit smoking called bupropion
- a blood pressure medicine called verapamil
- If you are taking any of these drugs, speak with your doctor or pharmacist

PROPER USE OF THIS MEDICATION

Usual dose:
The usual dosage of AG-Cyclobenzaprine 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.

Over Dosage:
High doses may cause temporary confusion, disturbed concentration, transient visual hallucinations, agitation, hyperactive reflexes, muscle rigidity, vomiting, or hyperpyrexia. Based on the known pharmacological actions of the drug, over dosage 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.

If you think you have taken too much AG-Cyclobenzaprine, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Talk to your doctor if you miss a dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

These are not all the possible side effects you may feel when taking AG-Cyclobenzaprine. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects of AG-Cyclobenzaprine include:

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

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention.
	Only if severe	In all cases	
Less common			
Fast heartbeat (tachycardia), irregular or abnormal heartbeats (arrhythmias)			✓
Rare or Uncommon			
Serotonin Syndrome - severe illness with some or all of: agitation, hallucinations, coma or other changes in mental status; coordination problems or muscle twitching (overactive reflexes); fast heartbeat, high or low blood pressure; sweating or fever; nausea, vomiting, or diarrhea; muscle stiffness or tightness			✓
Allergic reaction – including rash, hives, itching, and edema of the face and tongue, difficulty breathing.			✓
Rare			
Angle-closure Glaucoma [eye pain, changes in vision and swelling or redness in or around the eye			✓

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

HOW TO STORE IT

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

Keep out of reach and sight of children.

REPORTING SUSPECTED 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/health-canada/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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Angita Pharma Inc., at 450-449-9272

This leaflet was prepared by

Angita Pharma Inc.
Boucherville, Québec
J4B 5H3

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