AMRIX® (cyclobenzaprine hydrochloride extended-release capsules) is a muscle relaxant indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, and limitation of motion.

**INDICATIONS AND USAGE**

- Recommended adult dose for most patients is 15 mg taken once daily. Some patients may require 30 mg taken once daily.
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation is not recommended.
- Recommended to take doses at approximately the same time each day.
- Instruct patients to swallow AMRIX capsules intact or to sprinkle capsule contents onto a tablespoon of applesauce and swallow immediately without chewing.
- Use for periods longer than 2 or 3 weeks is not recommended.
- Use with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure and in patients taking anticholinergic medications.
- Hypersensitivity to any component of this product.
- Use in patients with hepatic impairment is not recommended.
- Use in patients with cerebral or spinal cord disease or in children with cerebral palsy.
- During the acute recovery phase of myocardial infarction, and in patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure.
- Use in the elderly is not recommended.

**CONTRAINDICATIONS**

- MAO Inhibitors: Life-threatening interactions may occur.
- Serotonergic Drugs: Serotonin syndrome has been reported.
- CNS Depressants: Effects of alcohol, barbiturates, and other CNS depressants may be enhanced.
- Tramadol: Seizure risk may be enhanced.
- Guanethidine: Antihypertensive effect may be blocked.

**ADVERSE REACTIONS**

Most common adverse reactions (incidence ≥3% in any treatment group and greater than placebo): dry mouth, dizziness, fatigue, constipation, nausea, dyspepsia, and somnolence.

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

- MAO Inhibitors: Life-threatening interactions may occur.
- Serotonergic Drugs: Serotonin syndrome has been reported.
- CNS Depressants: Effects of alcohol, barbiturates, and other CNS depressants may be enhanced.
- Tramadol: Seizure risk may be enhanced.
- Guanethidine: Antihypertensive effect may be blocked.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2018
AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)

5. WARNINGS AND PRECAUTIONS

5.1 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. The concomitant use of AMRIX with MAO inhibitors is contraindicated [see Contraindications (4)]. 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 AMRIX and any concomitant serotonin agents should be discontinued immediately if the above reactions occur and supportive symptomatic treatment should be initiated. If concomitant treatment with AMRIX and other serotonin drugs is clinically warranted, careful observation is advised, particularly during treatment initiation or dose increases.

5.2 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 (4)]. AMRIX may enhance the effects of alcohol, barbiturates, and other CNS depressants.

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. If clinically significant CNS symptoms develop, consider discontinuation of AMRIX.

5.3 Use in the Elderly

As a result of a 40% increase in cyclobenzaprine plasma levels and a 56% increase in plasma half-life following administration of AMRIX in elderly subjects as compared to young adults, use of AMRIX is not recommended in the elderly [see Clinical Pharmacology (12.3)].

5.4 Use in Patients with Hepatic Impairment

As a result of two-fold higher cyclobenzaprine plasma levels in subjects with mild hepatic impairment, as compared to healthy subjects, following administration of immediate-release cyclobenzaprine and because there is limited dosing flexibility with AMRIX, use of AMRIX is not recommended in patients with mild, moderate, or severe hepatic impairment [see Clinical Pharmacology (12.3)].

5.5 Atrypine-like Action

Because of its atropine-like action, AMRIX 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.

6. ADVERSE REACTIONS

6.1 Most Common Adverse Reactions in the AMRIX Clinical Trials

Most Common Adverse Reactions in the AMRIX Clinical Trials

The data described below reflect exposure to AMRIX in 253 patients in 2 clinical trials. AMRIX was studied in two double-blind, parallel-group, placebo-controlled, active-controlled trials of identical design. The data described below reflect exposure to AMRIX in 253 patients in 2 clinical trials. AMRIX was studied in two double-blind, parallel-group, placebo-controlled, active-controlled trials of identical design [see Clinical Studies (14)]. The study population was composed of patients with muscle spasms associated with acute musculoskeletal conditions. Patients received 15 mg or 30 mg of AMRIX taken orally once daily, cyclobenzaprine immediate-release (IR) 10 mg three times a day, or placebo for 14 days.

The most common adverse reactions (incidence ≥3% in any treatment group and greater than placebo) were dry mouth, dizziness, fatigue, constipation, nausea, dyspepsia, and somnolence (see Table 1).

Table 1: Incidence of the Most Common Adverse Reactions Occurring in ≥3% of Patients in Any Treatment Group* and Greater Than Placebo in the Two Phase 3, Double-Blind AMRIX Trials

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>AMRIX 15 mg</th>
<th>AMRIX 30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>6%</td>
<td>14%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Constipation</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*AMRIX 15 mg QD, AMRIX 30 mg QD, or cyclobenzaprine IR tablets TID

Additional Adverse Reactions from Clinical Studies and Postmarketing Experience

The following adverse reactions have been reported in clinical studies or postmarketing experience with AMRIX, cyclobenzaprine IR, or tricyclic drugs. Because some of these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In a postmarketing surveillance program of cyclobenzaprine IR, the adverse reactions reported most frequently were drowsiness, dry mouth, and dizziness and adverse reactions reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion.

The following adverse reactions have been reported in postmarketing experience (AMRIX or cyclobenzaprine IR), in clinical studies of cyclobenzaprine IR (incidence <1%), or in postmarketing experience with other tricyclic drugs:

Body as a Whole: Syncope; malaise; chest pain; edema.

Cardiovascular: Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension; hypertension; myocardial infarction; heart block; stroke.

Digestive: Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice, and cholestasis; paralytic ileus; tongue discoloration; stomatitis; parotid swelling.

Endocrine: Inappropriate ADH syndrome.

Hematologic and Lymphatic: Purpura; bone marrow depression; leukopenia; eosinophilia; thrombocytopenia.

Hypersensitivity: Anaphylaxis; angioedema; pruritus; facial edema; urticaria; rash.

Metabolic, Nutritional, and Immune: Elevation and lowering of blood sugar levels; weight gain or loss.

Musculoskeletal: Local weakness; myalgia.

Nervous System and Psychiatric: Seizures, ataxia, vertigo, dysarthria; tremors; vertigo; catatonic convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; psychosis, abnormal thinking and dreaming; hallucinations; excitement; parathesia; diplopia; serotonin syndrome; neuroleptic malignant syndrome; decreased or increased libido; abnormal gait; delusions; aggressive behavior; paranoia; peripheral neuropathy; Bell’s palsy; alteration in EEG patterns; extrapyramidal symptoms.

Respiratory: Dryness.

Skin: Sweating; photosensitization; alopecia.

Special Senses: Ageusia; tinnitus.

Urinary: Urinary frequency and/or retention; impaired urination; dilation of urinary tract; impotence; tachycardia; urinary urgency; nocturia; suprapubic pain;珍珠母.

Urogenital: Urinary frequency and/or retention; impaired urination; dilation of urinary tract; impotence; tachycardia; urinary urgency; nocturia; suprapubic pain;珍珠母.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies of AMRIX in pregnant women. Because animal reproduction studies are not always predictive of human response, AMRIX should be used during pregnancy only if clearly needed.

No treatment-related effects on embryo-fetal development were observed in mice and rabbits at approximately 3 and 15 times the maximum recommended human dose (MRHD), respectively (on a mg/m² basis at maternal doses of 20 mg/kg/day in both mice and rabbits).

Nonteratogenic Effects

Cyclobenzaprine has been shown to adversely affect pup postnatal development when dams were treated with the drug during pregnancy and lactation periods in rats. This study found that cyclobenzaprine decreased pup body weight and survival at approximately ≥3 times the MRHD (on a mg/m² basis at maternal doses of 10 and 20 mg/kg/day in rats).

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because cyclobenzaprine is closely related to the tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when AMRIX is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of AMRIX have not been studied in pediatric patients.

8.5 Geriatric Use

Clinical studies of AMRIX did not include sufficient numbers of patients aged 65 and over to determine the safety and efficacy of AMRIX in the elderly population. The plasma concentration and half-life of cyclobenzaprine are substantially increased in the elderly compared to the general patient population. Accordingly, use of AMRIX is not recommended in the elderly [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)].

8.6 Hepatic Impairment

The use of AMRIX is not recommended in patients with mild, moderate, or severe hepatic impairment [see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)].

9. DRUG ABUSE AND DEPENDENCE

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when AMRIX is administered, even though they have not

9.3 Dependence

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when AMRIX is administered, even though they have not
AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)

been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration rarely may produce nausea, headache, and malaise. These are not indicative of addiction.

10 OVERDOSAGE
Although rare, deaths may occur from overdosage with AMRIX. Multiple drug ingestion (including alcohol) is common in deliberate cyclobenzaprine overdose. As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity may develop rapidly after cyclobenzaprine overdose; therefore, hospital monitoring is required as soon as possible.

10.1 Manifestations
The most common effects associated with cyclobenzaprine overdose are drowsiness and tachycardia. Less frequent manifestations include tremor, agitation, coma, ataxia, hypertension, slurred speech, confusion, dizziness, nausea, vomiting, and hallucinations. Rare but potentially critical manifestations of overdose are cardiac arrest, chest pain, cardiac dysrhythmias, severe hypotension, seizures, and neuroleptic malignant syndrome. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of cyclobenzaprine toxicity. Other potential effects of overdose include any of the symptoms listed under Adverse Reactions (6).

10.2 Management
General
As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. In order to protect against the rare but potentially critical manifestations described above, obtain an ECG and immediately initiate cardiac monitoring. Protect the patient’s airway, establish an intravenous line, and initiate gastric decontamination. Observation of cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. Monitoring of plasma drug levels should not guide management of the patient. Dialysis is probably of no value because of low plasma concentrations of cyclobenzaprine.

Gastrointestinal Decontamination
All patients suspected of an overdose with AMRIX should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage and amnesia is contraindicated.

Cardiovascular
A maximal limb-lead QRS duration of 0.10 seconds may be the best indication of the severity of the overdose. Serum alkalization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and hyperventilation (as needed), should be instituted for patients with deep hypercarbia and/or QRS widening. A pH > 7.0 or a pCO2 < 20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or phenytoin. Type 1A and 1C antarrhythmic agents are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

CNS
In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a pharmacologist.

Psychiatric Follow-Up
Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management
The principles of management of child and adult overdosage are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

11 DESCRIPTION
AMRIX is a skeletal muscle relaxant which relieves muscle spasm of local origin without interfering with muscle function. The active ingredient in AMRIX extended-release capsules is cyclobenzaprine hydrochloride, USP. Cyclobenzaprine hydrochloride (HC) is a white, crystalline tricyclic amine salt with the empirical formula C_{20}H_{21}N·HCl and a molecular weight of 311.9. It has a melting point of 217°C, and a pK_a of 8.47 at 25°C. It is freely soluble in water and alcohol, sparingly soluble in isopropanol, and insoluble in hydrocarbon solvents. If aqueous solutions are made alkaline, the free base separates. Cyclobenzaprine HC is designated chemically as 3-(5H-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-1-propamine hydrochloride, and has the following structural formula:

\[
\text{HCH}_2\text{CH}_3\text{CH}_2\text{N(C}_3\text{H}_2\text{)}_2 \cdot \text{HCl}
\]

AMRIX extended-release capsules for oral administration are supplied in 15 and 30 mg strengths. AMRIX capsules contain the following inactive ingredients: diethyl phthalate NF, ethylcellulose NF (Ethocel Standard 10 Premium), gelatin, Opadry® Clear YS-1-7006, sugar spheres NF (20-25 mesh), and titanium dioxide. AMRIX 30 mg capsules also contain FD&C blue #1, FD&C blue #2, FD&C red #40, and FD&C yellow #6.

12 CLINICAL PHARMACOLOGY
12.1 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. In animal models, cyclobenzaprine reduced or abolished skeletal muscle hyperactivity. 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 the brain stem as opposed to the spinal cord level, although an overlapping 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 (γ) and alpha (α) motor systems. Pharmacological studies in animals demonstrated a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, noradrenaline potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

12.2 Pharmacokinetics
Following single-dose administration of AMRIX 15 mg and 30 mg in healthy adult subjects (n=15), C_{max}, AUC_{12h}, and AUC_{∞} increased in an approximately dose-proportional manner from 15 mg to 30 mg. The time to peak plasma cyclobenzaprine concentration (T_{max}) was 7 to 8 hours for both doses of AMRIX. A food effect study conducted in healthy adult subjects (n=15) utilizing a single dose of 15 mg demonstrated a statistically significant increase in bioavailability when AMRIX 30 mg was given with food relative to the fasted state. There was a 35% increase in peak plasma cyclobenzaprine concentration (C_{max}) and a 20% increase in exposure (AUC_{12h} and AUC_{∞}) in the presence of food. No effect, however, was noted on T_{max} or the shape of the mean plasma cyclobenzaprine concentration versus time profile. Cyclobenzaprine in plasma was first detectable in both the fed and fasted states at 1.5 hours. When the contents of AMRIX capsules were administered by sprinkling on apple sauce, it was found to be bioequivalent to the same dose when administered as an intact capsule.

In a multiple-dose study utilizing AMRIX 30 mg administered once daily for 7 days in a group of healthy adult subjects (n=35), a 2.5-fold accumulation of plasma cyclobenzaprine levels was noted at steady-state.

Metabolism and Excretion
Cyclobenzaprine is extensively metabolized and is excreted primarily as glucuronides via the kidney. Cytochromes P-450 3A4, 1A2, and, to a lesser extent, 2D6, mediate N-demethylation, one of the oxidative pathways for cyclobenzaprine. Cyclobenzaprine has an elimination half-life of 32 hours (range 8-37 hours; n=18); plasma clearance is 0.7 L/min following single-dose administration of AMRIX.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies were conducted in CD-1 mice and Sprague-Dawley rats with cyclobenzaprine to evaluate its carcinogenic potential. In an 81-week carcinogenicity study, metastatic hemangiosarcoma was seen in 3 of 21 male mice at 10 mg/kg/day (2 times the MRHD on a mg/m² basis). In a 105-week carcinogenicity study, malignant astrocytoma was seen in 3 of 50 male rats at 10 mg/kg/day (3 times the MRHD on a mg/m² basis). There were no tumor findings in female mice or rats. Cyclobenzaprine HC was not mutagenic or clastogenic in the following assays: an in vitro Ames bacterial mutation assay, in vitro Chinese hamster ovary (CHO) cell chromosomal aberration test, and in vivo mouse bone marrow micronucleus assay. Cyclobenzaprine HC had no effects on fertility and reproductive performance in male or female rats at oral doses up to 20 mg/kg/day (6 times the MRHD on a mg/m² basis).

13.2 Animal Toxicology and/or Pharmacology
In a 67-week study with rats that received cyclobenzaprine at oral doses of 10, 20, or 40 mg/kg/day (3 to 15 times the MRHD on mg/m² basis), there were findings in the liver consisting of monodonal vacuolation with lipidosis for males and mizid and central lobular necrosis 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 doses of 2.5, 5, 10, or 20 mg/kg/day, one monkey at 20 mg/kg/day (15 times the MRHD...
**AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)**

on mg/ml basis) was euthanized in week 17. Morbidity for this animal was attributed to findings of chronic pancreatitis, cholecystitis, cholangitis, and focal liver necrosis.

**14 CLINICAL STUDIES**

Efficacy was assessed in two double-blind, parallel-group, active-controlled, placebo-controlled studies of identical design of AMRIX 15 mg and 30 mg taken once daily, between 6:00 and 7:00 PM, cyclobenzaprine 10 mg three times a day, or placebo for 14 days in patients with muscle spasms associated with acute painful musculoskeletal conditions.

There were significant differences in the primary efficacy analysis, the patient’s rating of medication helpfulness, between the AMRIX 15 mg group and the placebo group at Days 4 and 14 in one study and between the AMRIX 30 mg group and the placebo group at Day 4 in the second study.

<table>
<thead>
<tr>
<th>Table 2: Patients’ Rating of Medication Helpfulness - Study 1*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients (%)</strong></td>
</tr>
<tr>
<td><strong>Day 4</strong></td>
</tr>
<tr>
<td>Placebo (N = 64)</td>
</tr>
<tr>
<td>AMRIX 30 mg (N = 64)</td>
</tr>
<tr>
<td>AMRIX 30 mg (N = 64)</td>
</tr>
<tr>
<td>Excellent</td>
</tr>
<tr>
<td>1 (2%)</td>
</tr>
<tr>
<td>3 (5%)</td>
</tr>
<tr>
<td>12 (19%)</td>
</tr>
<tr>
<td>15 (23%)</td>
</tr>
<tr>
<td>Very Good</td>
</tr>
<tr>
<td>5 (8%)</td>
</tr>
<tr>
<td>13 (20%)</td>
</tr>
<tr>
<td>9 (14%)</td>
</tr>
<tr>
<td>19 (30%)</td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>15 (23%)</td>
</tr>
<tr>
<td>22 (34%)</td>
</tr>
<tr>
<td>10 (16%)</td>
</tr>
<tr>
<td>15 (23%)</td>
</tr>
<tr>
<td>Fair</td>
</tr>
<tr>
<td>24 (38%)</td>
</tr>
<tr>
<td>20 (31%)</td>
</tr>
<tr>
<td>16 (25%)</td>
</tr>
<tr>
<td>10 (16%)</td>
</tr>
<tr>
<td>Poor</td>
</tr>
<tr>
<td>10 (16%)</td>
</tr>
<tr>
<td>5 (8%)</td>
</tr>
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<td>9 (14%)</td>
</tr>
<tr>
<td>4 (6%)</td>
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<tr>
<td>Missing</td>
</tr>
<tr>
<td>9 (14%)</td>
</tr>
<tr>
<td>1 (2%)</td>
</tr>
<tr>
<td>8 (13%)</td>
</tr>
<tr>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

*Percentages are rounded to the nearest whole percent.

In addition, one of the two studies demonstrated significant differences between the AMRIX 30 mg group and the placebo group in terms of patient-rated relief from local pain due to muscle spasm at Day 4 and Day 8, in patient-rated restriction of movement at Day 4 and Day 8, and in patient-rated global impression of change at Day 4, Day 8, and Day 14.

In both studies, there were no significant treatment differences between the AMRIX treatment groups and the placebo group in physician’s global assessment, patient-rated restriction in activities of daily living, or quality of nighttime sleep.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**16.1 How Supplied**

AMRIX extended-release capsules are available in 15 and 30 mg strengths, packaged in bottles of 60 capsules. AMRIX 15 mg capsules (NDC 63459-700-60) are orange/orange and are embossed in blue ink with “15 mg” on the body, and Cephalon “C” logo, “Cephalon”, and a dashed band on the cap. AMRIX 30 mg capsules (NDC 63459-701-60) are blue/red and are embossed in white ink with “30 mg” on the body, and Cephalon “C” logo “Cephalon”, and a dashed band on the cap.

**16.2 Storage and Handling**

Dispense in a tight, light-resistant container as defined in the USP/NF. Store at 25°C (77°F), excursions permitted to 15 - 30°C (59 - 86°F) [see USP Controlled Room Temperature].

**17 PATIENT COUNSELING INFORMATION**

See FDA-approved patient labeling (Patient Information).

- Instruct patients to swallow AMRIX capsules intact or to sprinkle capsule contents on a tablespoon of applesauce and swallow immediately without chewing.
- Advise patients to stop taking AMRIX and to notify their physician right away if they experience symptoms of an allergic reaction, such as difficulty breathing, hives, swelling of face or tongue, or itching.
- Advise patients that AMRIX should not be taken with MAO inhibitors or within 14 days after their discontinuation.
- Advise patients about the risk of serotonin syndrome with concomitant use of AMRIX and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. Advise patients of the signs and symptoms of serotonin syndrome [see Warnings and Precautions (5.1)] and instruct patients to seek medical care immediately if they experience these symptoms.

**18 PATIENT INFORMATION**

AMRIX® (am-rix) (cyclobenzaprine hydrochloride) Extended-Release Capsules

Read this Patient Information before you start taking AMRIX and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**What is AMRIX?**

AMRIX is a prescription medicine used along with rest and physical therapy to help treat muscle spasm due to acute, painful musculoskeletal problems.

AMRIX should only be used for up to 2 or 3 weeks. It is not known if AMRIX is effective when used for longer periods. It is not known if AMRIX is safe and effective in children.

**Who should not take AMRIX?**

Do not take AMRIX if you:

- are allergic to cyclobenzaprine or any of the ingredients in AMRIX. See the end of this Patient Information leaflet for a complete list of ingredients in AMRIX.
- have liver problems
- have heart problems or have had a heart attack
- have had 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)
- have symptoms of an allergic reaction such as:
  - difficulty breathing
  - hives
  - swelling of your face or tongue
  - itching
- are taking certain antidepressants, known as monoamine oxidase (MAO) inhibitors or it has been 14 days or less since you stopped taking a MAO inhibitor. Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.
- have had a recent heart attack
- have heart rhythm problems (arrhythmias)
- have heart failure
- have an overactive thyroid (hyperthyroidism)

Talk to your healthcare provider before taking this medicine if you have any of the conditions listed above.

**What should I tell my healthcare provider before taking AMRIX?**

Before you take AMRIX, tell your healthcare provider if you:

- have any of the conditions listed above.
- have symptoms of an allergic reaction such as:
  - difficulty breathing
  - hives
  - swelling of your face or tongue
  - itching
- are taking certain antidepressants, known as monoamine oxidase (MAO) inhibitors or it has been 14 days or less since you stopped taking a MAO inhibitor. Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.
- have had a recent heart attack
- have heart rhythm problems (arrhythmias)
- have heart failure
- have an overactive thyroid (hyperthyroidism)

Talk to your healthcare provider before taking this medicine if you have any of the conditions listed above.

**AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)**

- Advise patients to stop taking AMRIX and to notify their physician right away if they experience arrhythmias or tachycardia.
- Advise patients that AMRIX may enhance the impairment effects of alcohol. These effects may also be seen if AMRIX is taken with other CNS depressants.
- Caution patients about operating an automobile or other hazardous machinery until it is reasonably certain that AMRIX therapy will not adversely affect their ability to engage in such activities.
- Advise patients to take AMRIX at approximately the same time each day.
AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)

• are pregnant or plan to become pregnant. It is not known if AMRIX will harm your unborn baby.
• are breastfeeding or plan to breastfeed. It is not known if AMRIX passes into your breast milk. You and your healthcare provider should decide if you will take AMRIX or breastfeed. AMRIX may affect the way other medicines work, and other medicines may affect how AMRIX works.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take:
• a medicine 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

Ask your doctor or pharmacist if you are not sure if you take any of the medicines listed above. Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider or pharmacist when you get a new medicine.

How should I take AMRIX?
• Take AMRIX exactly as your healthcare provider tells you to take it.
• Your healthcare provider will tell you how much AMRIX to take and when to take it.
• Your healthcare provider may change your AMRIX dose if needed.
• Take AMRIX around the same time every day.
• AMRIX should only be taken for short periods (up to two or three weeks).
• If you take too much AMRIX, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking AMRIX?
You should not drink alcohol until you know how AMRIX affects you. Taking AMRIX with alcohol or other medicines that depress your central nervous system can slow your thinking and physical response times. Do not drive, operate machinery, or do other dangerous activities until you know how AMRIX affects you.

What are the possible side effects of AMRIX?
AMRIX may cause serious side effects that may lead to heart attack or stroke. Call your healthcare provider right away or go to the nearest hospital emergency room if you have:
• irregular or abnormal heartbeats (arrhythmias)
• fast heartbeat (tachycardia)

Serotonin syndrome is a serious medical condition that may happen when AMRIX is taken with certain other medicines. Call your healthcare provider right away or go to the nearest hospital emergency room if you become severely ill and have some or all of these symptoms:
• 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

The most common side effects of AMRIX include:
• dry mouth
• dizziness
• fatigue
• constipation
• nausea
• upset stomach
• drowsiness

Tell your healthcare provider if you get any side effect that bothers you or that does not go away. These are not all the possible side effects of AMRIX. For more information, ask your healthcare provider or pharmacist. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AMRIX?
• Store AMRIX at room temperature, between 59°F to 86°F (15°C to 30°C).
• Keep AMRIX in a tightly closed container, and keep AMRIX out of light.
• Keep AMRIX and all medicines out of the reach of children.

General information about the safe and effective use of AMRIX.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AMRIX for a condition for which it was not prescribed. Do not give AMRIX to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about AMRIX. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about AMRIX that is written for healthcare professionals.

For more information, go to www.AMRIX.com or call 1-888-483-8279.

What are the ingredients in AMRIX?
Active Ingredient: cyclobenzaprine hydrochloride USP
Inactive Ingredients: diethyl phthalate NF, ethylcellulose NF (Ethocel Standard 10 Premium), gelatin, Opadry® Clear YS-1-7006, sugar spheres NF (20-25 mesh), and titanium dioxide.
AMRIX 15 mg capsules also contain: FD&C yellow #10, FD&C green #3, and FD&C red #40.
AMRIX 30 mg capsules also contain: FD&C blue #1, FD&C blue #2, FD&C red #40, and FD&C yellow #6.

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