Looking for relief from painful muscle spasm?

Learn more inside
Understanding muscle spasm

This brochure can help you understand:

• What muscle spasm is
• How you and your doctor can help manage the condition
• How to perform some simple exercises that may help relieve the spasm

Inside, you will also learn about a prescription medication. If you have any questions, talk to your doctor.

The information in this brochure does not take the place of talking with your doctor about your medical condition or your treatment.
What is muscle spasm?

A muscle spasm is a painful sensation that occurs when a muscle becomes too tight.\(^1\) It’s like an intense cramp. It can be caused by:

- **Muscle tiredness**—when a muscle is overused or held in the same position longer than usual\(^2\)
- **Injury**—for example, as a result of playing sports or falling\(^1\)
- A “reflex”—sometimes, if part of your body has been hurt, the muscles around the injury can tighten up. This is the body’s way of protecting the injured part by acting as a splint\(^3\)

If you are suffering from painful muscle spasm, you may want to talk to your doctor about treatment options.\(^3\)

70% to 85% of adults have at least one episode of back spasm/pain in their lives\(^4\)

2 out of 3 adults will experience neck spasm/pain\(^5\)
How is muscle spasm treated?

Two common ways a doctor might recommend treating muscle spasm:

**Physical therapy**

Physical therapy is a series of exercises a physical therapist will teach you to help manage your muscle spasm. It works by improving overall muscle strength and endurance.

Your doctor may recommend additional things to do at home to help relieve muscle spasm. For example:
- Apply an ice pack or heat pad to the affected area
- Perform exercises to reduce discomfort; see pages 8-11 of this booklet

**Medicine**

Your doctor may prescribe medication to help treat pain and muscle spasm.
- Anti-inflammatory medicines can relieve pain by reducing swelling
- Muscle relaxants help relieve painful muscle spasms. They can be used to alleviate muscle spasm and associated back or neck pain
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.

Important Safety Information

Who should not take AMRIX?

Do not take AMRIX if you:

• are allergic to cyclobenzaprine or any of the components of AMRIX. Talk to your healthcare provider or get medical help right away if you have symptoms of an allergic reaction such as difficulty breathing, hives, swelling of your face or tongue, or 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.

Please see Patient Information Leaflet in the accompanying Full Prescribing Information.
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 possible side effects of AMRIX?

AMRIX may cause serious side effects that may lead to heart attack or stroke. Call your healthcare provider immediately 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, and 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, talk to your healthcare provider or pharmacist.
Speak to your doctor before starting any kind of exercise program. Once you are given the okay, discuss some of the following options with your healthcare provider. You should stretch before you exercise to get the blood flowing and prevent injury. It’s alright to feel mild aching while you exercise, but if your pain is more than mild or if it lasts 15 minutes or more, stop exercising and talk with your healthcare provider.

Here are some low-back exercises to get you started:

**Heel Slides**

1. Lie on your back.
2. Slowly bend and straighten your knee.
3. Repeat 10 times with each leg.

**Stomach Tightening**

1. Lie on your back with knees bent and hands resting on your stomach.
2. Tighten your stomach muscles to squeeze your ribs down toward your back.
3. Do not hold your breath.
4. Stay this way for 5 seconds.
5. Relax.
6. Repeat 10 times.
Straight Leg Raises

1. Lie on your back with one leg straight and one knee bent.
2. Tighten your stomach muscles to hold your low back still.
3. Slowly lift your leg straight up about 6 to 12 inches and hold it there for 1 to 5 seconds.
4. Lower your leg slowly.
5. Repeat 10 times with each leg.

Single Knee to Chest Stretch

1. Lie on your back with both knees bent.
2. Bring one knee up to your chest.
3. Hold it there for 20 seconds.
4. Relax.
5. Repeat 5 times with each leg.

Hamstring Muscle Stretch

1. Lie on your back with your knees bent.
2. Hold one thigh (behind knee) with both hands.
3. Slowly straighten your knee until a stretch is felt in the back of your thigh.
4. Hold this position for 20 seconds.
5. Relax.
6. Repeat 5 times with each leg.
Exercises for your neck

Speak to your doctor before starting any kind of exercise program. There are many exercises that can help you move your neck more easily and help control neck spasm. Here are a few you may use:

Neck Flexion\textsuperscript{13}

1. Bring your head forward so that your chin hits your chest and your face is staring straight down at the floor.
2. Return to your starting position.
3. Repeat slowly 5 times.

Neck Extension\textsuperscript{13,14}

1. Let your head go back until your face is looking straight up at the ceiling. Do this slowly and gently. Let your head hang back for a few seconds, then slowly bring it forward to where you started.
2. If you feel dizzy when you do this, stop.
3. Repeat slowly 5 times.
Side to Side

1. Keep your head facing straight ahead, and try to tip your ear down toward the same shoulder.
2. Do this 5 times to one side and then 5 times to the other side.

Neck Retraction

This is one of the most helpful neck movements because it helps strengthen the muscles responsible for good head and neck posture.

1. Keep your face straight ahead during the whole exercise, pulling your head back and your chin down slightly.
2. Hold the movement with your head pulled all the way back for at least 5 seconds.

Neck Turns

1. Turn your head around slowly to one side until it can’t easily go any further. When you’ve turned your head as far as it can easily go, hold it there for a few seconds. Then return to where you started.
2. If you feel dizzy when you do this, stop.
3. Once you have done 5 to one side, do the same on the other side.
Speak to your doctor before starting any kind of exercise program. Changing the way you sit, stand, reach, lift, and sleep may help your low-back spasm get better. Here are a few ideas on how to do these things:

**Sitting**

1. Sit as little as possible.
2. When you sit, put a rolled-up towel in the curve of your lower back.
3. Keep your hips and knees the way they look in this picture, and keep your feet flat on the floor.

**Reaching**

1. Use a foot stool or chair to bring yourself up to the level of what you are reaching.
2. Get your body as close as possible to the object you need.
3. Make sure you have a good idea of how heavy the object is you are trying to lift.
4. Use two hands to lift.
Standing

1. Keep your head up, shoulders straight, chest forward, and weight evenly balanced on both feet.
2. Don’t stand in the same position for too long.
3. Raise one foot by resting it on a stool or box, and switch feet every few minutes.

Lifting

1. Whenever possible, don’t lift.
2. If you have to lift, lift only light things and hold them next to your body.
3. Lift with your legs and not your back; bend your knees and hips, not your back.

Sleeping

A firm mattress often helps. You may want to place a board under your mattress.

- If you sleep on your side, bend your knees a little bit; placing a pillow between your legs may help.
- If you sleep on your back, support your neck with a pillow, and put a pillow under your knees or a rolled-up towel in the small of your back.
- If you sleep on your stomach, be careful. This can strain your back more. Decrease the stress on your back by placing a pillow under your hips and lower part of your stomach. Use a pillow under your head if that doesn’t hurt your back.
Fill out with your doctor:

Take AMRIX exactly as your doctor tells you to take it. AMRIX should be taken once a day, around the same time each day.

Take AMRIX at _____:_____ AM/PM each day.

Important Safety Information

Who should not take AMRIX?

Do not take AMRIX if you:

• are allergic to cyclobenzaprine or any of the components of AMRIX. Talk to your healthcare provider or get medical help right away if you have symptoms of an allergic reaction such as difficulty breathing, hives, swelling of your face or tongue, or 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.


Please see Important Safety Information on pages 6-7 and Patient Information Leaflet in the accompanying Full Prescribing Information.
AMRIX® (cyclobenzaprine hydrochloride extended-release capsules) is indicated as

**INDICATIONS AND USAGE**

- 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.

**CONTRAINDICATIONS**

- Hypersensitivity to any component of this product.

**WARNINGS AND PRECAUTIONS**

- Serotonin syndrome has been reported with cyclobenzaprine when used in combination with other serotonergic drugs (5.1).
- Use of cyclobenzaprine with other drugs that affect serotonin levels, such as MAO inhibitors, can increase the risk of serotonin syndrome (5.1, 7).
- The development of a potentially life-threatening serotonin syndrome has been reported (5.1).

**ADVERSE REACTIONS**

- Most common adverse reactions (incidence ≥5% in any treatment group and greater than placebo): dry mouth, dizziness, fatigue, constipation, nausea, dyspepsia, and somnolence

**DRUG INTERACTIONS**

- MAO Inhibitors: Life-threatening interactions may occur (4, 7).
- Use with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure and in patients taking anticholinergic medications (5.5).

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**1 INDICATIONS AND USAGE**

**2 DOSAGE AND ADMINISTRATION**

- Recommended adult dose for most patients is 15 mg taken once daily. Some patients may require 30 mg taken once daily. (2)
- Instruct patients to swallow AMRIX capsules intact or to sprinkle capsule contents on a tablespoon of applesauce and swallow immediately without chewing. (2)
- Recommended adult dose for most patients is 15 mg taken once daily. Some patients may require 30 mg taken once daily. (2)
- Instruct patients to swallow AMRIX capsules intact. Alternatively, the contents of the AMRIX capsule may be sprinkled over applesauce and then swallowed. This method is appropriate only for patients able to reliably swallow the applesauce without chewing. Other foods have not been tested and should not be substituted for applesauce.

**9 DRUG ABUSE AND DEPENDENCE**

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

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**12.3 Pharmacokinetics**

- Cyclobenzaprine is structurally related to tricyclic antidepressants which have been reported to produce adverse cardiovascular effects or CNS depressant effects (5.2).
- Use in the elderly is not recommended (5.3).
- Use in patients with hepatic impairment is not recommended (5.4).
- Use with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure and in patients taking anticholinergic medications (5.5).

**8.1 Pregnancy**

- Due to the potential for fetal harm, AMRIX extended-release capsules should not be used during or immediately before labor.

**8.5 Geriatric Use**

- In elderly patients, the recommended starting dose is 15 mg once daily. Dose may be increased to 30 mg once daily, if required.

**13 NONCLINICAL TOXICOLOGY**

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**17 PATIENT COUNSELING INFORMATION**

- Instruct the patient to:
  - Sprinkle the contents of the capsule onto a tablespoon of applesauce and consume immediately without chewing.
  - Rinse the mouth to ensure all of the contents have been swallowed.
  - Discard any unused portion of the AMRIX capsules after the contents have been sprinkled on applesauce.

**17.1 CONTRAINDICATIONS**

- Hypersensitivity to any component of this product.

**17.2 WARNINGS**

- Serotonin Syndrome: Clinical manifestations include mental status changes (e.g., agitation, confusion, hallucinations, coma), autonomic instability (e.g., tachycardia, diaphoresis, hypotension), neuromuscular abnormalities (e.g., hyperreflexia, rigidity, tremor, dystonia), and/or somnolence.

**17.3 ADVERSE REACTIONS**

- Most common adverse reactions (incidence ≥5% in any treatment group and greater than placebo): dry mouth, dizziness, fatigue, constipation, nausea, dyspepsia, and somnolence

**17.4 DRUG INTERACTIONS**

- MAO Inhibitors: Life-threatening interactions may occur (4, 7).
- Use with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure and in patients taking anticholinergic medications (5.5).

**17.5 OVERDOSAGE**

- The recommended adult dose for most patients is 15 mg taken once daily. Some patients may require 30 mg taken once daily. (2)
- Instruct patients to swallow AMRIX capsules intact. Alternatively, the contents of the AMRIX capsule may be sprinkled over applesauce and then swallowed. This method is appropriate only for patients able to reliably swallow the applesauce without chewing. Other foods have not been tested and should not be substituted for applesauce.
selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline 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 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). Tricyclic antidepressant with AMRIX and any concomitant serotoninergic agents should be discontinued immediately if the above reactions occur and supportive symptomatic treatment should be initiated. If concomitant treatment with AMRIX and other serotoninergic 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 Atropine-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
Most Common Adverse Reactions in the AMRIX Clinical Trials
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

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 painful 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></th>
<th>Placebo</th>
<th>AMRIX 15 mg</th>
<th>AMRIX 30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=128</td>
<td></td>
<td>N=127</td>
<td>N=126</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2%</td>
<td>6%</td>
<td>14%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Constipation</td>
<td>0%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1%</td>
<td>0%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*AMRIX 15 mg QD, AMRIX 30 mg OD, 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 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, anorexia, 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: Syncopa; malaise; chest pain; edema.
Cardiovascular: Tachycardia; arrhythmia; vasodilation; 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;
Musculoskeletal: Local weakness; myalgia.
Nervous System and Psychiatric: Seizures, ataxia; vertigo; dysarthria; tremors; drug-induced psychosis; arrows; agitation; akathisia; confusion; delirium; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; psychosis; abnormal thinking and dreaming; hallucinations; excitement; paresthesia; delirium; serotonin syndrome; neuroleptic malignant syndrome; decreased or increased libido; abnormal gait; delusions; excessive behavioral changes; paranoia; peripheral neuropathy; Bell’s palsy; alteration in EEG patterns; extrapyramidal symptoms.
Respiratory: Dyspnea.
Skin: Swelling; photosensitization; alopecia.
Special Senses: Ageusia; tinnitus.
Urogenital: Urinary frequency and/or retention; impaired urination; dilatation of urinary tract; impotence; testicular swelling; gynecomastia; breast enlargement; galactorrhea.

7. DRUG INTERACTIONS
Based on its structural similarity to tricyclic antidepressants, AMRIX may have life-threatening interactions with MAO inhibitors [see Contraindications (4)]. MAO may enhance the effects of alcohol, barbiturates, and other CNS depressants, may enhance the seizure risk in patients taking tramadol, and may block the antihypertensive action of guanethidine and similarly acting compounds.

Postmarketing cases of serotonin syndrome have been reported during combined use of cyclobenzaprine and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, mirtazapine, verapamil, or MAO inhibitors. [See Warnings and Precautions (5.1)]

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 embryofetal 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 has 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 when compared to the general population. Accordingly, use of AMRIX is not recommended in the elderly. [See Warnings and Precautions (5.3) 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 (5.3) and Clinical Pharmacology (12.3)]

9. DRUG ABUSE AND DEPENDENCE

9.1 Dependence

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when AMRIX is administered, even though they have not been reported to drug exposure.

Ampheta-mine-like effects have been reported following AMRIX overdose. These effects include delirium, excitement, hyperreflexia, tremor, tachycardia, palpitations, labile blood pressure, mydriasis, 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). Tricyclic antidepressant with AMRIX and any concomitant serotoninergic agents should be discontinued immediately if the above reactions occur and supportive symptomatic treatment should be initiated. If concomitant treatment with AMRIX and other serotoninergic drugs is clinically warranted, careful observation is advised, particularly during treatment initiation or dose increases.
AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)

AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)

10 OVERDOSAGE

Although rare, deaths may occur from overdose 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 Management

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

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 with 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 the drug.

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 emesis 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 acidosis and QRS widening ≥ 0.10 or ≥ 0.20 mm is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or phenytoin. Type 1A and 1C antiarrhythmics 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). Phystostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a poison control center. Psychiatric Follow-Up

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

Pediatric

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

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 (HCl) is a white, crystalline tricyclic amine salt with the empirical formula C18H19N·HCl and a molecular weight of 311.9. It has a melting point of 217°C, and a pKa 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 HCl is designated chemically as 3-(3-dimethylaminopropyl)4-cyclohexephenyl-5-oxide, N,N-dimethyl-1-propanamine hydrochloride, and has the following structural formula:

HCC=CH2CH2N(CH3)2 · 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 15 mg capsules also contain D&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.

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. 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. In each such study where 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 CNS tonus and somatic motor activity, influencing both gamma (α) 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, norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

12.3 Pharmacokinetics

Following single-dose administration of AMRIX 15 mg and 30 mg in healthy adult subjects (n=15), Cmax, AUC0-168h, and AUC0-∞ increased in an approximately dose-proportional manner from 15 mg to 30 mg. The time to peak plasma cyclobenzaprine concentration (Tmax) 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 AMRIX 30 mg demonstrated a statistically significant increase in bioavailability when AMRIX 30 mg was taken with food with respect to the fasted state. There was a 35% increase in peak plasma cyclobenzaprine concentration (Cmax) and a 20% increase in exposure (AUC0-168h and AUC0-∞) in the presence of food. No effect, however, was noted with Tmax or the shape of the mean plasma cyclobenzaprine concentration time profile. Cyclobenzaprine in plasma was first detectable in both the fasted and fed 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 2-3 hours (range 6-37 hours; n=18); plasma clearance is 0.7 L/min following single dose administration of AMRIX.

Special Populations

Elderly

Although there were no notable differences in Cmax or Tmax, cyclobenzaprine plasma AUC is increased by 40% and the plasma half-life of cyclobenzaprine is prolonged in elderly subjects greater than 65 years of age (50 hours) after dosing with AMRIX compared to younger subjects 18 to 45 years of age (32 hours). Pharmacokinetic characteristics of cyclobenzaprine following multiple-dose administration of AMRIX in the elderly were not evaluated.

Hepatic Impairment

In a pharmacokinetic study of immediate-release cyclobenzaprine in 16 subjects with hepatic impairment (15 mild, 1 moderate by Child-Pugh score), both AUC and Cmax were approximately double the values seen in the healthy control group. The pharmacokinetics of cyclobenzaprine in subjects with severe hepatic impairment is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in CD-1 mouse 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 HCl was not mutagenic or clastogenic in the following assays: an in vitro Ames bacterial mutation assay, in vitro Chinese hamster ovary (CHO) cell chromosomes aberration test, and in vivo mouse bone marrow micronucleus assay. Cyclobenzaprine HCl 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 97-week study with rats that received cyclobenzaprine at oral doses of 10, 20 or 40 mg/kg/day (3 to 5 times the MRHD on mg/m2 basis), there were findings in the liver consisting of midzonal vacuolization with lipidosis for males and midzonal and centrilobular hepatocellular enlargement for females. In addition, there were findings of centrilobular collapse 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 (3 times the MRHD on mg/m2 basis) was euthanized in week 17. Morbitidy for this animal was attributed to findings of chronic pancreatitis, cholecystitis, cholangitis, and focal liver necrosis.
AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)

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 2: Patients' Rating of Medication Helpfulness - Study 1*

<table>
<thead>
<tr>
<th>Number of Patients (%)</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 4</strong></td>
<td><strong>Day 14</strong></td>
</tr>
<tr>
<td>Placebo (N = 64)</td>
<td>AMRIX 30 mg (N = 64)</td>
</tr>
<tr>
<td>Excellent 1 (2%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Good 15 (23%)</td>
<td>22 (34%)</td>
</tr>
<tr>
<td>Fair 24 (38%)</td>
<td>20 (31%)</td>
</tr>
<tr>
<td>Poor 10 (16%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Missing 9 (14%)</td>
<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 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
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 Cephalexin “C” logo, 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 Cephalexin “C” logo, a “C” logo, and a dashed band on the cap.

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.
- Caution patients about the risk of serotonin syndrome with concomitant use of AMRIX and other drugs, such as SSRI, SNRI, 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.

- 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 breastfeeding or plan to breastfeeding. 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 do 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 1-800-896-5855.

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: D&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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