

## Greatest Weight Loss Effect With Combination Therapy

	Placebo	Naltrexone 48 mg	Bupropion 200 mg	Bupropion 200 mg and Naltrexone 32 mg
<b>Weight loss</b>	-1%	-2%	-3%	-7%
Body fat loss	-4%	-3%	-4%	-12%
Visceral fat loss	-5%	-0%	-2%	-14%
Waist circumference	-1 cm	-3.8 cm	-2.9 cm	-5.4 cm
Fasting glucose	+1.9 mg/dL	+3.4 mg/dL	+3.5 mg/dL	-2.0 mg/dL
Insulin	+0.9 U/mL	+1.7 U/mL	-0.5 U/mL	-3.0 U/mL
Triglycerides	-15 mg/dL	-17.6 mg/dL	-18.4 mg/dL	-43.6 mg/dL

Note: Based on a randomized study of 419 nondiabetic obese subjects treated for 24 weeks.

Source: Dr. Greenway

# Drug Combo Yields Better Weight Loss

BY FRAN LOWRY  
Orlando Bureau

NEW ORLEANS — Combination therapy with bupropion and naltrexone resulted in superior weight loss, compared with placebo or either drug alone, Dr. Frank L. Greenway said at the annual meeting of NAASO, the Obesity Society.

Patients randomized to the experimental bupropion-naltrexone combination achieved a 1.5- to twofold greater weight loss after 24 weeks of treatment than did those randomized to monotherapy with bupropion or naltrexone, or to placebo.

The combination patients also achieved a greater improvement in insulin resistance and markers of cardiovascular disease risk, such as waist circumference and triglyceride levels, said Dr. Greenway, chief of the outpatient clinic at Louisiana State University's Pennington Biomedical Research Center, Baton Rouge.

The multicenter trial randomized 419 healthy, nondiabetic obese subjects to receive 200 mg bupropion twice a day; 48 mg naltrexone once a day; 200 mg bupropion combined with 16, 32, or 48 mg naltrexone twice a day; or placebo. The patients also received an exercise prescription and were placed on a diet.

A subset of 75 randomized subjects had a DEXA scan to measure body fat, and 73 randomized subjects had a multislice abdominal CT scan to measure visceral fat. The measures were taken at baseline and at 24 weeks, as were insulin, glucose, and triglyceride analyses. Patients treated with the bupropion-naltrexone combination showed a statistically significant greater total body weight loss, compared with placebo or monotherapy subjects. Orexigen Therapeutics Inc., San Diego, provided the combination drug.

The greatest weight loss effect was observed for the combination that included naltrexone at the dose of 32 mg, he said. Subjects randomized to that regimen lost a mean of 7% of their body weight, 12% of their body fat, and 14% of their visceral fat. Waist circumference also was reduced by a mean of 5.4 cm.

In addition, their insulin levels declined by a mean of 3 mcU/mL, fasting glucose fell by a mean of 2 mg/dL, and triglyceride levels fell by a mean of 44 mg/dL, all of which were statistically significantly greater than the values for the other regimens.

The naltrexone-bupropion combination promotes hypothalamic proopiomelanocortin activity, which reduces appetite and stimulates energy expenditure, thereby preventing an early plateau or slowing down of weight loss.

Bupropion and naltrexone have been approved by the Food and Drug Administration for treating addictive disorders, but the combined formulation has not been approved. "We expect the new [combination] drug application to be submitted in 2009," said Dr. Greenway, who disclosed that he is a consultant for Orexigen Therapeutics. ■

## AMRIX™

(Cyclobenzaprine Hydrochloride Extended-Release Capsules)

Rx Only

**BRIEF SUMMARY** of Prescribing Information. The following is a brief summary only. Please see full Prescribing Information for complete product information.

### DESCRIPTION

AMRIX™ (Cyclobenzaprine Hydrochloride Extended-Release Capsules) 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.

AMRIX extended-release capsules for oral administration are supplied in 15 and 30 mg strengths.

### INDICATIONS AND USAGE

AMRIX is 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.

AMRIX 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.

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

### CONTRAINDICATIONS

- Hypersensitivity to any component of this product.
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation.
- Hyperpyretic crisis seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.
- During the acute recovery phase of myocardial infarction, and in patients with arrhythmias, heart block conduction disturbances, or congestive heart failure.
- Hyperthyroidism.

### WARNINGS

AMRIX is closely related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. In short term studies for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm, some of the more serious central nervous system reactions noted with the tricyclic antidepressants have occurred (see **WARNINGS**, below, and **ADVERSE REACTIONS** section of full Prescribing Information).

Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke. AMRIX may enhance the effects of alcohol, barbiturates, and other CNS depressants.

As a result of a 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 subjects with mild, moderate or severe hepatic impairment.

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 elderly.

### PRECAUTIONS

#### General

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.

#### Information for Patients

AMRIX, 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.

#### Drug Interactions

AMRIX may have life-threatening interactions with MAO inhibitors. (See **CONTRAINDICATIONS**.) AMRIX may enhance the effects of alcohol, barbiturates, and other CNS depressants. Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds. Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol (ULTRAM® [tramadol HCl tablets, Ortho-McNeil Pharmaceutical]) or ULTRACET® [tramadol HCl and acetaminophen tablets, Ortho-McNeil Pharmaceutical].

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

In rats treated with cyclobenzaprine for up to 67 weeks at doses of approximately 5 to 40 times the maximum recommended human dose, pale, sometimes enlarged, livers were noted and there was a dose-related hepatocyte vacuolation with lipidosis. Cyclobenzaprine did not affect the onset, incidence, or distribution of neoplasia in an 81-week study in the mouse or in a 105-week study in the rat. At oral doses of up to 10 times the human dose, cyclobenzaprine did not adversely affect the reproductive performance or fertility of male or female rats.

A battery of mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenic effects have provided no evidence for a mutagenic potential for cyclobenzaprine.

#### Pregnancy

**Pregnancy Category B:** Reproduction studies have been performed in rats, mice, and rabbits at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cyclobenzaprine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

#### 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.

#### Pediatric Use

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

#### Use in the Elderly

The plasma concentration and half-life of cyclobenzaprine are substantially increased in the elderly when compared to the general patient population (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Elderly** in full Prescribing Information). Accordingly, AMRIX should not be used in the elderly.

### ADVERSE REACTIONS

The most common adverse reactions in the two 14-day clinical efficacy trials are presented in Table 1.

	AMRIX 15 mg N = 127	AMRIX 30 mg N = 126	Placebo N = 128
Dry mouth	6%	14%	2%
Dizziness	3%	6%	2%
Fatigue	3%	3%	2%
Constipation	1%	3%	0%
Somnolence	1%	2%	0%
Nausea	3%	3%	1%
Dyspepsia	0%	4%	1%

In a postmarketing surveillance program (7607 patients treated with cyclobenzaprine 10 mg TID), the adverse reactions reported most frequently were drowsiness, dry mouth, and dizziness.

Among the less frequent adverse reactions, there was no appreciable difference in incidence in controlled clinical studies or in the surveillance program. Adverse reactions which were 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 post-marketing experience or with an incidence of less than 1% of patients in clinical trials with the 10 mg TID tablet:

**Body as a Whole:** Syncope; malaise.

**Cardiovascular:** Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension.

**Digestive:** Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice, and cholestasis.

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

**Musculoskeletal:** Local weakness.

**Nervous System and Psychiatric:** Seizures, ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; psychosis, abnormal thinking and dreaming; hallucinations; excitement; paresthesia; diplopia.

**Skin:** Sweating.

**Special Senses:** Ageusia; tinnitus.

**Urogenital:** Urinary frequency and/or retention.

### DRUG ABUSE AND DEPENDENCE

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when AMRIX (Cyclobenzaprine Hydrochloride Extended-Release Capsules) is administered, even though they have not 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.

### 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.

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.

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.

### DOSAGE AND ADMINISTRATION

The recommended adult dose for most patients is one (1) AMRIX 15 mg capsule taken once daily. Some patients may require up to 30 mg/day, given as one (1) AMRIX 30 mg capsule taken once daily or as two (2) AMRIX 15 mg capsules taken once daily.

It is recommended that doses be taken at approximately the same time each day.

Use of AMRIX for periods longer than two or three weeks is not recommended (see **INDICATIONS AND USAGE**).

**Dosage Considerations for Special Patient Populations:** AMRIX should not be used in the elderly or in patients with impaired hepatic function (see **WARNINGS**).

### HOW SUPPLIED

AMRIX extended-release capsules are available in 15 and 30 mg strengths, packaged in bottles of 60 capsules.

**KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN. IN CASE OF ACCIDENTAL OVERDOSE, SEEK PROFESSIONAL ASSISTANCE OR CONTACT A POISON CONTROL CENTER IMMEDIATELY.**

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