

SCD-HeFT Results Swayed CMS

ICD, from page 1

meet all CMS coverage requirements for a cardiac resynchronization therapy device, according to the decision memo.

This expanded coverage is more generous than those discussed in a draft decision issued in September, which proposed excluding patients with an LVEF of at least 30% or NYHA class IV disease.

"When you look at the difference between the proposed rule and the final rule, [CMS] clearly listened to the medical profession and took our advice" along

with considering the evidence from clinical trials, said Stephen C. Hammill, M.D., president of the Heart Rhythm Society.

The ICD coverage decision came 1 week after publication of the results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) on Jan. 20 (N. Engl. J. Med. 2005;352:225-37). CMS is required to base its decisions on evidence published in peer-reviewed medical journals.

The SCD-HeFT trial, which involved more than 2,500 patients, looked at

whether ICDs improved survival compared with amiodarone or placebo in patients with NYHA Class II and Class III heart failure and a left ventricular ejection fraction less than 35%. The trial included patients with nonischemic as well as ischemic dilated cardiomyopathy. Researchers found that patients with ICDs had 23% lower mortality than did the placebo group, a statistically significant result.

The CMS decision also addressed the issue of a patient registry. In its September coverage proposal, CMS required that patients receiving ICDs be placed in a yet-to-be-developed patient registry so that researchers could track outcomes and best

practices. But the Heart Rhythm Society and other specialty groups complained that it would be impossible to set the registry up by Jan. 1, as CMS wanted (INTERNAL MEDICINE NEWS, Dec. 1, 2004, p. 4).

Instead, CMS will cover the device in patients who are registered in an already existing registry called Quality Network Exchange, or QNet, which is maintained by the Iowa Foundation for Medical Care.

"The QNet will be the first part of the registry until a more sophisticated registry ... is put together and goes into place sometime in the next 6 months," said Dr. Hammill, who is among those charged with setting up the new registry.

Dr. Hammill, who is director of heart rhythm services at the Mayo Clinic, Rochester, Minn., estimated that 500,000 patients will be candidates for ICD coverage under the new criteria. "But we know that in the past, with other indications for defibrillators, only about 20% of the patients who are candidates actually get the device," which costs between \$30,000 and \$40,000, he said.

Each year, 65,000-70,000 new patients will become candidates, he added. ■

Campral[®] (acamprosate calcium) Delayed-Release Tablets

Rx only

Brief Summary:

For complete details, please see full Prescribing Information for CAMPRAL.

INDICATIONS AND USAGE

CAMPRAL (acamprosate calcium) is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation. Treatment with CAMPRAL should be part of a comprehensive management program that includes psychosocial support. The efficacy of CAMPRAL in promoting abstinence has not been demonstrated in subjects who have not undergone detoxification and not achieved alcohol abstinence prior to beginning CAMPRAL treatment. The efficacy of CAMPRAL in promoting abstinence from alcohol in polydependent abusers has not been adequately assessed.

CONTRAINDICATIONS

CAMPRAL is contraindicated in patients who previously have exhibited hypersensitivity to acamprosate calcium or any of its components. CAMPRAL is contraindicated in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min).

PRECAUTIONS

Use of CAMPRAL does not eliminate or diminish withdrawal symptoms. **General: Renal Impairment** Treatment with CAMPRAL in patients with moderate renal impairment (creatinine clearance of 30-50 mL/min) requires a dose reduction. Patients with severe renal impairment (creatinine clearance of ≤ 30 mL/min) should not be given CAMPRAL (see also CONTRAINDICATIONS). **Suicidality** In controlled clinical trials of CAMPRAL, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but were more common in CAMPRAL-treated patients than in patients treated with placebo (1.4% vs 0.5% in studies of 6 months or less; 2.4% vs 0.8% in year-long studies). Completed suicides occurred in 3 of 2272 (0.13%) patients in the pooled acamprosate group from all controlled studies and 2 of 1962 patients (0.10%) in the placebo group. Adverse events coded as "depression" were reported at similar rates in CAMPRAL-treated and placebo-treated patients. Although many of these events occurred in the context of alcohol relapse, no consistent pattern of relationship between the clinical course of recovery from alcoholism and the emergence of suicidality was identified. The interrelationship between alcohol dependence, depression and suicidality is well-recognized and complex. Alcohol-dependent patients, including those being treated with CAMPRAL, should be monitored for the development of symptoms of depression or suicidal thinking. Families and caregivers of patients being treated with CAMPRAL should be alerted to the need to monitor patients for the emergence of symptoms of depression or suicidality, and to report such symptoms to the patient's health care provider. **Information for Patients** Physicians are advised to discuss the following issues with patients for whom they prescribe CAMPRAL. Any psychoactive drug may impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, until they are certain that their ability to do so is not impaired. Patients should be advised that they may affect their ability to engage in such activities. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast-feeding. Patients should be advised to continue CAMPRAL therapy as directed, even in the event of relapse and should be re-evaluated for need to continue therapy. In an *in vitro* bacterial reverse point mutation assay CAMPRAL has been shown to help maintain abstinence only when used as a part of a treatment program that includes counseling and support. **Drug Interactions** The concomitant intake of alcohol and CAMPRAL does not affect the pharmacokinetics of either alcohol or acamprosate. Pharmacokinetic studies indicate that administration of disulfiram or diazepam does not affect the pharmacokinetics of acamprosate. Co-administration of naltrexone with CAMPRAL produced a 14% and a 33% increase in the AUC and C_{max} of acamprosate, respectively. No adjustment of dosage is recommended in such patients. The pharmacokinetics of naltrexone and its major metabolite 6-beta-naltrexol were unaffected following co-administration with CAMPRAL. Other concomitant therapies: In clinical trials, the safety profile in subjects treated with CAMPRAL concomitantly with anticonvulsants, hypnotics and sedatives (including benzodiazepines) was similar to that of subjects taking placebo with these concomitant medications. Patients taking CAMPRAL concomitantly with antidepressants more commonly reported both weight gain and weight loss, compared with patients taking either medication alone.

Carcinogenicity, Mutagenicity and Impairment of Fertility A carcinogenicity study was conducted in which Sprague-Dawley rats receiving oral doses of 150, 300, or 600 mg/kg/day (approximately 10, 20, or 40 times the maximum recommended human daily oral dose on a mg/m² basis) had no effect on tumor incidence. There was no evidence of an increased incidence of tumors in this carcinogenicity study in the rat. An adequate carcinogenicity study in the mouse has not been conducted. Acamprosate calcium study was negative in all genetic toxicology studies conducted. Acamprosate calcium demonstrated no evidence of genotoxicity in an *in vitro* bacterial reverse point mutation assay (Ames assay) or an *in vitro* mammalian cell gene mutation test using Chinese Hamster Lung V79 cells. No clastogenicity was observed in an *in vitro* chromosomal aberration assay in human lymphocytes and no chromosomal damage detected in an *in vivo* mouse micronucleus assay. Acamprosate calcium had no effect on fertility after treatment for 70 days prior to mating in male rats and for 14 days prior to mating, throughout mating, gestation and lactation in female rats at doses up to 1000 mg/kg/day (approximately 10 times the maximum recommended human daily oral dose on a mg/m² basis). In mice, acamprosate calcium administered orally for 60 days prior to mating and throughout gestation in females at doses up to 2400 mg/kg/day (approximately 5 times the maximum recommended human daily oral dose on a mg/m² basis) had no effect on fertility.

Pregnancy Category C: Teratogenic Effects Acamprosate calcium has been shown to be teratogenic in rats when given in doses that are approximately equal to the human dose (on a mg/m² basis) and in rabbits when given in doses that are approximately 3 times the human dose (on a mg/m² basis). Acamprosate calcium produced a dose-related increase in the number of fetuses with malformations in rats at oral doses of 300 mg/kg/day or greater (approximately 3 times the maximum recommended human daily oral dose on a mg/m² basis). The malformations included hydronephrosis, malformed iris, retinal dysplasia, and retroesophageal subcutaneous artery. No findings were observed at an oral dose of 50 mg/kg/day (approximately one-fifth the maximum recommended human daily oral dose on a mg/m² basis). An increased incidence of hydronephrosis was also noted in Burgundy Tawny rabbits at oral doses of 400 mg/kg/day or greater (approximately 3 times the maximum recommended human daily oral dose on a mg/m² basis). No developmental effects were observed in New Zealand white rabbits at oral doses up to 1000 mg/kg/day (approximately 8 times the maximum recommended human daily oral dose on a mg/m² basis). The findings in animals should be considered in relation to known adverse developmental effects of ethyl alcohol, which include the characteristics of fetal alcohol syndrome (craniofacial dysmorphism, intrauterine and postnatal growth retardation, retarded psychomotor development, and behavioral malformations of neurological and behavioral disorders in humans). There are no adequate and well controlled studies in pregnant women. CAMPRAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic Effects** A study conducted in pregnant mice that were administered acamprosate calcium by the oral route at a dose of 150 mg/kg/day throughout the end of lactation on postnatal day 28 demonstrated an increased incidence of still-born fetuses at doses of 950 mg/kg/day or greater (approximately 2 times the maximum recommended human daily oral dose on a mg/m² basis). No effects were observed at a dose of 320 mg/kg/day (approximately one-half the maximum recommended human daily oral dose on a mg/m² basis). **Labor and Delivery** The pharmacokinetics of acamprosate calcium in lactating rats were similar to those in non-lactating rats. **Breastmilk Use** Forty-one of the 4234 patients in double-blind, placebo-controlled, clinical trials of CAMPRAL were 65 years of age or older, while none were 75 years of age or over. There were too few patients in the ≥ 65 age group to evaluate any differences in safety or effectiveness for geriatric patients compared to younger patients. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The adverse event data described below reflect the safety experience in over 7000 patients exposed to CAMPRAL for up to one year, including over 2000 CAMPRAL-exposed patients who participated in placebo-controlled trials.

Adverse Events Leading to Discontinuation In placebo-controlled trials of 6 months or less, 8% of CAMPRAL-treated patients discontinued treatment due to an adverse event, as compared to 6% of patients treated with placebo. In studies longer than 6 months, the discontinuation rate due to adverse events was 7% in both the placebo-treated and the CAMPRAL-treated patients. Only discontinuation due to adverse events occurred in more than 1% of patients (2% of CAMPRAL-treated vs. 0.7% of placebo-treated patients). Other events, including nausea, depression, and anxiety, while accounting for discontinuation in less than 1% of patients, were nevertheless more commonly cited in association with discontinuation in CAMPRAL-treated patients than in placebo-treated patients. **Common Adverse Events Reported in Controlled Trials** Adverse events were collected spontaneously in some controlled studies and using a checklist in other studies. The overall profile of adverse events was similar using either method. Table 1 shows those events that occurred in any CAMPRAL

treatment group at a rate of 3% or greater and greater than the placebo group in controlled clinical trials with spontaneously reported adverse events. The reported frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed, without regard to the causal relationship of the events to the drug.

Table 1. Events Occurring at a Rate of at Least 3% and Greater than Placebo in any CAMPRAL Treatment Group in Controlled Clinical Trials with Spontaneously Reported Adverse Events

Body System/ Preferred Term	CAMPRAL 1332 mg/day	CAMPRAL 1598 mg/day*	Placebo Pooled	Placebo 2019
Number of Patients in Treatment Group	397	1539	2019	1706
Number (%) of Patients with an AE	248 (62%)	910 (59%)	1231 (61%)	955 (56%)
Body as a Whole	121 (30%)	513 (33%)	685 (34%)	517 (30%)
Accidental Injury [†]	17 (4%)	44 (3%)	70 (3%)	52 (3%)
Asthenia	29 (7%)	79 (5%)	114 (6%)	93 (5%)
Pain	6 (2%)	56 (4%)	65 (3%)	55 (3%)
Digestive System	85 (21%)	440 (29%)	574 (28%)	344 (20%)
Anorexia	20 (5%)	33 (2%)	57 (3%)	44 (3%)
Diarrhea	39 (10%)	257 (17%)	329 (16%)	166 (10%)
Flatulence	4 (1%)	55 (4%)	63 (3%)	28 (2%)
Nausea	11 (3%)	69 (4%)	87 (4%)	58 (3%)
Nervous System	150 (38%)	417 (27%)	598 (30%)	500 (29%)
Anxiety	32 (8%)	80 (5%)	118 (6%)	95 (6%)
Depression	23 (6%)	63 (4%)	102 (5%)	87 (5%)
Dizziness	15 (4%)	49 (3%)	67 (3%)	44 (3%)
Dry mouth	13 (3%)	23 (1%)	36 (2%)	28 (2%)
Insomnia	34 (9%)	94 (6%)	137 (7%)	121 (7%)
Paresthesia	11 (3%)	29 (2%)	40 (2%)	34 (2%)
Skin and Appendages	26 (7%)	150 (10%)	187 (9%)	160 (10%)
Pruritus	12 (3%)	68 (4%)	82 (4%)	58 (3%)
Sweating	11 (3%)	27 (2%)	40 (2%)	39 (2%)

*Includes events coded as "fracture" by sponsor; [†]Includes events coded as "neurosis" by sponsor

[†]Includes 258 patients treated with acamprosate calcium 2000 mg/day, using a different dosage strength and regimen. [‡]Includes all patients in the first two columns as well as 83 patients treated with acamprosate calcium 3000 mg/day, using a different dosage strength and regimen.

Other Events Observed During the Premarketing Evaluation of CAMPRAL

In 20 clinical trials (4461 patients treated with CAMPRAL, 3526 of whom received the maximum recommended dose of 1998 mg/day for up to one year in duration). This listing does not include those events already listed above; events for which a drug cause was considered remote; event terms which were not general or likely to be uninformative; and events reported only once which were not likely to be acutely life-threatening. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the summary of adverse events in controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Body as a Whole** - Frequent: headache, abdominal pain, back pain, infection, flu syndrome, chest pain, chills, suicide attempt; Infrequent: fever, intentional overdose, malaise, allergic reaction, abscess, neck pain, hernia, intentional injury; Rare: ascites, face edema, photosensitivity reaction, abnormal enlarged, sudden death. **Cardiovascular System** - Frequent: palpitation, syncope; Infrequent: hypotension, tachycardia, hemorrhage, angina pectoris, myocardial infarction, phlebitis, postural hypotension; Rare: heart failure, mesenteric arterial occlusion, cardiomyopathy, deep thrombophlebitis, shock. **Digestive System** - Frequent: vomiting, dyspepsia, constipation, increased appetite; Infrequent: liver function tests abnormal, gastroenteritis, gastritis, dysphagia, eructation, gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage, liver cirrhosis, esophagitis, hematemesis, nausea and vomiting, hepatitis; Rare: melena, stomach ulcer, cholecystitis, colitis, duodenal ulcer, mouth ulceration, carcinoma of liver. **Endocrine System** - Rare: goiter, hypothyroidism. **Hemic and Lymphatic System** - Infrequent: anemia, ecchymosis, eosinophilia, lymphocytosis, thrombocytopenia; Rare: leukopenia, lymphadenopathy, monocytosis. **Metabolic and Nutritional Disorders** - Frequent: peripheral edema, weight gain; Infrequent: weight loss, hyperglycemia, SGOT increased, SPT increased, gout, thirst, hypernatremia, diabetes mellitus, avitaminosis, bilirubinemia; Rare: alkaline phosphatase increased, creatinine increased, hyponatremia, lactic dehydrogenase increased. **Musculoskeletal System** - Frequent: myalgia, arthralgia; Infrequent: leg cramps; Rare: rheumatoid arthritis, myopathy. **Nervous System** - Frequent: somnolence, libido decreased, amnesia, thinking abnormal, tremor, vasodilatation, hypertension; Infrequent: convulsion, confusion, libido increased, vertigo, withdrawal syndrome, apathy, suicidal ideation, neuralgia, hostility, agitation, nervous, abnormal dreams, hallucinations, hypesthesia; Rare: alcohol craving, psychosis, hyperkinesia, twitching, depersonalization, increased salivation, paranoid reaction, torticollis, encephalopathy, manic reaction. **Respiratory System** - Frequent: rhinitis, cough increased, dyspnea, pharyngitis, bronchitis; Infrequent: asthma, epistaxis, pneumonia; Rare: laryngismus, pulmonary embolus. **Skin and Appendages** - Frequent: rash; Infrequent: acne, eczema, alopecia, maculopapular rash, dry skin, urticaria, exfoliative dermatitis, vesiculobullous rash; Rare: psoriasis. **Special Senses** - Frequent: abnormal vision, taste perversion; Infrequent: tinnitus, amblyopia, deafness; Rare: ophthalmitis, diplopia, photophobia. **Urogenital System** - Frequent: impotence; Infrequent: orchitis, urinary frequency, urinary tract infection, sexual function abnormal, urinary incontinence, vaginitis; Rare: kidney calculus, abnormal ejaculation, hematuria, menorrhagia, nocturia, polyuria, urinary urgency. **Serious Adverse Events Observed During the Non-US Postmarketing Evaluation of CAMPRAL (acamprosate calcium)** Although no causal relationship to CAMPRAL has been found, the serious adverse event of acute kidney failure has been reported to be temporally associated with CAMPRAL treatment in at least 3 patients and is not described elsewhere in the labeling.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class Acamprosate calcium is not a controlled substance. **Physical and Psychological Dependence** CAMPRAL did not produce any evidence of withdrawal symptoms in patients in clinical trials at therapeutic doses. Post marketing data, collected retrospectively outside the U.S., have provided no evidence of CAMPRAL abuse or dependence.

OVERDOSE

In all reported cases of acute overdose with CAMPRAL (total reported doses of up to 56 grams of acamprosate calcium), the only symptom that could be reasonably associated with CAMPRAL was diarrhea. Hypercalcemia has not been reported in cases of acute overdose. A risk of hypercalcemia should be considered in chronic overdose only. Treatment of overdose should be symptomatic and supportive.

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CMS Poised to Expand Carotid Stent Coverage

In December, Centers for Medicare and Medicaid Services issued a draft decision memo that advises expanding coverage of carotid artery stenting.

Currently, the stents are covered only in the context of a clinical trial. Under the proposed criteria, stents would be covered in high-risk candidates for endarterectomy and in patients who have symptomatic carotid artery stenosis of at least 70%.

The draft also addresses the competency requirements, noting that stenting should be performed "in facilities and by physicians who have been determined to be competent in performing the evaluation, procedure, and follow-up necessary to ensure optimal patient outcomes. ... Competency will be determined through a national evaluation process by a recognized entity using approved standards."

The Society for Cardiovascular Angiography and Interventions (SCAI) expressed appreciation for CMS's work on the guidelines. "CMS did a thoughtful job in making its decision," said Joseph Babb, M.D., SCAI past president and chair of its advocacy committee. "But the society is also concerned that there were certain areas that did not seem to get adequate attention."

In a letter to the agency, SCAI noted: "The decision severely limits patient access to carotid stenting in asymptomatic high surgical risk patients in need of carotid revascularization, thereby relegating them to one of two potential therapeutic courses: medical or surgical. While we are strong supporters of aggressive medical therapy for all patients with or at risk of atherosclerotic disease, it remains unproven as to its effectiveness in high-surgical-risk patients, and therefore should not be designated as a default strategy."

—Joyce Frieden