

# CV Risk Not Caused by Radioiodine Therapy

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VANCOUVER, B.C. — The increased risk of vascular death seen in a recent study of hyperthyroid patients treated with radioiodine was confined to the period before they became hypothyroid and went on thyroxine replacement therapy, Jayne A. Franklyn, M.D., said at the annual meeting of the American Thyroid Association.

"We can speculate that the increased risk of vascular deaths was seen only in patients before they became hypothyroid because developing an underactive thyroid is an indicator of the complete cure of hyperthyroidism," said Dr. Franklyn, professor of medicine at the University of Birmingham (England).

In an earlier population-based study of 7,209 hyperthyroid Birmingham-area patients treated with radioiodine between 1950 and 1989 with 105,000 person-years of

follow-up, all-cause mortality was 13% greater than in the age- and gender-matched general U.K. population. Mortality rates due to cardiovascular and cerebrovascular disease, thyroid disease, and fracture of the femur were all significantly increased, which raised the possibility that the increased mortality might be due to an adverse effect of radioiodine. However, Dr. Franklyn and her coinvestigators noted that the excess mortality was greatest in the first year following radioiodine therapy

and might be a result of the hyperthyroidism, which was often most severe around the time of radioiodine therapy, they said (N. Engl. J. Med. 1998;338:712-8).

In her latest study, Dr. Franklyn reported on 2,668 Birmingham-area patients over age 40 who received radioiodine for hyperthyroidism in 1984-2002. During nearly 16,000 person-years of follow-up, all-cause mortality rose by 14% vs. that in a matched U.K. general population, while vascular mortality was increased by 19%.

The key finding was that the mortality increase was confined to the 1,456 patients who had not received thyroxine after radioiodine therapy, typically because their hyperthyroidism had not been completely cured. Patients who had not received T4 had a 26% greater all-cause and 32% greater vascular mortality, compared with the matched general population. In contrast, patients on T4 replacement had non-significant 8%-10% reductions in mortality relative to the general population. ■

## Campral<sup>®</sup> (acamprostate calcium) Delayed-Release Tablets

Rx only

### Brief Summary:

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

### INDICATIONS AND USAGE

CAMPRAL (acamprostate 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 polysubstance abusers has not been adequately assessed.

### CONTRAINDICATIONS

CAMPRAL is contraindicated in patients who previously have exhibited hypersensitivity to acamprostate calcium or any of its components. CAMPRAL is contraindicated in patients with severe renal impairment (creatinine clearance  $\leq 30$  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  $\leq 30$  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 2772 (0.13%) patients in the pooled acamprostate 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 patients 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 reasonably certain that CAMPRAL therapy does not 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 reminded to discuss any renewed drinking with their physician. Patients should be advised that 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 acamprostate. Pharmacokinetic studies indicate that administration of disulfiram or diazepam does not affect the pharmacokinetics of acamprostate. Co-administration of naltrexone with CAMPRAL produced a 14% and a 33% increase in the C<sub>max</sub> of acamprostate in an adjustment of dosage is recommended in such patients. The pharmacokinetics of naltrexone and its major metabolite 6-beta-naltrexone were unaffected following co-administration with CAMPRAL. Other concomitant therapies: In clinical trials, the safety profile in subjects treated with CAMPRAL concomitantly with antipsychotics, 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 received acamprostate calcium at doses of 25, 100 or 400 mg/kg/day (0.2, 0.7 or 2.5-fold the maximum recommended human dose based on an AUC comparison). 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. Acamprostate calcium was negative in all genetic toxicology studies conducted. Acamprostate 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. Acamprostate 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 4 times the maximum recommended human daily oral dose on a mg/m<sup>2</sup> basis). In mice, acamprostate 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/m<sup>2</sup> basis) had no effect on fertility.

**Pregnancy Category C Teratogenic Effects** Acamprostate calcium has been shown to be teratogenic in rats when given in doses that are approximately equal to the human dose (on a mg/m<sup>2</sup> basis) and in rabbits when given in doses that are approximately 3 times the human dose (on a mg/m<sup>2</sup> basis). Acamprostate 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 to the maximum recommended human dose (on a mg/m<sup>2</sup> basis) and in rabbits (on a mg/m<sup>2</sup> basis). The malformations included hydronephrosis, malformed ribs, retinal dysplasia, and retroesophageal subclavian 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/m<sup>2</sup> basis). An increased incidence of hydronephrosis was also noted in Burdigandy 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/m<sup>2</sup> 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/m<sup>2</sup> 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 retardation, retardation of maturation, and behavioral abnormalities), and malformations of neuropsychological 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 acamprostate calcium 100 mg/kg/day (1.5 x of gestation dose) from one of the 4234 patients in a 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  $\geq 65$  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 diarrhea was the most common reason for discontinuation of 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** Over the course of the clinical 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 192 mg/day	CAMPRAL 1000 mg/day*	Placebo Pool†	2019	1706
<b>Number of Patients in Treatment Group</b>	<b>397</b>	<b>1539</b>	<b>1539</b>	<b>2019</b>	<b>1706</b>
<b>Number (%) of Patients with an AE</b>	<b>248 (62%)</b>	<b>910 (59%)</b>	<b>1231 (61%)</b>	<b>955 (65%)</b>	
<b>Body as a Whole</b>					
Accidental Injury*	121 (30%)	513 (33%)	685 (34%)	517 (30%)	
Asthenia	17 (4%)	44 (3%)	70 (3%)	52 (3%)	
Pain	29 (7%)	79 (5%)	114 (6%)	93 (5%)	
Digestive System	6 (2%)	56 (4%)	65 (3%)	55 (3%)	
Digestive System	85 (21%)	440 (29%)	574 (28%)	344 (20%)	
Anorexia	20 (5%)	35 (2%)	57 (3%)	44 (3%)	
Diarrrhea	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	33 (8%)	63 (4%)	102 (5%)	67 (4%)	
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%)	
<b>Skin and Appendages</b>	<b>26 (7%)</b>	<b>150 (10%)</b>	<b>157 (8%)</b>	<b>160 (10%)</b>	
Pruritus	13 (3%)	64 (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 "nervousness" by sponsor  
\* includes 258 patients treated with acamprostate 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 acamprostate calcium 3000 mg/day, using a different dosage strength and regimen.

### Other Events Observed During the Premarketing Evaluation of CAMPRAL

Table 1 is a list of events that reflect treatment-emergent adverse events reported by patients treated with 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 so general as 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 are shown 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, abnormal pain, infection, flu syndrome, chest pain, chills, suicide attempt; Infrequent: fever, intentional overdose, malaise, allergic reaction, abscess, neck pain, hernia, interstitial injury; Rare: ascites, face edema, photosensitivity reaction, abdomen enlarged, sudden death.

**Cardiovascular System** — Frequent: palpitation, syncope; Infrequent: hypotension, tachycardia, hemorrhage, angina pectoris, migraine, varicose vein, myocardial infarct, 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, hyperthyroidism. **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, SGPT increased, gout, thirst, hyperuricemia, diabetes mellitus, avitaminosis, bilirubinemia; Rare: alkaline phosphatase increased, creatinine increased, hyponatremia, lactate 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, neurosis, 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: optic neuritis, diplopia, photophobia. **Urogenital System** — Frequent: impotence; Infrequent: metrorrhagia, urinary frequency, urinary incontinence, sexual union abnormal. **Other** — Frequent: urinary calculus, kidney calculus, abnormal ejaculation, hematuria, menorrhagia, nocturia, polyuria, urinary urgency. **Serious Adverse Events Observed During the Non-Use Postmarketing Evaluation of CAMPRAL (acamprostate 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** Acamprostate 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.

### OVERDOSAGE

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

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## Food Interferes With Rapid- Release L-T4

VANCOUVER, B.C. — Bioavailability of even the newer rapid-release formulation of levothyroxine known as Levoxyl is reduced 40% by taking the tablets close to a meal, Michael J. Lamson, Ph.D., said at the annual meeting of the American Thyroid Association.

The hope was that Levoxyl's rapid release might permit a new flexibility in dosing, allowing patients to take the drug in proximity to meals instead of on an empty stomach, as recommended for L-T4 therapy. But that wasn't the case in the first large study to assess the effects of a meal on oral absorption of L-T4 using the Food and Drug Administration's formal bioequivalence methodology, said Dr. Lamson of King Pharmaceuticals R&D in Cary, N.C.

He reported on 48 healthy participants in a randomized, three-way crossover trial. They took two 300-mcg tablets of Levoxyl on three occasions, each separated by a 35-day washout. One dose was taken under fasting conditions. The second dose was taken 10 minutes before eating a meal and the third dose was taken just after a meal.

Bioavailability of L-T4 was reduced by 40% regardless of whether subjects took the drug shortly before or immediately after the meal. This is a clinically significant finding, because it is well established that even small changes in L-T4 bioavailability can have a profound impact upon the success of oral replacement therapy.

In clinical terms, this means that taking rapid-release L-T4 in proximity to a meal or a medication known to interfere with L-T4 renders a 100-mcg dose of Levoxyl equivalent to a 60-mcg dose, Dr. Lamson said. Patients who have been taking their L-T4 with meals may require a dose correction of up to 40%. —Bruce Jancin