Obese Lose 14% of Weight on Novel Combo Drug

BY JANE SALODOF MACNEIL
Senior Editor

PHOENIX — Obese individuals lost 14% of their weight on average at the highest dose in a blinded, randomized, placebo-controlled trial of a novel weight loss drug combining slow-release formulations of the anticonvulsant zonisamide and the antidepressant bupropion.

Weight loss was reported as of 48 weeks, with nearly a third of the original participants continuing in a 24-week extension trial after a 24-week dose-optimization study of the experimental drug. At 48 weeks, each of 6 doses tested in the study had produced a median weight loss of 10% or more in study completers.

"And this is absent diet and exercise," Dr. Gary Tollefson, president and CEO of the study's sponsor, Orexigen Therapeutics Inc. of La Jolla, Calif., said in an interview.

Orexigen is developing the combination under the brand name Empatic. If adding diet and exercise can bring average weight loss to 20%, that would be comparable to invasive procedures such as bariatric surgery, according to Dr. Tollefson, who presented 48-week data at the annual meeting of the Obesity Society.

All told, 623 obese individuals were randomized into 7 groups (6 doses and 1 placebo) at 14 sites in the initial 24-week dose-optimization study. About 70% were white, and women comprised 80% of the baseline population. They had an average age in the mid-40s, average weight of 220 lbs, and average body mass index (BMI) of 36 kg/m^2. No one had a major medical complication such as diabetes.

By 24 weeks, average weight loss ranged from 4.5% to 8.6% with the zonisamide-bupropion combination, according to Dr. Tollefson, and was higher in those who stayed on drug (5.3%-10.3%). Meanwhile, the placebo group lost 1.2% on average.

Adverse events and adverse events leading to discontinuation were notably higher at the three highest doses tested, but the discontinuation rate at the top dose was not significantly different from placebo: 16.9% vs. 9.1%. The most common adverse events at this point were insomnia, headache, and nausea, occurring, respectively, in 16.9%, 13.5%, and 12.4% of patients at the top dose (360 mg zonisamide SR/360 mg bupropion SR, once daily).

Participants still in the study at 24 weeks had the option of continuing in a blinded extension trial. Of 87 people randomized to the highest dose, 64 completed the first 24 weeks and 56 stayed the full 48 weeks. This final group had an average weight loss of 14% at 48 weeks, with two-thirds achieving a weight loss of 10% or more.

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DR. TOLLEFSON

Orexigen has already started a phase II study at this dose and at a lower dose (120 mg zonisamide SR/360 mg bupropion SR, once daily). Dr. Tollefson said the company hopes to market the drug in more than one formulation. In the group that had been randomized to the lower dose, 71 of 85 patients completed the first 24 weeks, and 45 stayed the full 48 weeks. This last group averaged 12.5% weight loss, and 55% reached the benchmark of 10% or more.

These highest- and lower-dose groups showed improvement in secondary metabolic, cardiovascular, and quality of life end points reported by Dr. Tollefson. Among the statistically significant changes in both groups were an increase in HDL (+ 7.8 mg/dL in the low group and + 7.4 mg/dL in the high group), and reductions in waist circumference (–8.5 cm and –11 cm, respectively), and in systolic blood pressure (–2.5 mmHg and –4.5 mmHg, respectively).

At the highest dose, changes in the following measures were highly significant statistically: triglycerides (–24 mg/dL), insulin (–3.7 mcU/mL), diastolic blood pressure (–2 mm Hg), and pulse rate (3 bpm). Scores on the Impact of Weight on Quality of Life-Lite scale improved significantly at both doses.

Meanwhile, fewer adverse events were reported in the highest- and lower-dose groups during weeks 25-48. The most common adverse events in this period were dry mouth, constipation, and upper respiratory infection, reported respectively in 8.9%, 10.7%, and 12.5% of the high-dose group. One patient at the lower dose discontinued after experiencing major depression and suicidal ideation.

Concern about the weight loss drug rimonabant causing depression and suicidality led a Food and Drug Administration advisory committee to recommend against U.S. approval in 2007, even though it had been approved in Europe. Merck & Co. recently stopped development of another weight-loss drug, taranabant, because of similar concerns about psychiatric adverse events. (Joseph Proietto, Ph.D., of the University of Melbourne, presented phase III data on taranabant at the meeting. He said Merck had just notified him about the decision.)

One in five obese individuals suffers from some form of depression, according to Dr. Tollefson. They could benefit from the incorporation of bupropion, a drug used for depression (Wellbutrin) and smoking cessation (Zyban), into Empatic and a second combination weight loss drug that Orexigen is developing under the brand name Contrave.

The latter combines bupropion with naltrexone (Vivitrol), a drug used for narcotic addiction and alcohol dependency. It is in phase III trials, and the company aims to submit a new drug application to the FDA for Contrave late next year. In addition to Dr. Tollefson, the investigators included the founder of Orexigen and a vice president of the company. ■

Meal Replacements Double Weight Loss, Support Maintenance

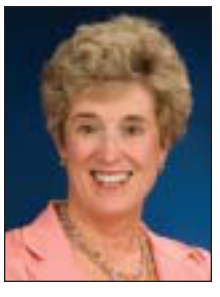
BY MIRIAM E. TUCKER
Senior Writer

WASHINGTON — What is a safe, drug-free, and effective method for treating obesity and its comorbidities in patients with diabetes or those who are at risk for it? Tell them to try prepackaged, nutritionally balanced, and calorie-controlled meal replacements.

"Meal replacements are considered state-of-the-art dietary treatment for overweight and obesity. They produce double the weight loss of traditional weight loss plans and they improve long-term maintenance," Anne Daly said at the annual meeting of the American Association of Diabetes Educators.

The benefits extend beyond weight loss, with data showing improved metabolic outcomes in patients with diabetes and other cardiovascular risk factors, said Ms. Daly, a certified diabetes educator and registered dietitian who is cofounder of the Springfield (Ill.) Diabetes and Endocrine Center.

Meal replacements have been used in several major clinical trials sponsored by the National Institutes of Health, including the Diabetes Prevention Program (DPP), Action for Diabetes in Health (Look AHEAD), and Reach Out to Enhance Wellness in Older Survivors (RENEW). Meal replacement is also mentioned in the 2007 Nutrition Position Paper of the American Diabetes Association, and is supported by the American Dietetic Association's Evidence Analysis Library, which cites eight randomized clinical trials in which patients who replaced between one and three meals a day lost 2.5-3.0 kg more than those who followed traditional low-calorie diets, about 7% from baseline.



Meal replacements provide a simple way to structure meal planning, with no calorie 'mysteries.'

MS. DALY

A "meal replacement" is any prepackaged food product—such as shakes, soups, puddings, entrees, or snack bars—that is portion controlled, calorie controlled, and high nutrition. They are used to replace an entire meal or snack with the aim of reducing calorie intake and promoting weight loss. Typically, they contain about 150-300 calories, 10-45 g carbohydrate, 10-20 g protein, and 3-9 g fat per serving. With certain meal plans, patients are encouraged to supplement the packaged foods with fresh fruits and vegetables (within prescribed carbohydrate limits for diabetic patients).

Ms. Daly's facility has had a 20-year relationship with a Boston-based company called Health Management Resources (HMR), which provides weight-loss management program services in addition to shelf-stable packaged foods that patients can buy on-site (www.hmrprogram.com). These services can be additional revenue generators for clinical practices, she noted.

However, she said, "This is not a sales pitch for HMR. Everything I say is applicable to anything out there that is a meal replacement. Try them all, taste them, and see which ones you and your patients like." Examples of well-known meal-replacement brands available in stores include Lean Cuisine, Healthy Choice, and Slimfast, while commercial weight-loss programs that sell packaged foods, such as Jenny Craig and Medifast, also fall under the heading.

Meal replacements provide a simple way to structure meal planning, with no calorie "mysteries." They achieve both portion control and predictable weight loss, while decreasing "decision anxiety" among patients who are uncertain about what they should and shouldn't eat. "Patients do better when you tell them what *to* do, rather than what not to do," Ms. Daly said.

Full meal replacement can be less costly for patients than what they're already spending on food. The U.S. Department of Agriculture estimates that the average American spends about $101 per week on food, while the HMR regimens range in cost from $73 to $92 per week.

And that's not counting the savings in medical costs. In a 12-week study of 75 patients with type 2 diabetes treated with oral agents only (of whom 57 completed the study), those randomized to receive one of two meal-replacement regimens lost more weight (6.4% and 6.7% vs. 4.9% of total body weight) than did those who followed a traditional exchange diet plan. Fasting glucose, total cholesterol, and LDL cholesterol levels were all significantly reduced among the meal-replacement patients as well (Obes. Res. 2001;9 [suppl. 4]:341S-7).

In a more recent study of 118 patients who each lost more than 100 pounds using meal replacements and increased physical activity, medications for comorbidities were discontinued in 66% at a cost savings of $100/month per patient. The patients, whose weight loss averaged 61 kg in 44 weeks, maintained a 30-kg weight loss at 5 years by continuing to replace at least one meal and one snack per day, while they were allowed unlimited fruits and vegetables (Am. J. Clin. Nutr. 2007;86:301-7).

Data from HMR on 1,000 patients show similar results. Over a 2-year period, patients lost an average of 43 pounds, with a 14% reduction in total cholesterol/HDL cholesterol level, 25% in triglycerides, and 10% in fasting glucose. Systolic blood pressures dropped an average of 8 mm Hg, and diastolic by 6 mm Hg. Approximately 21% of patients came off at least one medication. ■