

Lorcaserin Produced Significant Weight Loss

BY MARY ANN MOON

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Lorcaserin, a serotonin receptor agonist similar to fenfluramine and dexfenfluramine but designed to avoid the serotonin-related valvulopathy associated with those drugs, produces significant weight loss compared with placebo, according to a randomized trial of more than 3,000 subjects.

In conjunction with a behavior modi-

fication program, twice-daily lorcaserin enabled twice as many obese or overweight patients to lose 5% or more of their body weight during 1 year compared with placebo. The active drug also helped study subjects maintain their weight loss for a second year, compared with placebo, said Dr. Steven R. Smith of Florida Hospital's Translational Research Institute for Metabolism and Diabetes, Winter Park, and his associates.

However, as with other large studies of weight loss, this trial had a dropout rate of nearly 50% at 1 year, and nearly 40% of those subjects dropped out before 2 years.

The investigators reported the results of a prospective clinical trial evaluating the efficacy and safety of lorcaserin, conducted during September 2006–February 2009 at 98 academic and private sites, and involving 3,182 subjects.

The study subjects had a body mass index of 30–45 kg/m², or a BMI of 27–45 kg/m² plus at least one weight-related condition such as cardiovascular disease, impaired glucose tolerance, or sleep apnea. Patients with existing valvulopathy were excluded,

as were those with frank diabetes, hypertension, or depression or other psychiatric disease. Echocardiography was performed to assess valvular disease at five intervals during the course of the study.

Both the active-treatment and the placebo groups attended monthly sessions of individual nutritional and exercise counseling, and were encouraged to exercise moderately for 30 minutes per day and to reduce their daily caloric intake to 600 kcal below their estimated energy requirements.

After 1 year, 47% of the subjects taking lorcaserin had lost 5% or more of their baseline body weight, compared with 20% of those taking placebo, a statistically significant difference. Subjects receiving lorcaserin lost an average of 6% of their body weight, compared with an average 2% weight loss with placebo. Significantly more subjects in the lorcaserin group (23%) lost 10% or more of their body weight than in the placebo group (8%).

Among subjects who achieved a weight loss of 5% or more at 1 year, a greater proportion of those who continued taking lorcaserin in year 2 maintained that weight loss (70%) compared with subjects who were assigned to placebo in year 2 (50%).

Use of lorcaserin also was associated with significant declines in adverse metabolic measures such as fasting glucose levels, insulin levels, and glycated hemoglobin levels; waist circumference; adverse lipid measures such as total cholesterol, LDL cholesterol, and triglycerides; and

markers of cardiovascular risk such as C-reactive protein levels, fibrinogen levels, blood pressure, and heart rate.

Both study groups showed improvement in quality of life measures, with a greater improvement in the lorcaserin group, Dr. Smith and his colleagues wrote (*N. Engl. J. Med.* 2010; 363:245–56).

There were no significant differences between lorcaserin and placebo in the development of valvulopathy (less than 3% in both groups), and no severe mitral or aortic insufficiency was found. The two groups also showed no differences in change in pulmonary-artery systolic pressure.

However, “the actual incidence of [Food and Drug Administration]-defined valvulopathy was below the pretrial estimates; as a result, the trial was slightly underpowered regarding the primary echocardiographic safety end point,” the investigators noted.

Rates of serious adverse events were similarly low in both study groups, as were rates of depression, depressive symptoms, depressed mood, and suicidal thoughts.

Rates of headache and nausea were higher with lorcaserin than with placebo, but the symptoms tended to be mild and to resolve even with continued use of the agents.

The study was limited by its high dropout rate. It remains unknown whether the findings are applicable to patient groups that were excluded from the trial such as those with a BMI over 45, an eating disorder, or diabetes. ■

VITALS

Major Finding: More obese subjects taking twice-daily lorcaserin (47%) than taking placebo (20%) lost 5% or more of their body weight at 1 year. Subjects taking lorcaserin were more likely to maintain their weight loss for another year.

Data Source: Two-year double-blind multicenter randomized clinical trial comparing lorcaserin with placebo in 3,182 obese or overweight subjects.

Disclosures: The study was supported by Arena Pharmaceuticals, which employed several of the coauthors and was involved in study design, data analysis, data review, and writing and revising of the manuscript.

Pataday™ (olopatadine hydrochloride ophthalmic solution) 0.2%

INDICATIONS AND USAGE

PATADAY™ solution is indicated for the treatment of ocular itching associated with allergic conjunctivitis.

CONTRAINDICATIONS

Hypersensitivity to any components of this product.

WARNINGS

For topical ocular use only. Not for injection or oral use.

PRECAUTIONS

Information for Patients

As with any eye drop, to prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use. Patients should be advised not to wear a contact lens if their eye is red.

PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% should not be used to treat contact lens related irritation. The preservative in PATADAY™ solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least ten minutes after instilling PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% before they insert their contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 40 µL drop size and a 50 kg person, these doses were approximately 150,000 and 50,000 times higher than the maximum recommended ocular human dose (MROHD). No mutagenic potential was observed when olopatadine was tested in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* mammalian chromosome aberration assay or an *in vivo* mouse micronucleus test. Olopatadine administered to male and female rats at oral doses of approximately 100,000 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of approximately 15,000 times the MROHD level.

Pregnancy:

Teratogenic effects: Pregnancy Category C

Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 150,000 times the MROHD and rabbits treated at 400 mg/kg/day, or approximately 100,000 times the MROHD, during organogenesis showed a decrease in live fetuses. In addition, rats treated with 600 mg/kg/day of olopatadine during organogenesis showed a decrease in fetal weight. Further, rats treated with 600 mg/kg/day of olopatadine during late gestation through the lactation period showed a decrease in neonatal survival and body weight. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

Nursing Mothers:

Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% is administered to a nursing mother.

Pediatric Use:

Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

Geriatric Use:

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Symptoms similar to cold syndrome and pharyngitis were reported at an incidence of approximately 10%.

The following adverse experiences have been reported in 5% or less of patients:

Ocular: blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, pain and ocular pruritus.

Non-ocular: asthenia, back pain, flu syndrome, headache, increased cough, infection, nausea, rhinitis, sinusitis and taste perversion. Some of these events were similar to the underlying disease being studied.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop in each affected eye once a day.

HOW SUPPLIED

PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% is supplied in a white, oval, low density polyethylene DROP-TAINER® dispenser with a natural low density polyethylene dispensing plug and a white polypropylene cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

NDC 0065-0272-25

2.5 mL fill in 4 mL oval bottle

Storage:

Store at 2°C to 25°C (36°F to 77°F)
U.S. Patents Nos. 4,871,865; 4,923,892; 5,116,863; 5,641,805; 6,995,186

Rx Only

References:

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Studies Needed to Confirm Safety

The history of many pharmacologic therapies for obesity—including rimonabant, sibutramine, fenfluramine, and dexfenfluramine—is characterized by withdrawal from the market after postmarketing discovery of serious adverse effects. Given this history, “the justification for using lorcaserin to manage obesity is not greater efficacy than currently available drugs, but rather an apparently much better safety and adverse-event profile,” said Dr. Arne Astrup.

Lorcaserin therapy also was associated with “slight, but clinically relevant, improvements in almost all reported surrogate measures of diabetes and cardiovascular risk. These findings are important in light of the problems with drugs such as rimonabant and sibutramine, which do not produce similar reductions in

blood pressure, heart rate, and levels of [LDL] cholesterol that would be expected with the weight loss achieved,” he noted.

“Lorcaserin use does not seem to increase the risk of valvulopathy, pulmonary hypertension, depression, or suicidal thoughts, but phase III studies will be required to confirm these initial findings in larger populations of patients,” he added.

DR. ASTRUP is in the department of nutrition at the University of Copenhagen in Frederiksberg, Denmark. He reported being a board member and receiving grants from Novo Nordisk, Neurosearch, and Merck. These comments are taken from his editorial accompanying Dr. Smith's report (*N. Engl. J. Med.* 2010;363:288–90).



MY TAKE