ACS Chemical Neuroscience pubs.acs.org/acschemicalneuroscience

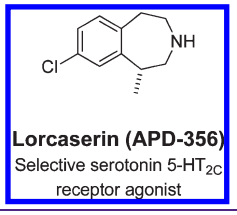
Viewpoint

ACS Chemical Neuroscience Molecule Spotlight on Lorcaserin

Corey R. Hopkins

Department of Pharmacology and Vanderbilt Program in Drug Discovery, Vanderbilt University Medical Center, Vanderbilt University, Nashville, Tennessee 37232-6600

Abstract



Lorcaserin (APD-356) is the first in a new class of selective serotonin 5-hydroxytryptamine$_{2C}$ (5-HT$_{2C}$) receptor agonists. On December 22, 2009, the compound's developer (Arena Pharmaceuticals) submitted an NDA to the FDA for approval for weight management.

Keywords: Lorcaserin, selective serotonin 5-HT$_{2C}$ receptor agonist, weight loss

Lorcaserin (APD-356) is a novel, selective human 5-hydroxytryptamine$_{2C}$ agonist in late-stage development by Arena Pharmaceuticals as a potential treatment for weight management. The NIH reported in 2007 that ~65% of US adults are overweight or obese, and reports put the medical burden of obesity in the US to be approximately $147 billion in 2008 (*1*). Excess weight and obesity are known risk factors for other diseases such as diabetes, heart disease, stroke, hypertension, and some forms of cancer. In addition, obesity is associated with other disorders such as high blood cholesterol and depression. Although obesity is widely recognized as a major impacting stress on the overall health care industry, very few drugs to help treat obesity have made a major impact on the community. There have been several drugs to hold promise in this area; however, two of the more widely heralded drugs ended up either being pulled from the market (Phen-Fen) or were never approved in the US (Accomplia/Rimonabant). Phen-Fen, removed from the market due to its associations with cardiovascular complication, was a nonselective agonist of both central and peripheral 5-HT$_{2B}$ receptors. Rimonabant was a CB$_1$ blocker that did not gain approval due to its side effect profile.

Unlike Phen-Fen, Lorcaserin works as a selective agonist of the 5-HT$_{2C}$ receptor in the hypothalamus. Lorcaserin has a K_i value of 15 nM versus human 5-HT$_{2C}$ and is 7.5-fold selective versus 5-HT$_{2A}$ (112 nM) and 11.6-fold selective versus 5-HT$_{2B}$ (174 nM) (*2*). In addition, lorcaserin is a full agonist for the 5-HT$_{2C}$ receptor in a functional inositol phosphate accumulation study with 18-fold and 104-fold selectivity versus 5-HT$_{2A}$ and 5-HT$_{2B}$ (*2*). Rats maintained on a high fat diet that were chronically (daily) dosed with lorcaserin showed a dose-dependent reduction in food intake and body weight gain (*2*). These were maintained during the 4-week study, and upon discontinuation, body weight returned to control levels. These preclinical studies demonstrate Lorcaserin's effectiveness, with potential for the treatment of obesity.

On the basis of the favorable preclinical data, Lorcaserin was advanced into clinical evaluation and has recently completed two phase 3 clinical trial programs. In total, Lorcaserin has been evaluated in 18 clinical trials totaling >8,500 patients (*3*). The two pivotal phase 3 clinical trials, BLOOM and BLOSSOM, were both double-blind, randomized, placebo-controlled trials evaluating obese patients (BMI 30 to 45) with or without comorbid conditions, and overweight patients (BMI 27 to 29.9) with at least one comorbid condition (hypertension, etc.) (*3*). Key findings of the two studies are as follows: about two-thirds of patients achieved at least 5% weight loss (with one-third achieving 10%); on average, patients lost about 8% of their weight (17 to 18 lbs.); and heart rate and blood pressure were lowered (*4*). The only adverse event that exceeded the placebo rate by 5% was mild to moderate transient headache (*5*).

On February 26, 2010, Arena Pharmaceuticals announced that the US FDA had assigned a Prescription Drug User Fee Act (PDUFA) date of October 22, 2010 for the review of the NDA (New Drug Application) for Lorcaserin (*3*). This acceptance signifies that the application is sufficiently complete to permit a review and that the PDUFA data is the date set by the FDA

Received Date: June 16, 2010
Accepted Date: June 21, 2010
Published on Web Date: November 17, 2010

© 2010 American Chemical Society

DOI: 10.1021/cn100059u | *ACS Chem. Neurosci.* (2010), *1*, 718–719

to complete its review of the NDA. Arena plans to have Lorcaserin on the market with 12-weeks of US regulatory approval, which would be the first new weight loss drug in a decade (*6*).

References

1. Flegal, K. M., Carroll, M. D., Ogden, C. L., and Curtin, L. R. (2010) Prevalence and trends in obesity amound US adults, 1999−2008. *J. Am. Med. Assoc.*235–241.

2. Thomsen, W. J., Grottick, A. J., Menzaghi, F., Reyes-Saldana, H., Espitia, S., Yuskin, D., Whelan, K., Martin, M., Morgan, M., Chen, W., Al-Shamma, H., Smith, B., Chalmers, D., and Behan, D. (2008) Lorcaserin, a novel selective human 5-hydroxytrptamine$_{2C}$ agonist: in vitro and in vivo pharmacological characterization. *J. Pharmacol. Exp. Ther. 325*, 577–587.

3. www.drugs.com/nda/lorcaserin_100226.html.

4. http://www.arenapharm.com/wt/page/bloom.html.

5. http://www.arenapharm.com/wt/page/lho.html.

6. http://www.reuters.com/article/idUSN1225473220100312.

© 2010 American Chemical Society

DOI: 10.1021/cn100059u | *ACS Chem. Neurosci.* (2010), *1*, 718–719