

Acomplia (Rimonabant) and OTC Orlistat for Weight Loss

Background

An estimated 64% of Americans are either overweight (body mass index [BMI]=25 to 29.9 kg/m²) or obese (BMI>30 kg/m²).^{1,2} Obesity is now an epidemic in the U.S. and can lead to numerous health problems such as diabetes, cardiovascular disease, sleep apnea, and certain types of cancer.^{1,2}

Many overweight patients turn to dietary weight-loss supplements, herbal products, or fad diets in hopes of shedding extra pounds. However these non-FDA approved weight loss products are often associated with harmful side effects. Currently there are only two prescription products approved by the FDA for long-term management of obesity: Meridia (sibutramine) and Xenical (orlistat). Sibutramine is an appetite suppressant and orlistat is a lipase inhibitor, which reduces the body's ability to absorb dietary fat by about one-third. Several other prescription products (appetite suppressants) are approved for short-term weight loss: phentermine (Ionamin), diethylpropion (Tenuate), phendimetrazine, and benzphetamine (Didrex).

A new class of anti-obesity agent (selective cannabinoid type 1 inhibitor), Acomplia (rimonabant), is currently under FDA review. In addition, the FDA advisory committee recently recommended approval of the OTC version of orlistat.

OTC Orlistat

If approved, the OTC version of orlistat will be sold under the name Alli.³ Alli will be available as 60 mg capsules, which is half the strength of prescription Xenical (remaining on the market).³ Alli will be indicated for short-term use (<6 months) to promote weight loss in overweight adults in addition to reduced calorie and low fat diet. The pricing for Alli is anticipated to be about 60 cents per capsule.³ GlaxoSmithKline plans on packaging the product as a starter pack or refill pack containing reference guides and tools to promote healthy eating.⁴ GlaxoSmithKline also plans on promoting their behavioral support programs to help users of OTC orlistat adopt and maintain a healthy eating plan and physical activity.⁴ The behavioral support program is a 12-month web-based behavioral support program available free to OTC orlistat users.⁴ If approved, the product is expected to be available the third quarter of this year.³

Safety Concerns with OTC Orlistat

The FDA advisory committee raised several safety concerns of orlistat being available without a prescription. Although a relatively safe agent, orlistat may increase the risk of fat-soluble vitamin deficiencies and potentially interact with cyclosporine (subtherapeutic cyclosporine levels) and warfarin (marked elevation in INR).⁵ There are concerns that the proposed nonprescription labeling for orlistat may not adequately direct the safe use of the drug. In a pilot nonprescription study, 50% of patients who were on cyclosporine or warfarin failed to realize that they were not supposed to take orlistat while on these medications.^{5,6} In the same study, only 35% of diabetic patients realized that orlistat is not recommended for their use after reading the fact sheet for OTC orlistat.^{5,6} There is also concern of misuse by teens or non-overweight individuals with eating disorders. In addition, concerns of orlistat being used during a high fat binge and enabling poor eating behaviors were also raised.⁶

Some also questioned the purpose of having a short-term weight loss agent available. Being overweight and obesity tend to be chronic problems. Lost weight is quickly regained once weight-loss treatment is discontinued. Short-term weight loss is not associated with long-term clinical benefits.⁶ Moreover, only modest weight loss was observed after four to six months of orlistat treatment (average 1.2 to 2.9 kg, relative to placebo).⁶

The most commonly-experienced side effects with orlistat are gastrointestinal: fecal urgency, diarrhea, and fatty stool.⁴ However, it's suggested that the low dose and short-term OTC orlistat regimen is less likely to cause these side effects and that there is less potential for fat-soluble vitamin deficiencies.⁴

In response to the safety concerns, GlaxoSmithKline plans on promoting Alli along with a weight-loss program with reference guides and a web-based behavioral support program to promote healthy eating. The FDA advisory committee ultimately recommended approval for the OTC version of orlistat. The advisory committee believes that

having an FDA-approved OTC weight loss drug available gives consumers a safer option than the numerous non-FDA approved weight loss dietary supplements or herbal products, many of which contain stimulants. Of note, orlistat has been available as a nonprescription product in Australia and New Zealand since 2004 and 2005, respectively, but it is sold "behind the counter" requiring face-to-face consultation with a pharmacist.⁷

Acomplia (Rimonabant)

Rimonabant is a selective inhibitor of the CB1 receptor, which is one of two receptors found in the endocannabinoid (EC) system.⁸ In obesity, it is thought that an over-activated EC system results in excessive food intake and fat accumulation.⁸ Over activation of the EC system may also be associated with nicotine dependence.⁸ Inhibition of the CB1 receptors results in decreased food intake and decreased craving for nicotine, while peripherally, rimonabant affects adipocytes to increase levels of adiponectin, which leads to a reduction in insulin resistance, improved glucose tolerance, a reduction in serum triglyceride levels, and increased HDL levels.⁸

Clinical trial data have shown rimonabant to be an effective treatment for obesity and smoking cessation.⁸ In addition to weight loss, patients treated with rimonabant had significant reductions in waist circumference and triglyceride levels, and increases in HDL cholesterol.⁸ Preliminary data also suggest rimonabant may have positive effect on metabolic syndrome and possibly slow the progression of atherosclerosis.⁸ Sanofi-Aventis recently announced a new phase III trial (STRADIVARIUS [Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant-The Intravascular Ultrasound Study]) to examine the effect of rimonabant on atherosclerosis.⁹

Rimonabant was generally well tolerated in clinical trials. In RIO-Europe (one year trial), the most common adverse effects with rimonabant

20 mg once daily were depressed mood (3.7%), anxiety (1.0%), nausea (3.5%), and headache (0.7%).⁸ In patients treated with 5 mg, depressed mood occurred in 2.3%, headaches in 0.3%, nausea in 0.2%, and no patients reported anxiety or vomiting.⁸ Rimonabant's negative effect on mood is related to its selective inhibition of CB1 receptor, which works opposite of CB1 agonists such as marijuana.

Two year data from the RIO-North America trial was recently published. The results from the study showed that patients treated with rimonabant 20 mg daily vs. placebo had significant mean reduction in weight (-6.3 + 0.2 kg vs. -1.6 + 0.2 kg, $p < 0.01$), waist circumference (-6.1 + 0.2 cm vs. -2.5 + 0.3 cm, $p < 0.001$) and triglyceride levels (-5.3% + 1.2% vs. 7.9% + 2%, $p < 0.001$), and a greater increase in HDL level (12.6% + 0.5% vs. 5.4% + 0.7, $p < 0.001$).¹⁰ Patients who were switched from rimonabant 20 mg to placebo in the second year of the trial had regained weight while those who continued with rimonabant maintained their weight loss and favorable changes in cardiometabolic risk factors.¹⁰ Rimonabant was generally well tolerated. The most commonly reported drug-related side effect was nausea (11.2% rimonabant vs. 5.8% placebo). However, the drop-out rate was high (45% with rimonabant 20 mg vs. 50% with placebo) at one year.¹⁰ More studies are required to examine the long-term effects of rimonabant.

Rimonabant represents an exciting new class of medications that could have a significant impact in the treatment of obesity, nicotine dependence, and metabolic syndrome.⁸ While initial results appear promising, there are many unanswered questions, including long-term adverse effects and drug interactions.

Conclusion

Both Alli and Acomplia are pending FDA approval. Sanofi-Aventis submitted separate NDA's for Acomplia's two indications. At this time Acomplia is "approvable" for weight loss but "not approvable" for smoking cessation.¹¹ If approved, consumers will have greater access to an FDA-approved weight-loss drug (Alli). In addition, the approval of Acomplia would offer another prescription weight-loss drug that works differently than the current available products. However, it is important to counsel patients that Alli and Acomplia are not magic bullets. They should be used as an adjunct to diet and exercise to manage obesity/weight loss. Patients should be counseled about the importance of diet and exercise for disease prevention and weight management.

Project Leader in preparation of this Detail-Document: Wan-Chih Tom, Pharm.D.

References



We Take Our Drugs Seriously.

1. Snow V, Barry P, Fitterman, et al. Pharmacologic and surgical management of obesity in primary care: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2005;142:525-31.
2. Diets and supplements for weight loss. *Pharmacist's Letter/Prescriber's Letter* 2004;20(1):200110.
3. Personal communication, Alli spokesperson. GlaxoSmithKline. Research Triangle Park, NC 27709. February 10, 2006.
4. FDA Advisory Committee briefing document. Orlistat 60 mg capsules. NDA21-887. Joint meeting of the Nonprescription Drugs. January 23, 2006. Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee. http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4201B1_01_GSK-Brief.pdf. (Accessed February 7, 2006).
5. Golden J. Orlistat nonprescription briefing document. Joint Nonprescription Drugs advisory committee and Endocrine and Metabolic Drugs Advisory Committee Meeting. January 23, 2006. http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4201B1_02_03-FDA-Clinical-Review.pdf. (Accessed February 6, 2006).
6. Weiss S. Review of Label Comprehension Study, NDA 21-887 GlaxoSmithKline Healthcare Orlistat 60 mg capsules for weight loss. FDA Center for Drug Evaluation and Research. Office of Nonprescription Products. December 10, 2005. http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4201B1_02_06-FDA-Label-Review.pdf. (Accessed February 6, 2006).
7. Roche Pharmaceuticals New Zealand News Release. Xenical available from pharmacists starting today. March 10, 2005. http://www.roche.co.nz/attachments/news_21.pdf. (Accessed February 7, 2006).
8. Investigational drug: rimonabant (Acomplia). *Pharmacist's Letter/Prescriber's Letter* 2004;20(11):201114.
9. Anon. New Acomplia trial announced, but enrollment said almost completed. <http://www.acompliareport.com/News/news-020106.htm>. (Accessed February 6, 2006).
10. Pi-Sunyer FX, Aronne LJ, Heshmati HM, et al. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients. RIO-North America: a randomized controlled trial. *JAMA* 2006;295:761-75.
11. Acomplia is "not approvable" for smoking cessation, "approvable" for weight loss. *FDC Reports-"The Pink Sheet Daily."* February 17, 2006.