Rimonabant adds appetizing choice to slim obesity market

If there's going to be a Prozac of obesity, it might well be rimonabant. A pill that could hit the market as early as spring 2006, rimonabant is being touted as a blockbuster that could net six billion dollars in annual sales by 2010. But the checkered history of diet drugs has some experts worried about the pill's potential side effects.

To fight fat, rimonabant cleverly harnesses the endocannabinoid neurotransmitter system. Activating the endocannabinoid receptor CB1 in the brain gives marijuana users the munchies. Rimonabant (trade name Acomplia) blocks that same receptor and triggers the reverse. In one trial in Europe, 363 participants taking the highest daily dose of the drug dropped 8.6 kilograms on average in a year (*Lancet* **365,** 1389–1397; 2005). The drug also acts on CB1 receptors elsewhere in the body, including fat cells, where it is thought to make obese patients burn fat more quickly.

In the languishing obesity market, that's cause for celebration.

"If rimonabant lives up to its promise, this single-handedly will change the [obesity] marketplace," Bernice Welles, vice president of development at DiObex, a San Francisco-based biotechnology company, told an obesity conference in September 2005.

Others are more cautious—with good reason, perhaps. Obesity drugs have a troubled past, from decades-old misuse of amphetamines to the fen-phen debacle of the mid-1990s, when one component of the popular pill combination was found—but only after several years on the market—to cause irreversible heart valve damage.

When drugs target the central nervous system to control appetite, "how they influence peripheral function only comes out after people have been on the drugs for a period of time," notes Jeffrey Bland, president of Metagenics, a California-based maker of nutritional products. Because weight loss usually requires long-term treatment, he says, the risks of chronic adverse effects become more significant.

Sanofi-Aventis, the drug's maker, points out that it has tested the drug in clinical trials with 13,000 subjects, some on the drug for two years, without seeing serious side effects. "Obviously once a drug comes into the marketplace we learn much more," says Douglas Greene, vice president for corporate medical and regulatory affairs at the Paris-based company. He says the company recently enrolled another 17,000 patients in a five-year trial to monitor cardiovascular effects.

The company is betting that the new trial will strengthen a case for the drug's use beyond weight loss. In initial clinical trials, rimonabant helped smokers kick the habit without gaining weight, boosted insulin sensitivity and improved cholesterol and blood lipid levels (*New Engl. J. Med.* **353**, 2121–2134, 2005). "This is a medical drug for people at medical risk that have no treatment, rather than a diet pill," says Greene. "Our clinical program has been focused on establishing that."

Despite its promise as a metabolic magic bullet, rimonabant will have to overcome skepticism about its side effects. Trial subjects regained their weight when they stopped taking the pill, suggesting that they would need to take it indefinitely. The most common reported side effects have been nausea, dizziness, diarrhea and joint pain, which investigators described as "mild and transient."

However, in that same study, investigators also reported that ten participants taking the drug—compared to two in the placebo group—dropped out of the trial because of depression. In a 2005 survey of 142 doctors conducted by Decision Resources, a Massachusetts-based pharmaceutical market research firm, more than 80% listed depression triggered by the drug as their primary concern; insomnia ran a distant second at 45%.

Still, physicians trying to help a burgeoning obese population don't have many alternatives. The drugs on the market—Abbott's Meridia (sibutramine, marketed as Reductil in Europe) and Roche's Xenical (orlistat)—offer ho-hum effectiveness and side effects ranging from high blood pressure to fecal incontinence. What's more, because insurers refuse to reimburse for the pills, patients are quick to give up on them.

This set of circumstances bodes well for rimonabant, notes Donny Wong, an analyst with Decision Resources. "It comes at a time when there's a lot of dissatisfaction with existing drugs," he says, "and it will be the only novel therapy to emerge on the market for at least another three, four or perhaps five years."

Meredith Wadman, Washington DC

Major obesity drugs on the US market

Drug	Manufacturer	Mechanism of action	Launched	2004 US sales	Side effects	Daily cost (approx.)
Orlistat (Xenical)	Roche	Blocks fat absorption in the gut	1998	$102 million	Oily spotting, abdominal pain, fecal urgency	$3.40
Sibutramine (Meridia)	Abbott	Inhibits reuptake of neurotransmitters, producing feeling of fullness	1999	$73 million	Headache, dry mouth, anorexia, constipation, insomnia, high blood pressure	$3.10
Phentermine (Adipex-P, Ionamin)	Gate Pharmaceuticals, Medeva Pharmaceuticals	Increases levels of catecholamines, producing feeling of fullness.	1970	$49 million	Tremor, increased heart rate, palpitations, insomnia, high blood pressure	$1.00

Selected obesity drugs in development

Drug	Manufacturer	Mechanism of action	Stage of development	Side effects
Rimonabant (Acomplia)	Sanofi-Aventis	CB1 receptor antagonist	Under FDA review	Nausea, dizziness, diarrhea, joint pain
ATL-962 (Cetilistat)	Alizyme	Blocks fat absorption in the gut	Phase 3 to begin in 2006	Some gastrointestinal side effects
AOD9604	Metabolic Pharmaceuticals	Human growth hormone fragment that promotes fat-burning	Phase 2b	Some gastrointestinal effects at high doses
APD356	Arena	Selectively stimulates serotonin receptor in hypothalamus, decreasing appetite	Phase 2b	Nausea, headache
CP-946,598	Pfizer	CB1 receptor antagonist	Phase 2	Similar to other CB1 antagonists
PYY3-36	Nastech Pharmaceuticals/Merck	Synthetic form of the appetite-suppressing hormone PYY	Phase 1	Nausea, headache, dizziness
SLV-319	Solvay Pharmaceuticals, Bristol-Myers Squibb	CB1 receptor antagonist	Phase 1	Undisclosed

Sources: IMS Health, Decision Resources

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