PHARMACEUTICALS

Slim spoils for obesity drugs

Drug makers struggle to find viable treatments for global epidemic.

BY HEIDI LEDFORD

When an obesity drug that he had helped to invent came up before a panel of US Food and Drug Administration (FDA) advisers last week, physiologist Michael Cowley couldn't bear to watch. "It's like watching your favourite team," says Cowley, director of the Monash Obesity and Diabetes Institute in Victoria, Australia. "You worry that if you pay too much attention they'll lose."

Many thought that Cowley's drug, Contrave, didn't stand a chance. The same panel had already voted against two obesity drugs this year and said a third should be pulled off the market.

But, defying expectations, the panel voted in favour of Contrave, making it the first obesity drug to win a recommendation for approval in more than a decade. It was a rare taste of success for a field that has progressed so slowly that many have abandoned it altogether. "There is surprisingly little activity now given the potential size of the market and the high unmet need," says Michael Hay, an analyst at the market-research firm Sagient Research Systems, based in San Diego, California.

Effective obesity drugs have proven enormously difficult to develop. The brain circuits responsible for appetite overlap with those that control other important functions, including mood, raising the risk of side effects. And obese patients would probably have to take a drug for years, with testing involving large patient populations, driving up development costs.

Most devastating to the field was the failure of drugs designed to block receptors in the brain that respond to appetite-stimulating chemicals called cannabinoids. Several major pharmaceutical firms had pursued this angle, but gave up after the FDA's advisory panel voted down Paris-based Sanofi-aventis's drug rimonabant in 2007. The London-based European Medicines Agency had already approved rimonabant, but in 2008 it advised doctors not to prescribe it given the risk of suicidal tendencies.

Hopes were running high for a turnaround, with three obesity drugs coming before the FDA this year. First up was a drug called Qnexa from Vivus, based in Mountain View, California. Qnexa is a combination of two drugs already on the market. One, phentermine, is a brain stimulant that suppresses appetite. The other, topiramate, is a treatment for epilepsy. On 15 July, FDA advisers said that the drug's modest weight-loss benefit was not sufficient to counterbalance the risk of its side effects, which include memory problems and birth defects.

The next drug to go before the panel was lorcaserin, made by Arena Pharmaceuticals in San Diego. But on 16 September, the panel again voted no. The drug simply didn't work well enough to make it worth the safety risks, says Abraham Thomas, an endocrinologist at the Henry Ford Hospital in Detroit, Michigan, who chaired the committee.

By the time Contrave took the stage, market investors had become sceptical (see graph). Contrave, developed by Orexigen Therapeutics, based in La Jolla, California, and co-founded by Cowley, is also a blend of two approved drugs. One, bupropion, is an antidepressant that blocks the effects of the neurotransmitter noradrenaline. The other, naltrexone, inhibits the effects of opioids on the brain and is used to treat alcoholism. Together, the two boost the activity of a brain circuit called the POMC pathway, which reduces hunger. A final decision on Contrave is expected early next year.

But even if approved, Contrave will hardly spell the end of the obesity epidemic. In one recent study, those who took the drug lost only about 8% of their body weight over six months — little better than orlistat, the only over-the-counter obesity drug currently available in the United States. Most US health-insurance plans don't cover weight-loss drugs, making a minimally effective drug even less appealing .

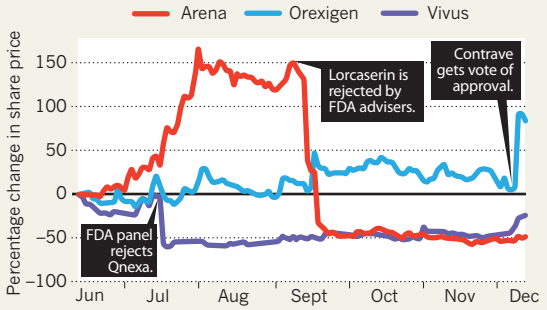
A change of fortune may require a change of strategy, says Thomas Hughes, chief executive of Zafgen, an obesity drug company in Cambridge, Massachusetts. In the past, most companies pursued drugs that would restrict appetite. Now, he says, they're looking for new ideas, "but those ideas are few and far between".

The next obesity drugs likely to face the FDA target metabolism, says Hay (see table). Victoza (liraglutide), developed by Novo Nordisk, based in Bagsvaerd, Denmark, to treat type 2 diabetes, mimics a gut hormone called 'glucagon-like peptide 1', which boosts insulin sensitivity and slows stomach emptying.

Although more than a dozen other drugs are in early clinical trials, Thomas remains pessimistic. Many of them target pathways that have already been tried, he notes, or are reformulations of drugs that didn't make it the first time around. "You can see what's in phase I clinical trials now and the answer is 'nothing very exciting'," agrees Stephen Bloom, an endocrinologist at Imperial College London. "The obesity problem is unsolved, and looks like it's going to stay that way for quite some time." ■

MARKET MOVEMENTS

Only one of a trio of obesity drugs submitted to a Food and Drug Administration panel got the green light.



SOURCE: GOOGLE FINANCE

UP-AND-COMING: THE NEXT OBESITY DRUGS IN THE PIPELINE

Drug	Developer	Target	Clinical trial status	Estimated approval date	Projected revenue
Victoza (liraglutide)	Novo Nordisk	GLP-1 receptor	Phase III	2015	$780.4 million
Empatic (zonisamide/bupropion)	Orexigen Therapeutics	Dopamine and noradrenaline reuptake	Phase IIb	2017	$443.0 million
Symlin (pramlintide)/metreleptin	Takeda/Amylin	Amylin receptor, leptin receptor	Phase IIb	2015	$898.0 million
Velneperit	Shionogi & Co.	Neuropeptide Y/peptide YY receptors	Phase IIb	2014	—
Tesofensine	NeuroSearch	Dopamine, noradrenaline and serotonin reuptake	Phase IIb	—	—

SOURCE: BIOMEDTRACKER