Merck's statin first to receive over-the-counter status

The successful OTC designation for simvastatin in the United Kingdom does not necessarily mean that rival statin manufacturers will follow suit.

Cormac Sheridan

The UK Department of Health has announced that, starting this month, it will permit over-the-counter (OTC) sales of a low-dose, 10-mg formulation of simvastatin (Zocor Heart Pro; Merck) to people at moderate risk of coronary heart disease.

This is the first time such a move has been sanctioned for a statin. It follows earlier, unsuccessful applications by Bristol-Myers Squibb and by Merck to the US FDA in 2000 to gain OTC status for pravastatin (Pravachol) and lovastatin (Mevacor), respectively.

Merck's recent move is interpreted by one analyst as a response to the threat from generics — simvastatin lost its patent protection in the UK last year — rather than an attempt to gain market share from its main rivals. "If they did £20 million in [OTC sales in] the UK, I'd be amazed," says Anthony Colletta, head of pharmaceuticals equity research at Dresdner Kleinwort Wasserstein in London. (Statins cost the UK's National Health Service around £700 million a year.) "It's really draining the last few drops out of it."

BMS faces a similar issue, as pravastatin will come off-patent in the US in April 2006. "We are continuing to explore the potential of Pravachol as an over-the-counter therapy for patients in whom treatment is appropriate," says BMS spokeswoman Julie Keenan, although she declines to comment on the status of that process, or on whether it extends to markets outside the United States. The FDA is also remaining tight-lipped, and the UK Department of Health says it has received no additional applications for an OTC switch for a statin.

Neither Pfizer nor AstraZeneca intends to react should BMS and Merck succeed in gaining OTC status in the United States for their respective statins. "We would only look at it if agencies asked us to. We are not dependent on what our competitors do," says Pfizer Associate Medical Director Michael Zaiac. AstraZeneca's rosuvastatin (Crestor) is not a candidate for an OTC switch any time soon, given its recent market launch. "Our key focus is to go after those patients who should be treated under the care of their general practitioners," says

Simvastatin now has OTC status in the UK.

Neil Brickel, UK physician for Crestor at AstraZeneca.

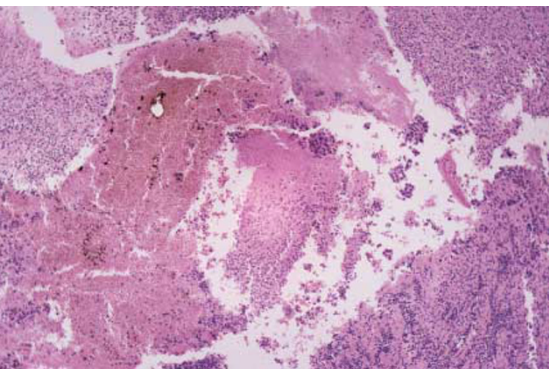
Any further statin OTC approvals, according to a research note written by Frazer Hall, a London-based analyst at Credit Suisse First Boston, are also likely to be at low doses and would be aimed at patients with a relatively low risk of developing cardiovascular disease. "Also, given recent clinical data, the market may polarize in the future, with the more efficacious products, such as Lipitor [atorvastatin; Pfizer] and Crestor left largely unaffected by the OTC availability of other products," Hall wrote.

Lessons learnt from Genasense's failure

If primary endpoint data for cancer treatments aren't met, positive secondary endpoint data will not guarantee approval, says the FDA.

Simon Frantz

The US FDA advisory committee's rejection of Genta/Aventis's antisense treatment oblimersen sodium (Genasense) for malignant melanoma provides a lesson on the agency's expectations for survival data for regulatory approval.



Data for Genasense did not show adequate effectiveness against malignant melanoma.

The agency has stated that for some forms of cancer, the use of progression-free survival (PFS) is an appropriate endpoint. In these conditions, PFS can indicate attractive therapeutic options, and can provide an informative clinical marker in patients who are not expected to live for long.

But the advisory committee voted 13 to 3 that the PFS data that Genta provided for oblimersen could not be considered substantial evidence of effectiveness, because PFS was submitted as the secondary endpoint after the primary endpoint of overall survival failed.

Genta's submission data were based largely on an open-label 771-patient trial (GM-301) of oblimersen combined with dacarbazine. There was no statistically significant effect on overall survival. Patients on oblimersen/dacarbazine had a median survival of 274 days, compared with 238 days for dacarbazine alone ($p = 0.18$). Secondary endpoints did show a significant effect: PFS was 74 days for oblimersen/dacarbazine, compared with 49 days for dacarbazine ($p = 0.003$). Antitumour response rate was 11.7% for oblimersen/dacarbazine, compared with 6.8% dacarbazine ($p = 0.019$).

However, the FDA said that efficacy results based on these secondary endpoints were only to be considered supportive or exploratory if there was a statistically significant finding in overall survival. The agency cited Schering-Plough's application for approval of temozolomide (Temodar) for melanoma in 1999, which was not approved under similar criteria.

Another concern was the control of the trial conduct. In particular, the agency noted that the five-day difference in assessment times between the two treatment groups could potentially bias the estimation of treatment effect and could lead to a false positive inference in a large study.

"These were secondary outcomes that we are looking at, so that the way that one would rigorously define these and ascertain them is

"Overall, we see no major threat to other prescription category brands from possible OTC moves."

Pfizer and AstraZeneca are critical of a switch to OTC statin therapy in the absence of any obligation to monitor clinical parameters such as blood pressure, low-density lipoprotein and total cholesterol. "If you work on lipids you must measure your success," says Zaiac.

Another concern is the lack of trial data for OTC statins for primary prevention of heart disease. Insufficient safety and efficacy data for statins in an OTC setting was the reason the FDA rejected the applications for pravastatin and lovastatin.

OTC status could potentially contribute to a greater incidence of adverse events, says Beatrice Golomb of the University of California at San Diego (UCSD), principal investigator of the UCSD statin study, although it is not the most crucial issue. "My own concerns are less about OTC versus prescription status than about awareness of the spectrum of effects, so that when possible adverse effects arise, appropriate decisions can be made about whether to continue the drug."

somewhat missing," said committee voting consultant Ralph D'Agostino, Professor of Mathematics, Statistics and Public Health at Boston University. "I am stuck with the … difficulty with progression-free survival and how it can move around depending on assumptions."

The decision has proved costly for Genta. The company withdrew its New Drug Application (NDA) for oblimersen and has stopped marketing gallium nitrate (Ganite) for hypercalcaemia, which was intended to help establish its sales force before the launch of oblimersen. Genta says this will allow it to devote its remaining money — an estimated US $67 million — to re-submitting approval data for oblimersen.

Although the advisory committee rejected the treatment, it did hint that there might be an approvable effect. "There might be something here, but it just isn't clear," noted committee member Stephen George, professor of biostatistics at Duke University Medical Center, Durham, North Carolina.

NEWS IN BRIEF

GSK accused of suppressing negative trial data

New York state's Attorney General Eliot Spitzer has filed a civil lawsuit against GlaxoSmithKline, accusing the company of fraudulently suppressing negative trial data indicating that its antidepressant paroxetine (Paxil, Seroxat) is ineffective and unsafe in children. The suit claims that GSK published only one trial, which had mixed results, and suppressed other trial data indicating that children were at an increased risk of suicidal thoughts and actions. GSK said that it had disclosed the data in journals and conferences, and had informed physicians in a letter. In the interests of transparency GSK released data from nine studies on its website. Four of the studies show that although no children committed suicide, a higher percentage of children on paroxetine had suicidal thoughts or actions than those on placebo. The case has reignited discussions about whether there should be a national trials registry in the United States that would record all clinical trials from commencement. Merck has openly supported the idea, and GSK said it will create a public database of all its trials, which will be available in the third quarter this year and will contain data going back four years.

Gene therapy trial resumes

The French gene-therapy trial for X-linked severe combined immunodeficiency that was halted when two patients developed leukaemia looks set to restart after a 22-month suspension. The suspension had led to a moratorium on gene-therapy trials in several countries, as researchers sought to discover the mechanism for this adverse effect. It is now known that the *gamma-C* gene that the two patients received, which should allow their immune cells to grow normally, activated the oncogene *LMO2*. The trial team, led by Alain Fischer of the Necker Hospital, Paris, will adjust its treatment plans to minimize risks from this switching effect. For example, in most cases Fischer will now only treat children older than six months, because they might be less vulnerable to cancer than the very young babies who developed cancer in the trial, and will also place an upper limit on the number of corrected cells that are injected into the children.

BIO launches global health initiative

The Biotechnology Industry Organization (BIO)2004 conference in San Francisco saw the launch of BIO Ventures for Global Health (BVGH), a new non-profit organization devoted to enlisting the biotechnology industry in the fight against neglected diseases (http://www.bvgh.org). With a US $1-billion start-up grant from the Bill & Melinda Gates Foundation, the BVGH will initially create business cases for specific developing-world products, assess market opportunities, form partnership and finance strategies, and map the clinical regulatory and distribution pathways.

Targeted cancer treatments showcased at ASCO

The American Society of Clinical Oncology meeting in New Orleans was dominated by positive Phase III data from epidermal growth factor receptor inhibitors. Merck and Bristol-Myers Squibb announced that in 424 patients with head and neck carcinoma, 69% and 56% of patients on cetuximab (Erbitux) plus high-dose radiation met the primary endpoint of locoregional control at one and two years, respectively, compared with 59% and 48% of patients on radiation alone ($p = 0.02$). Median overall survival for patients on cetuximab/radiation was 54 months, compared with 28 months with radiation alone. Genentech and Roche announced that in 731 patients with relapsed non-small-cell lung carcinoma, erlotinib HCl (Tarceva) showed a 42.5% improvement in median survival and a 41% improvement in one-year survival rates compared with placebo. Median overall survival for patients on erlotinib HCl was 6.7 months, compared with 4.7 months for placebo ($p = 0.001$).

Regulations tightened on rosuvastatin

European regulators have tightened the labelling on rosuvastatin (Crestor; AstraZeneca) following concerns about adverse effects from high doses. The Dutch Medicines Evaluation Board, which was responsible for the initial approval of rosuvastatin in the European Union and follow-up monitoring of the drug, has told physicians to seek specialist advice before prescribing the highest dose (40 mg) after a number of reports of rhabdomyolysis, the potentially fatal muscle-weakening condition that led to Bayer's cerivastatin being withdrawn from the market in 2001. Patients should start on the lowest dose of 10 mg and only move up to 20 mg after a minimum of four weeks. In response to these labelling changes, the FDA issued a public health advisory to healthcare providers.

Schering AG restructures to focus on oncology

Schering AG is spinning off its dermatology operations and cutting 900 jobs as part of restructuring plans aimed at boosting profit margins. The company needed to restructure because currency fluctuations and a healthcare overhaul in Germany led its margins on earnings to drop to 13%, compared with an average of 20% in other large pharmaceutical companies. To raise operating margins to 18%, Schering will increase the focus of its R&D on its oncology division, as well as gynaecology and andrology, diagnostic imaging and specialized therapeutics. It will end R&D projects in cardiovascular and central nervous system diseases, with the exception of multiple sclerosis and a Phase II treatment for Parkinson's disease.