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FRESH FROM THE PIPELINE

# Market indicators

Five main classes of agent have been used for the treatment of dyslipidaemias, with reduction of serum levels of LDL-C being the main focus, although growing attention has been given in recent years to the importance of raising levels of HDL-C and reducing levels of triglycerides Fibrates and niacin primarily target triglycerides and HDL-C, whereas bile-acid sequestrants, probucol and statins primarily target LDL-C.

Statins have proved very successful since their introduction in the late 1980s owing to their high efficacy in reducing LDL-C, and they now dominate the lucrative market for lipid-regulating drugs (FIG. 1). Simvastatin (Zocor; Merck) and atorvastatin (Lipitor; Pfizer) were the two best-selling drugs in 2001, with global sales of ~US $6.7 billion and ~ US $6.5 billion, respectively. However, the recent launch of the "superstatin" rosuvastatin (Crestor; AstraZeneca) in the Netherlands means this class of compound is crowded. Also, many physicians feel that the maximum benefit attainable with statins is being approached.

Commercially, the biggest threat to the statin market is that many of the agents are starting to lose patent protection (FIG. 2). This, and the presence of a patient population whose needs are not fully served by statins, in particular those who cannot tolerate high statin doses that might be needed to reach lipid goals, has spurred the development of novel lipid-lowering therapies (TABLE 1), such as ezetimibe.

### Impact of ezetimibe

Ezetimibe is being developed as a monotherapy, and as a combination therapy with simvastatin, which is 18% more effective at reducing LDL-C than simvastatin alone. We believe that the single-pill combination, which is now in Phase III trials, will have the most significant market impact. However, misgivings about the safety of combination therapies following the prominent withdrawal of cerivastatin in 2001, which was linked to co-prescription with fibrates, mean that strong data showing the safety of the ezetimibe/simvastatin combination are likely to be needed before physicians will be comfortable prescribing it.

The single pill, which is expected to be priced aggressively relative to atorvastatin, is an important development for Merck because it permits the company to prolong its Zocor franchise for years beyond its scheduled patent expirations in Germany and the United Kingdom in 2003, and the United States in 2005 (FIG. 2). The monotherapy is likely to take a small piece of the market; however, the additional potency of the single-pill combination and the marketing power of Merck will see greater market penetration, with predicted sales of over US $3 billion by 2011 (FIG. 1).

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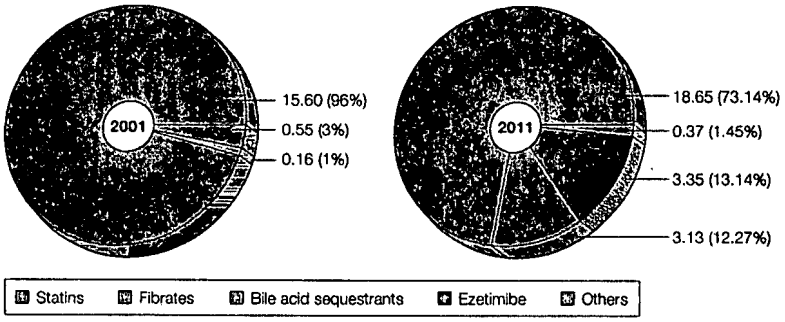


Figure 1 | **Global sales of anti-hyperlipidaemic drugs.** Ezetimibe reflects monotherapy and combination therapy with simvastatin.

Table 1 | **Selected novel anti-hyperlipidaemic drugs in development**

| Drug class | Compound | Highest phase | Marketing company |
|---|---|---|---|
| ACAT inhibitor | Avasimibe (CI-1011) | Phase III | Pfizer |
| CETP inhibitor | CP-529414 | Phase II | Pfizer |
| CETP inhibitor | JTT-705 | Phase II | Japan Tobacco |
| MTTP inhibitor | Implitapide | Phase II | Bayer |

ACAT, acyl coenzyme A cholesterol acetyltransferase; CETP, cholesteryl ester transfer protein; MTTP, microsomal triglyceride transfer protein.

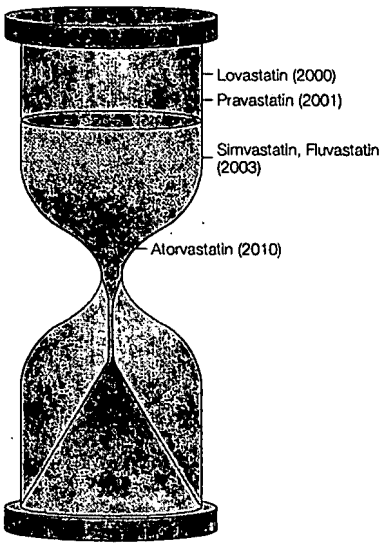


Figure 2 | **Patent expirations of statins.** Data reflect the first patent expiration in the seven major pharmaceutical markets (France, Germany, Italy, Japan, Spain, United Kingdom and United States)



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