

newsletter

Statins

The first patents for some of the group of drugs known as statins (cholesterol-lowering drugs) will shortly be expiring. This will set a market segment in motion that is important both from an economic and insurance perspective.

Avoidable causes of death; therapies generating largest revenues

High cholesterol ranks number seven on the list of avoidable causes of death (see table). The market segment for cholesterol-lowering drugs is predictably large. In 2002, worldwide sales of cholesterol- and lipid-lowering drugs amounted to USD 21.7 billion.

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1. Lack of food
 2. Unsafe sex
 3. High blood pressure
 4. Tobacco
 5. Alcohol
 6. Unsafe water and sanitation
 7. High cholesterol
 8. Indoor smoke from solid fuels
 9. Iron deficiency
 10. Obesity
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Reference: WHO Report 2002

Therapeutic class	2002 global sales (US \$billion)	% growth in 2002
1. Anti-ulcerants	21.9	9
2. Cholesterol & triglyceride reducers	21.7	12
3. Antidepressants	17.1	5
4. Antirheumatic NSAIDs	11.3	1
5. Calcium antagonists plain	9.9	-1
6. Antipsychotics	9.5	19
7. Erythropoietin products	8.1	18
8. Oral antidiabetics	8.0	2
9. ACE inhibitors plain	7.8	0
10. Cephalosporins	7.6	-3

* The review tracks actual sales of approximately 90% of all prescription drugs and some over-the-counter products in more than 80 countries. Reference: IMS Health Report, 2002

Cholesterol-lowering; statins

There are currently two ways of treating a high cholesterol level: by improving one's diet or by undergoing medical treatment with cholesterol synthesis inhibitors (CSE inhibitors, statins), nicotinic acid or ion exchangers. In the case of medical treatment, statins constitute the most important group of drugs. The first active substance (lovastatin) was brought onto the market in 1989. In 2002 sales of atorvastatin (Pfizer; USD 8.6 billion) and simvastatin (Merck; USD 6.2 billion) were larger than for any other prescription drug worldwide (see overview below).

Active Ingredient/Product	Company	Therapeutical class	Global sales in 2002 [US \$billion]	% growth in 2002
1. Atorvastatine (Lipitor®)	Pfizer	Cholesterol reducer	8.6	20
2. Simvastatine (Zocor®)	Merck	Cholesterol reducer	6.2	13
3. Omeprazole (Losec®/Prilosec®)	AstraZeneca	Anti-ulcerant	5.2	-19
4. Olanzapine (Zyprexa®)	Eli Lilly	Antipsychotic	4.0	21
5. Amlodipine (Norvasc®)	Pfizer	Calcium antagonist	4.0	6
6. Epoetin alfa (Erypo®)	Johnson & Johnson	Erythropoietin product	3.8	18
7. Lansoprazole (Ogastro®/Prevacid®)	TAP Pharmaceutical	Anti-ulcerant	3.6	3
8. Paroxetine (Seroxat®/Paxil®)	GlaxoSmithKline	Antidepressant	3.3	13
9. Celecoxib (Celebrex®)	Pharmacia	Antirheumatic NSAID	3.1	-1
10. Sertraline (Zoloft®)	Pfizer	Antidepressant	2.9	12

Reference: IMS Health Report, 2002

Mode of action Statins are specific inhibitors of the key enzyme in cholesterol biosynthesis (HMG-CoA reductase). The inhibition of this enzyme reduces the level of cholesterol synthesis taking place in the cells, particularly liver cells. This, in turn, results in more low-density lipoprotein-bound cholesterol (LDL or "bad" cholesterol) being absorbed into the cell from the blood, thereby reducing the amount of LDL cholesterol by 30-40%. This significantly reduces the likelihood of a patient succumbing to a vascular wall disorder and suffering resulting health impairments such as heart attack or stroke. A projection of the results of various studies revealed that treating risk patients with statins could prevent approximately 9,000 deaths in Germany every year.

Side effects: rhabdomyolysis Ever since the first clinical studies were carried out in the early 1980s, the medical profession has been aware that statins may, in rare instances, lead to rhabdomyolysis, causing striated muscle fibres in the body to disintegrate. The catabolites from this process may cause damage to the kidneys and other organs. Kidney failure, in particular, may result in death. This risk may be amplified in cases where patients consume a combined dose of statins and fibrates (lipid-lowering medication). As a higher occurrence rate of this disease was observed in patients taking cerivastatin (Lipobay®, Baycol®, Zenas®) – usually in larger doses or in combination with the fibrate gemfibrozil – than in those being treated with other statins, this active substance was voluntarily withdrawn from the market in August 2001.

Patent expiry: simvastatin, lovastatin In 2003 the patents for simvastatin and lovastatin will expire in May and June respectively. This means that two active substances, which are highly attractive from a commercial point of view, are shortly to become available generically. Hexal and Betapharma will be the first companies to launch products using simvastatin preparations (brand names: Simvahexal® or Simvabeta®) under licence agreements. Others will enter the market once the patents have expired.

Active Ingredient	Trade name	on the market since	patent expiration	Turnover [million€]
Atorvastatin	Sortis®	1997	08/2011	690
Simvastatin	Zocor®, Denan®	1990	05/2003	415
Pravastatin	Pravasin®, Mevalotin®	1991	08/2004	195
Flovastatin	Locol®, Cranoc®	1994	08/2008	115
Lovastatin	Mevinacor®	1989	06/2003	55

Reference: Arznei-telegramm 2003, Jg. 34, Nr.3

Simvastatin is one of the statins that has been researched the most comprehensively. Its effectiveness as a drug was established in the important "4S-Study" (Scandinavian Simvastatin Survival Study) involving 4,444 patients who had already suffered a heart attack or were suffering from a coronary disease. The study, which was conducted over a period of five years, indicated a reduction in risk (number of deaths) from 11.5 % to 8.2 %. Subsequent studies on this or similar statins – including some that were carried out on patients that demonstrated high levels of fatty substances in their blood but had no record of heart disease – produced comparable risk reductions.

Rosuvastatin (Crestor®)

Rosuvastatin (Crestor®), also referred to as a "superstatin", is a new product, the effects of which are alleged to be positive both for patients and doctors. To date, the clinical development programme for Crestor® includes more than 15,000 patients that have taken part in a series of comparative studies. Crestor® has proven to be more effective than other previously prescribed statins (atorvastatin, simvastatin and pravastatin) as a means of lowering the LDL cholesterol level in the blood. Furthermore, dose adjustments are required less frequently. The manufacturers (Astra Zeneca) admit, however, that the total incidence and severity of clinically relevant, undesired side effects resulting from rosuvastatin is comparable to that of other statins currently available. The Food and Drug Administration (FDA) has delayed issuing an approval to market the drug in the US and is demanding more data: it has expressed safety concerns, notably in connection with the health effects of large doses. Rosuvastatin is currently approved for sale in Canada and Holland.

Conclusions

The patents for the statins simvastatin and lovastatin are due to expire in the near future, making them available as generic drugs. In the case of simvastatin, this means that a blockbuster drug will become available generically. Rosuvastatin, promoted as a "superstatin", is a new active substance in this group. It is authorised for sale in Canada and Holland and is likely to be approved in the US and EU next year.

Information for the underwriter

Generally speaking, insurers should treat statins critically. This is of particular importance in the case of the commonly prescribed combined dose treatments involving fibrates, as the withdrawal of cerivastatin (Baycol®, Lipobay®) from the market made all too clear.

In the near future several companies will be bringing products that contain simvastatin or lovastatin onto the market. This increases the accumulation risk for the insurer, as a larger number of products and companies will be impacted in the event of a loss.

In the case of "rosuvastatin" we have not yet had sufficient experience to determine the risk accurately. If the drug is approved for sale in other countries and new studies become available, we should re-evaluate our position with regard to this drug.

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