

Merck & Co

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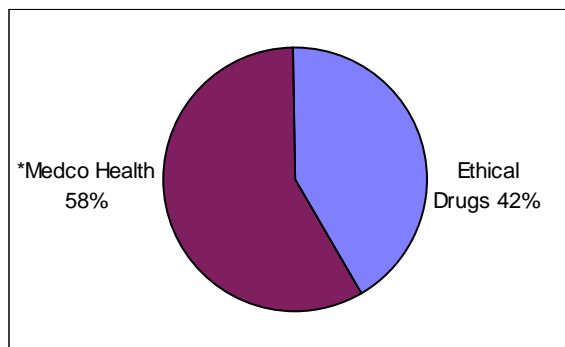
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Merck & Co

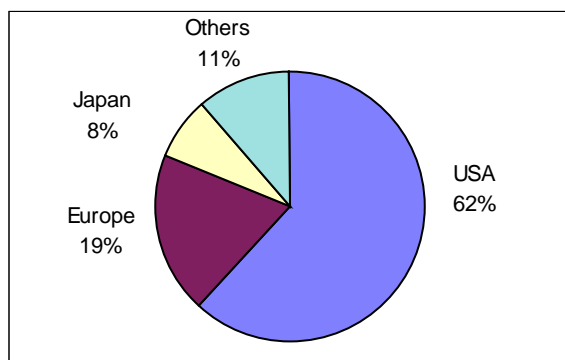
1. Executive Summary

1.1 Breakdown of Sales by Sector (2002)

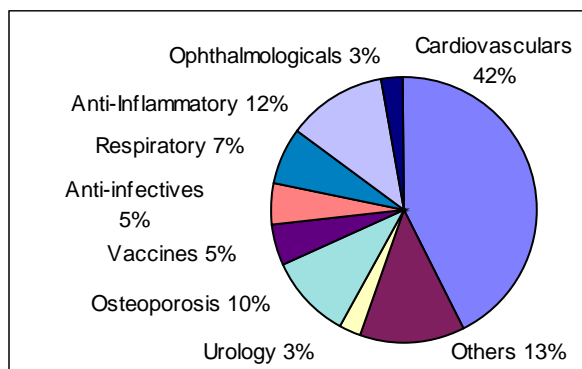


* Planned divestiture of Medco Health – Q3 2003.

1.2 Geographical Breakdown of Ethical Drug Sales (2002)



1.3 Therapeutic Breakdown of Ethical Drug Sales (2002)



Comment

In 2002, total group sales for Merck & Co. increased by 8.5% to reach \$51,790m. Ethical drug sales rose by 1.3% to \$21,631m driven by the company's five key growth products – the statin *Zocor* (+6% to \$5580m); the Cox-2 inhibitor *Vioxx* (+8% to \$2530m); the osteoporosis agent *Fosamax* (+38% to \$2250m); the A-II antagonist *Cozaar / Hyzaar* (+21% to \$2190m); and asthma product *Singulair* (+19% to \$1505m).

Medco Health managed care division continued its strong growth (+14% to \$30,159m). Despite announcing its intention to divest this division during 2002, by July of that year, Merck had withdrawn its IPO application, citing a lack of investor enthusiasm. Nevertheless, Merck intends to pursue the spin-off (this time to Merck shareholders), with a new estimated date of completion of Q3 2003.

Comment

The US continues to dominate Merck's business, reflecting the effectiveness of Merck's marketing messages within this receptive market for key products such as *Zocor*, *Cozaar*, *Fosamax* and *Singulair*.

In Europe, Merck's ability to demonstrate the cost benefits of its core products has proven attractive to cost-conscious healthcare payers. This has aided the company's performance despite its relatively narrow portfolio.

Merck remains one of the leading foreign pharmaceutical companies in Japan. This strong position is likely to be further consolidated following the successful "buy-out" of Banyu (as of March 2003, Merck owns 95% of Banyu, compared to a previous 51%).

Comment

Although cardiovascular remains Merck's dominant therapeutic area, this franchise has come under intense pressure of late from the patent expiry of the ACE inhibitors *Vasotec* and *Prinivil* and significant competition to the statin *Zocor* from Pfizer's *Lipitor*. *Cozaar* maintains its leading position within the angiotensin II antagonist class.

Merck has firmly established itself as a key player in the osteoporosis market (through *Fosamax*), aided by an extensive clinical trial programme and line extensions.

The company's foray into the respiratory sector (through *Singulair*) has proven particularly successful, establishing itself as the leader in the leukotriene antagonist market.

Although Merck enjoyed initial success by re-entering the anti-inflammatory sector through the Cox-2 inhibitor *Vioxx*, competitive pressure from Pfizer's *Celebrex*, concerns over cardiovascular side-effects and increasing saturation of the Cox-2 market has led to a significant slowing of growth.

1.4 Research & Development

- In 2002, Merck spent \$2677m on R&D (+9.0% YoY), all of which was spent on ethical drug R&D (12.4% of ethical drug sales). Reflecting the continued pressure on its ethical drug portfolio, Merck has stated that it intends to increase its R&D spending in 2003 by an estimated 10-12%.
- Merck's stated goal in R&D is "to introduce innovative, unique-in-class medicines" in as many new therapeutic areas as possible. The company's overall R&D strategy is specific and focused – it concentrates on developing novel therapies for common diseases that are inadequately treated.
- Historically, a major strength of Merck's R&D effort has been its highly focused and commercially orientated approach. When necessary, Merck has been able to transfer resources to its most promising compounds, leading to their rapid advance through the R&D pipeline. Consequently, within the industry, Merck has long had an enviable reputation for its R&D productivity.
- Following a period of exceptional R&D productivity in the late 1990s, Merck's pipeline would currently appear to offer an extremely limited number of products with significant market potential. Hence, Merck has sought to increase its in-licensing activities to supplement its internal R&D activities (e.g. access to the novel hypolipidaemic agent Zetia through a joint-venture with Schering-Plough).
- In contrast to many of its peers, Merck was initially slow to form collaborations with specialist biotechnology companies to gain access to new products and technologies. However, that has begun to change - witness the acquisition of a majority stake in Sibia Neurosciences (1999) and the purchase of the bio-informatics company Rosetta Inpharmatics (2001).

Key compounds in Merck's late-stage development pipeline include:

Aprepitant – a substance P antagonist with utility as both an anti-emetic (launched in the US in March 2003 branded **Emend**) and as an anti-depressant (Phase III). While the compound's true commercial potential lies in the lucrative depression market, we believe that Merck has pursued the rapid development of aprepitant (as Emend) in chemotherapy induced nausea and vomiting as a route to an early market entry.

MK-0767 – a dual PPAR agonist in-licensed from Kyorin. Currently in Phase III development as a once daily, oral anti-diabetic. Phase II clinical trial results have shown substantial effects on both blood glucose levels and lipid profiles. Clearly, the successful commercialisation of this compound would provide Merck with a point of entry to the growing diabetes market.

1.5 Conclusion and Key Issues

Merck was the world's leading pharmaceutical company throughout much of the 1990s. Unlike many of its peers, this leading position was built organically, largely on the back of the company's leading cardiovascular franchise and its highly productive R&D engine.

However, Merck is now facing major internal and external challenges. Over the past two years, Merck has lost US patent protection on four key products - Vasotec (2000), Pepcid (2001), Mevacor (2001) and Prinivil (2002). As a result, Merck has slipped to third position in the world pharma rankings and an ever-widening gap has opened up between it and the industry leader Pfizer. In addition to these near term challenges, Merck also faces a significant threat to longer term growth in the form of US patent expiry of its leading product Zocor (anticipated mid-2006). With Zocor's growth already under pressure from Pfizer's Lipitor, a well executed life-cycle management strategy will be essential to minimise the impact of generics.

In response to these challenges, Merck has renewed its focus on driving growth of its five key brands – Zocor, Cozaar, Vioxx, Fosamax and Singulair – in order to offset the near term effects of generic erosion of its older products. However, given the competitive environment that these brands face, this represents a major challenge for Merck. Merck also plans to spin-off its pharmacy benefits subsidiary, Medco Health, in order to focus solely on its core pharma division. This move reflects the relatively limited synergies between Merck's two businesses and Medco's relatively low profit margins. Clearly, Merck hopes that this move will stimulate a revival in investor confidence in the company by further highlighting the profitability of its pharma business.

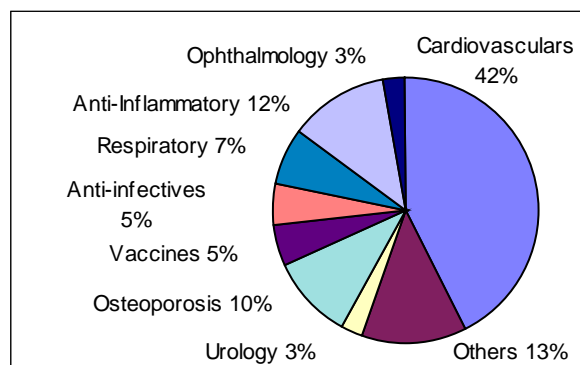
Whilst we commend Merck on these efforts to streamline its operations, we believe that the company's ethical drugs business is likely to remain somewhat exposed in terms of growth. As a result, Merck may have to consider some form of M&A activity.

Key issues for Merck include:

- Completion of the planned spin-off of Medco Health, thereby allowing senior management to focus solely on driving growth of the core pharma business.
- Ability to drive growth of its key brands (e.g. Zocor, Cozaar, Fosamax, Vioxx and Singulair) in order to compensate for the loss of revenues following the raft of recent patent expiries.
- To capitalise on its alliance with Schering-Plough by maximising future revenues from the hypolipidaemic Zetia, both as a stand alone product and as a core part of Zocor's life-cycle management strategy.
- In comparison to recent years, Merck's R&D pipeline now looks fairly depleted. Thus, we believe significant in-licensing activity is now warranted.

6. Therapeutic Profile

Therapeutic Breakdown of Ethical Drug Sales (2002)



6.1 Overview

Merck's position as one of the world's leading pharmaceutical companies was built largely on the back of its dominant **cardiovascular portfolio**, which includes products from most of the key therapeutic classes. As a result of the success of large, clinical outcomes studies, the hypolipidaemic Zocor (supported by the 4S study) and the ACE inhibitor Vasotec (supported by the CONSENSUS and SOLVD studies) became the leading products in their respective market segments. However, Zocor is now experiencing considerable competitive pressure from Pfizer's Lipitor, while Vasotec lost US patent protection in October 2000. Nevertheless, strong sales of its leading angiotensin II antagonist anti-hypertensive Cozaar, together with the significant revenue generating potential of the hypolipidaemic agent Zetia (both as a Zetia / Zocor combination and as a separate therapy) should help to maintain the company's strong position in the cardiovascular sector.

Merck also possesses leading therapeutic franchises in the **ophthalmology** and **vaccines** sectors. However, the restricted size of these markets precludes them from being of key strategic significance for the company.

Merck's portfolio is notable for the number of key products that are not supported by leading therapeutic franchises. Over recent years, the company has enjoyed significant success with the **osteoporosis** treatment Fosamax, the **respiratory** therapy Singulair and the **migraine** therapy Maxalt. In addition, Merck has also re-emerged in the **anti-inflammatory** sector via the Cox-2 selective NSAIDs, Vioxx and Arcoxia.

Indeed it is the continued success of these products, combined with a strong performance from its key cardiovascular brands – Zocor, Zetia and Cozaar – that will ultimately determine whether Merck can overcome the raft of recent patent expiries i.e. Vasotec and its follow-up Prinivil, the anti-ulcer therapy Pepcid and the hypolipidaemic Mevacor.

Of greater significance perhaps is the influence that the success of these products will have on Merck's future standing with respect to its industry peers, particularly in relation to the pharmaceutical behemoth Pfizer.

6.2 Cardiovasculars

Product	Generic Name	Product Class	Developer	Date of Launch
Vasotec	enalapril	ACE inhibitor	Merck	1984
Prinivil	lisinopril	ACE inhibitor	Merck	1988
Cozaar	losartan	angiotensin II antagonist	DuPont Merck	1995
Mevacor	lovastatin	hypolipidaemic	Sankyo/Merck	1987
Zocor	simvastatin	hypolipidaemic	Merck	1988
Aggrastat	tirofiban	gpIIb/IIIa antagonist	Merck	1998
Zetia	ezetimibe	hypolipidaemic	Schering-Plough	2002

Merck possesses a broad cardiovascular franchise, holding premier positions in the hypolipidaemic (Zocor/Mevacor/Zetia), and angiotensin II antagonist (Cozaar) sectors. These products have built upon the company's historical presence in the cardiovascular sector, effected through mature products such as the ACE-inhibitors (Vasotec/Prinivil), the centrally-acting anti-hypertensive Aldomet (methyldopa), the diuretic Moduretic (amiloride/hydrochlorothiazide) and the beta-blocker Blocadren (timolol).

The current cardiovascular franchise is now increasingly mature, with Vasotec, Mevacor and Prinivil having recently succumbed to US patent expiry. Thus, Merck must rely upon Zocor, Cozaar and the more recently launched Zetia to drive growth of its cardiovascular franchise.

Vasotec

Introduction

Following its launch in 1984, Vasotec (enalapril) significantly eroded the market share of Bristol-Myers Squibb's ACE inhibitor Capoten (captopril). This reflected the strength of Merck in the cardiovascular area and a clear marketing message which focused on enalapril's once daily dosing compared to the multiple daily doses required with Capoten. However, Merck's dominance of the ACE inhibitor sector has come to an end following US patent expiry of Vasotec in August 2000. Over 40% of total Vasotec sales were derived from the US before patent expiry.

Life-cycle management

After initially becoming well established in the **hypertension** market, **congestive heart failure** (CHF) proved to be an area of further expansion for enalapril. Only three years after Vasotec's first launch, the Co-operative North Scandinavian Enalapril Survival Study (CONSENSUS) showed that enalapril (in combination with diuretics and digoxin) improved survival in patients with severe heart failure. The CONSENSUS trial represented an important milestone, as this was the first time that an ACE inhibitor had been shown to reduce mortality in heart failure.

Encouraged by the positive results of CONSENSUS, Merck conducted further trials, including the Studies of Left Ventricular Dysfunction (SOLVD), which demonstrated that enalapril (again in combination with diuretics and digoxin) significantly decreased mortality in patients with mild to moderate heart failure. In addition, SOLVD also showed a significant reduction in the risk of myocardial infarction, unstable angina and cardiac mortality in patients with asymptomatic left ventricular dysfunction. The SOLVD trials therefore showed that enalapril is of benefit in early stage heart failure, thus supporting its use in this large patient population (with major revenue benefits for Merck). Merck was particularly successful in developing cost-effectiveness models from the SOLVD trial to emphasise the benefits of the wider use of ACE inhibitors in heart failure. However, to an extent this message was diluted by physician interpretation of an ACE inhibitor class effect.

Conclusion

Interestingly, Merck did not attempt to extend Vasotec's indication base pre-patent expiry into the treatment of additional conditions such as usage post acute myocardial infarction (evidence from the SAVE, ISIS-4 and GISSI-3 studies) or treatment of nephropathy caused by insulin-dependent diabetes. Indeed, Merck's defence of its ACE inhibitor franchise rested instead with transferring sales to the follow-on product **Prinivil** (lisinopril), and via the development of the angiotensin II antagonist **Cozaar** (losartan), which has become established as the leading product in this rapidly growing therapeutic class. Reflecting the relatively minor position Vasotec has now assumed in the company's cardiovascular portfolio, in May 2002, Merck divested US rights to Vasotec (and the combination product Vaseretic – enalapril plus hydrochlorothiazide) to Biovail Corporation.

Prinivil

At the beginning of 1988, Merck launched the Vasotec follow-up, Prinivil (lisinopril). Developed by Merck, lisinopril is also marketed by AstraZeneca in most world markets (excluding Japan), branded Zestril. The former Zeneca obtained co-marketing rights to lisinopril in 1987 under a quid pro quo deal in which Merck agreed to co-develop and co-market the aldose reductase inhibitor ponalrestat for the treatment of diabetic complications; ponalrestat, however, failed to reach the market.

Initially, Merck had a significant problem in introducing Prinivil at a relatively early stage in Vasotec's life, and consequently feared that reducing the price of Prinivil would cannibalise sales of Vasotec. Thus, in the US, Prinivil was positioned as being particularly suited to the elderly hypertensive patient. However, this strategy has to some extent been undermined as rival Zeneca adopted an aggressive sales campaign, emphasising the broad utility of lisinopril. Zeneca also followed an aggressive pricing strategy with Zestril, a factor that enabled it to gain a greater market share than Prinivil.

In Europe, the problem of positioning Prinivil in relation to Vasotec was rectified in 1992, by transferring the rights to both Prinivil and Prinzide (a diuretic combination) in major markets to the DuPont Merck joint-venture. Following the termination of this joint-venture in mid-1998, DuPont (now BMS) gained European rights to these products.

By the late-1990s, Prinivil accounted for less than 15% of Merck's total ACE inhibitor product sales; reflecting the company's continued marketing focus on the highly successful Vasotec. Nevertheless following Vasotec's US patent expiry in August 2000, Prinivil's sales grew strongly. This reflects Merck's efforts to place Prinivil as the preferred ACE inhibitor brand in Medco programmes. However, since Prinivil's US patent expiry in June 2002, Merck's entire focus has switched to the angiotensin II antagonist Cozaar.

Cozaar

Introduction

The angiotensin II (A-II) antagonist Cozaar (losartan) was launched in the USA in 1995 and subsequently rolled-out across Europe for the treatment of hypertension. To assist in its uptake, Merck adopted a similar line extension strategy to that employed for its ACE inhibitors, by developing a hydrochlorothiazide (diuretic) containing combination product, Hyzaar. That product was launched simultaneously with Cozaar in the US and now accounts for over 30% of the combined sales of the two brands. In Japan, losartan (branded Nu-lotan) was launched by Banyu in Q3 1998.

Losartan was originally sourced from DuPont and developed in collaboration with the former DuPont Merck joint-venture. Importantly, however, Merck's sale of its stake in DuPont Merck in mid-1998 had no impact on the marketing arrangements for Cozaar/Hyzaar. Nevertheless, from H2 2000, DuPont began to benefit fully from a complex profit sharing arrangement involving this product, whereby DuPont (now BMS) receives 50% of Cozaar and Hyzaar profits in the US.

In all major markets, Cozaar was the first of the A-II antagonists to become available. A-II antagonists are closely related to the ACE inhibitor class as both act by reducing the effects of angiotensin II, a naturally occurring peptide which causes vasoconstriction and promotes aldosterone secretion. However, the precise mechanisms of action differ: while ACE inhibitors block the enzyme responsible for conversion of angiotensin I to angiotensin II, the A-II antagonists act by directly blocking angiotensin II receptors. Through their inhibition of ACE, the ACE inhibitors also cause an accumulation of bradykinin, an effect which has been implicated in causing the dry cough which is often seen with this class of drugs. By contrast, A-II antagonists do not affect bradykinin levels and so have not been associated with this nuisance side-effect. Indeed, the absence of dry cough is considered to be the A-II antagonists' key advantage over the ACE inhibitors.

At the time of launch, Merck was faced with the challenge of positioning Cozaar without cannibalising its existing and lucrative ACE inhibitor franchise (consisting of Vasotec and Prinivil). However, Merck's indisputable marketing skills came to the fore, with the company initially able to maintain growth trends for both of its ACE inhibitor products, while simultaneously driving growth of Cozaar. Merck's strategy was to position Cozaar (at a premium price) as the first of a new class of anti-hypertensive agents, which offer a cleaner side-effect profile (and potentially increased compliance) than existing treatments. In particular, Merck emphasised Cozaar's suitability for patients who were not well controlled on their existing anti-hypertensive regimen (including those patients with troublesome ACE inhibitor-induced cough). Meanwhile, Merck continued to promote its ACE inhibitors as being appropriate for the vast majority of patients with hypertension, while also highlighting their unique role in the treatment of congestive heart failure (CHF).

Competition

Although Cozaar was the first A-II antagonist to reach the market, its exclusivity was short lived - Novartis' Diovan (valsartan) was launched onto the market in late 1996. Today, many of the world's leading pharmaceutical companies are involved in the A-II antagonist market and, not surprisingly, competition is fierce. Reflecting Cozaar's marketing lead and its status as the leader in the A-II antagonist market, almost all of Merck's competitors have attempted to show that their product offers some advantage over Cozaar. In particular, many of Merck's competitors have highlighted the relatively short half-life of Cozaar compared with the newer A-II antagonists (this potentially increases the risk of loss of blood pressure control over a 24-hour period). However, as Cozaar is widely approved for once-daily dosing, the clinical relevance of its shorter half-life is debatable. Thus, to date, Merck has successfully maintained its lead of the A-II antagonist market.

Life Cycle Management

Following the patent expiry of Vasotec (August 2000) and more recently that of Prinivil (June 2002), Merck endeavoured to expand Cozaar's indication base beyond hypertension to include **congestive heart failure** (CHF), in an attempt to produce a true follow-up to its older ACE inhibitors. Initially, in 1997 Merck received approval for the use of Cozaar as a first-line treatment for CHF in a number of minor European markets. This approval was partly based on data from the preliminary ELITE-1 trial (Evaluation of Losartan In the Elderly), which suggested a benefit over the ACE inhibitor captopril in the treatment of CHF.

In order to generate additional mortality data to support the submission of a similar application in the US – the world's largest CHF market – Merck initiated the ELITE-II trial. The aim of ELITE-II was to confirm Cozaar's superiority over captopril in the treatment of CHF in a large scale clinical trial. However, end-point results (reported in Q4 1999) failed to show any clinical advantages in using Cozaar in CHF. As a result of this finding, Merck was unable to seek US approval for the product in the treatment of heart failure, and elected to remove CHF from Cozaar's list of indications in Europe. Clearly, this was a significant setback to Merck's ambitions to expand the utility of Cozaar, particularly as its main competitor Diovan received US approval for the treatment of CHF (in conjunction with standard therapies) in August 2002.

Beyond the treatment of CHF, Merck intends to maximise sales of Cozaar by pursuing a number of additional indications through a series of clinical outcome studies. These are as follows:

- **LIFE** (Losartan Intervention For Endpoint reduction in hypertension) study to evaluate Cozaar's potential compared to beta-blockers (atenolol) in reducing cardiovascular deaths and non-fatal heart attacks or strokes in hypertensive patients with left ventricular hypertrophy (LVH). Results, published in March 2002, suggested that whilst both losartan and atenolol reduced blood pressure to similar levels in the trial, patients taking losartan had a significantly lower risk of cardiovascular death, heart attack and stroke. As a result, in March 2003, the US FDA approved Cozaar for the **reduction of stroke in patients with hypertension and LVH** (although there is evidence that this benefit does not apply to black patients). Cozaar is the first A-II antagonist to be approved for this indication.
- **RENAAL** (Reduction of Endpoints in Non-insulin dependent diabetes with the Angiotensin-II Antagonist Losartan). Results, when reviewed by a US FDA advisory committee in conjunction with results from BMS / Sanofi-Synthelabo's similar trial (the Irbesartan Diabetic Neuropathy Trial) on their A-II antagonist Avapro/Aprovel (irbesartan), supported the September 2002 approval of Cozaar for the **treatment of nephropathy in Type 2 diabetic patients**.
- **OPTIMAAL** (Optimal Trial In Mycocardial infarction with the Angiotensin Antagonist Losartan) study to assess the potential mortality and morbidity benefits of Cozaar versus captopril following **acute myocardial infarction**. However, in September 2002, Merck reported that the difference between the two drugs was insignificant.

Conclusion

In conclusion, despite intense competition from a plethora of similar products and its failure to include the treatment of CHF within its list of indications, Cozaar is expected to retain its leading position in the angiotensin II antagonist market for the foreseeable future. We believe that this reflects its first to market status as well as the strength of Merck's cardiovascular franchise, particularly in the US. In addition, we expect that Cozaar's future growth will continue to be well-supported by clinical outcomes data from the major Merck-sponsored trials, particularly recent positive results from the LIFE study.

Mevacor

Merck's entry into the hypolipidaemic sector came with the US launch of Mevacor (lovastatin) in 1987. However, as lovastatin was co-discovered by Sankyo, Merck's access to the product outwith the US was restricted (Germany is the only other major market where lovastatin is available through Merck).

Mevacor was the first HMG-CoA reductase inhibitor ("statin") to reach the US market. Initially, competition consisted mainly of Bristol-Myers Squibb's bile acid sequestrant Questran (cholestyramine) and fibrates such as Warner-Lambert's (now Pfizer's) Lopid (gemfibrozil). As the statins possess far greater cholesterol-lowering properties than products from these alternative therapeutic classes, Mevacor quickly became established as the leading hypolipidaemic agent in the US.

Indeed, the early entrants in the statin class – Mevacor; BMS' Pravachol (pravastatin) and Merck's follow-up product Zocor (simvastatin) – proved to be the catalyst for the exceptional growth that has since been witnessed in the hypolipidaemic market. Consequently, this growth enabled Merck to successfully establish both of its statins in the US market.

Merck's marketing of Mevacor was initially based on the combined results of three studies; the Monitored Atherosclerosis Regression Study; the Canadian Coronary Atherosclerosis Intervention Trial; and the Familial Atherosclerosis Treatment Study. These studies provided clinical evidence that Mevacor can slow the progression of atherosclerosis in patients with raised plasma cholesterol and coronary artery disease. A further study (the Asymptomatic Carotid Artery Progression Study) demonstrated that Mevacor reverses atherosclerosis in patients with no history of coronary artery disease, an effect that was subsequently included in the US labelling.

Such a wealth of supportive clinical data ensured that Mevacor became the leading statin in the US market in the early 1990s. However, that was before the publication of results from the 4S study (see Zocor below), which enabled Merck to aggressively promote its in-house developed statin Zocor as the first member of this class to have demonstrated mortality benefits i.e. the secondary prevention of cardiovascular events. Although the success of the 4S study helped to further expand the hypolipidaemic market, Mevacor was not a beneficiary of this growth, as by this time Merck's marketing focus had clearly switched to Zocor. Mevacor's sales have slumped further following the dramatic success of Pfizer's second generation statin Lipitor (atorvastatin) since its launch in 1997 and the expiry of its US patent (in December 2001).

In an attempt to prolong Mevacor's life cycle, Merck has sought to pursue an Rx to OTC switch for the product (through its OTC joint-venture with Johnson & Johnson). A similar life-cycle extension strategy has been adopted by BMS for Pravachol. However, we would note that both J&J-Merck and BMS' first attempts at gaining OTC status for low-dose versions of their respective statins were rejected by the FDA in Q3 2000. These applications were rejected due to concerns that patients would not consult their physicians prior to (or during) hypolipidaemic therapy. Although J&J-Merck is still pursuing this switch, we believe that it is unlikely that regulatory authorities will endorse such a move, at least in the near-term, bearing in mind the safety concerns surrounding Bayer's statin Baycol, which led to its worldwide withdrawal.

Zocor

Introduction

Zocor was first introduced in Europe in 1988 followed by Japan (as Lipovas) three years later. Co-marketing support in Europe was provided by Sanofi-Winthrop in France, Boehringer Ingelheim in Germany and by various companies in Italy. Zocor did not reach the US market until 1992 - this significant delay in approval was considered indicative of the FDA's reluctance to push through "follow-up" medicines (i.e. before the era of user-fee deadlines). Thus, when Zocor reached the US market in early 1992, Mevacor was an established brand with sales in excess of \$1bn.

In the USA, to avoid cannibalisation of Mevacor sales and help to expand the market through promotion to a broader physician base, Merck initially set up a co-promotional deal with SmithKline Beecham. The introduction of Zocor followed shortly after the US launch (1991) of Bristol-Myers Squibb's Pravachol (pravastatin). Pravachol had been priced at a 5-10% discount to Mevacor, a price that Merck matched with Zocor. While BMS directed its early marketing towards the greater liver specificity of pravastatin, Merck instead focused on expanding the market by highlighting the cost-benefits of statin products including longer-term health management.

Although Merck continued to dominate the market, it was perceived that the sales growth of Zocor had not benefited sufficiently from the co-promotional arrangement with SmithKline Beecham. That perhaps reflected the lack of a clear differentiating message for the product and SB's limited cardiovascular experience. As a result, the deal with SB was terminated.

The publication of the landmark **Scandinavian Simvastatin Survival Study (4S)** in 1994 provided the catalyst for growth of Zocor. 4S ran for four and a half years and involved 4,444 secondary care patients (i.e. those who suffered from angina or post myocardial infarction). The trial demonstrated that simvastatin decreased coronary mortality by 42%, major coronary events decreased by 34% and total mortality decreased by 30%. Merck exploited such a dramatic result in the development of an appropriate disease management programme and also received regulatory approval from the FDA for the use of Zocor (with diet) to prevent heart attacks in patients with coronary artery disease and hyperlipidaemia. Further retrospective analysis of 4S has shown that simvastatin also reduces the risk of stroke or transient ischaemic attack (TIA), and the incidence of heart attacks in patients with high cholesterol who also suffer from diabetes and heart disease. These positive results enabled Merck to direct its marketing resources heavily behind Zocor at the expense of the co-developed (and thus lower margin) Mevacor.

As a result, sales of Zocor overtook those of Mevacor by 1995, with the product becoming Merck's best-selling brand by 1996.

Competitive environment

Growth rates of Zocor slowed dramatically following the phenomenally successful launch of **Warner-Lambert / Pfizer's potent statin Lipitor** (atorvastatin) in 1997. Despite the lack of supportive clinical outcome data for Lipitor, Warner-Lambert / Pfizer succeeded in convincing physicians that the benefits seen with Zocor in the 4S study (and the various outcome studies performed by BMS to support Pravachol) are a class effect of the statins, and, by extension, that the most effective statin (Lipitor) offers the greatest clinical benefits.

To counter the threat of Lipitor, Merck developed a higher (80mg) strength of Zocor and amended the product's labelling to double the recommended starting dose for the majority of patients (to 20mg). The higher dose tablet, which was launched in the US in Q3 1998, induces a slightly greater reduction in LDL cholesterol than the lower (40mg) strength, although it has been associated with a higher incidence of side-effects. In particular, the recommendation for liver function monitoring has been expanded. Indeed, it is worth noting that Merck had previously discontinued development of a 160mg Zocor tablet because of an unacceptably high incidence of muscle toxicity (rhabdomyolysis).

As an incentive to physicians, Merck has introduced a **flat pricing policy for the various strengths of Zocor** – Merck claims that Zocor is the only statin in the US with the same price from the starting dose to the maximum dose. In further support of its leading brand, Merck introduced a "Get to Goal Guarantee" DTC advertising campaign (which offers patients their money back if they fail to achieve the cholesterol target set by their physicians while taking the 80mg dose).

In order to improve Zocor's competitiveness against Lipitor, Merck has focused on the **perceived benefits of Zocor in improving the HDL:LDL cholesterol ratio**. Thus, in August 1999, Zocor was approved in the US for its ability to increase HDL (or "good cholesterol"). To enhance the marketing message, Merck published a study in March 2000 comparing Zocor with Lipitor, which showed that Zocor raised HDL levels to a greater extent than Lipitor.

Reflecting this clinical profile, Merck's marketing message now concentrates on the **"Triple Power" of Zocor**. Triple Power relates to Zocor's ability

- to lower LDL-cholesterol
- to lower triglycerides, and
- to raise HDL cholesterol.

In addition to the threat posed by Lipitor, Merck also faced further competition from Bayer's Baycol (cerivastatin). Benefiting from the introduction of higher dose formulations, cerivastatin was making a notable impact on the statin market, its growth rates suggesting billion dollar potential. However, it was subsequently discovered that cerivastatin caused a higher risk of rhabdomyolysis (muscle wasting) in patients taking concomitant fibrate treatment (gemfibrozil) than other statin treatments. This resulted in the product's withdrawal in August 2001. As a result, all statin manufacturers aggressively targeted former Baycol users, through the likes of DTC advertising to claim a share of Baycol's market share. Interestingly, in what can be viewed primarily as a "safety precaution", **Merck subsequently strengthened Zocor's safety warnings** to clarify the risk of myopathy and rhabdomyolysis at higher doses and when used in combination with certain medications.

For the future, the competitive nature of the statin market looks set to further intensify with **AstraZeneca's Crestor** (rosuvastatin, launched in certain minor geographies in Q1 2003). Results from Phase III studies have demonstrated the superiority of Crestor over Zocor (as well as Lipitor and Pravachol) in reducing LDL cholesterol levels, while inducing equivalent or larger increases in HDL cholesterol. However, concerns also exist over the incidence of rhabdomyolysis and renal toxicity at the highest doses of Crestor. Indeed, it is these concerns which have thus far delayed the launch of the product in the key US market.

Life Cycle Management

While Merck has been highly successful at promoting the clinical outcome benefits of the 4S study, the following major endpoint studies have also now been initiated to drive continued growth and maintain competitive positioning:

- The **Oxford Heart Protection Study** (HPS-1), assessing the effect of a combination of Zocor and anti-oxidant vitamin therapy in patients at high risk of myocardial infarction with normal / near normal total cholesterol levels. The five-year study involved more than 20,000 patients (primary and secondary, diabetic and cerebrovascular risk). Results, published in November 2001, demonstrated that Zocor (at a daily dose of 40mg) can reduce the risk of vascular events not only in patients with coronary heart disease, but also in diabetics, stroke victims or patients with occlusive artery disease, including those with average and below average cholesterol levels. As a result, in April 2003, the US FDA approved a change to Zocor's prescribing information supporting its use (at a 40mg starting dose) in people with coronary heart disease or diabetes. Clearly, this will considerably expand the size of Zocor's potential treatment population – updated federal guidelines, which state that people with diabetes are at an elevated risk from CV disease, have increased the number of people in the US who are eligible for statin therapy by an estimated 20 million.
- **COURAGE** (Clinical Outcomes Utilising Revascularisation and Aggressive drug Evaluation), to determine the benefits of Zocor therapy in patients with angina. All patients receive aspirin, plus a dose of simvastatin designed to achieve an LDL level of 85mg/dl (i.e. below the current recommended guidelines for LDL cholesterol of 100mg/dl). Follow-up will continue for 3 to 6 years, with a primary end-point of all cause mortality.
- The **A to Z study** (Aggrastat to Zocor), which, amongst other issues, aims to address whether the aggressive lowering of cholesterol immediately after an unstable angina attack is beneficial. A to Z intends to recruit 5,800 patients who will initially be randomised to receive Merck's gpIIb/IIIa antagonist Aggrastat (tirofiban) with Aventis' low molecular weight heparin Lovenox (enoxaparin) or regular unfractionated heparin. 4,500 patients will then go on to receive early therapy with Zocor (40mg/day) starting 1 to 4 days after the anginal attack increasing to 80mg after one month or treatment as currently recommended starting at four months (20mg). The primary endpoint will be the incidence of death, myocardial infarction (MI) or re-admission for unstable angina. The lipid lowering part of the A to Z study is closely comparable to Pfizer's MIRACL study that reported in late 2000. Merck, however, is clearly keen to provide evidence of the value of initiating therapy post MI with Aggrastat followed closely by long-term treatment with Zocor; illustrating the advantages of possessing such a comprehensive CV portfolio.
- The **SEARCH** study (Study for the Effectiveness of Additional Reductions in Cholesterol and Homocysteine), is designed to assess the incremental effects of low dose (20mg) versus high dose (80mg) Zocor on clinical outcomes and levels of plasma homocysteine (a marker for coronary event risk) in post-myocardial infarction patients.

These major clinical trials should ensure steady newsflow and act as the catalyst for growth up to **patent expiry**. In that regard, Zocor's substance-of-matter patent expires in the US in December 2005. However, a six-month paediatric patent extension will extend US marketing exclusivity until June 2006. In Japan, the basic patent expires in 2001, while in Europe the majority of patents expire between 2003 and 2009.

With these patent expiries in mind, Merck is seeking to extend Zocor's life-cycle by developing a **line extension product** through its partnership with Schering-Plough. This oral preparation, being jointly developed by the two companies (Phase III), aims to combine simvastatin with Schering-Plough's cholesterol absorption inhibitor Zetia (ezetimibe) in a once-daily combination tablet. The product will be entitled to an additional period of market exclusivity. Merck expects to file the Zocor / Zetia combination in late 2003 – see below for further analysis of Zetia, both as a monotherapy and in combination with other statins.

Conclusion

Clearly, a well-executed life-cycle management strategy will be essential to minimise the impact of generics on Zocor's sales base (Zocor currently accounts for more than 25% of Merck's ethical drug sales). With a paucity of high potential products in its development pipeline, the rapid and successful commercialisation of the Zocor / Zetia combination (coupled with an aggressive switch from Zocor to the new combi product) will be key to Merck's future growth.

Zetia

Introduction

Merck gained access to Schering-Plough's novel hypolipidaemic agent Zetia (ezetimibe) through the formation of a 50:50 joint-development agreement with that company. Under the terms of the agreement, the j-v has focused on the development of Zetia as a once daily

- monotherapy
- therapy for co-administration with statins and
- combination therapy with Merck's leading statin Zocor.

Whilst the combination product remains in Phase III development, in November 2002, Zetia was launched in the US for use either by itself or together with a statin to reduce LDL cholesterol (and total cholesterol) in patients with high cholesterol. The FDA also approved Zetia for use in two rare genetic disorders, namely homozygous familial hypercholesterolemia and homozygous sitosterolemia. Subsequently, in April 2003, ezetimibe began roll-out across Europe (branded Ezetrol).

Although Merck has highlighted Zetia as a potential blockbuster, we would note that the company will only record 100% of revenues of the Zocor combination product (sales of Zetia on its own will be consolidated depending on the nature of Merck's agreement with S-P in specific geographies).

Product Positioning

Whilst clinical trial results have suggested that Zetia has limited utility as a monotherapy (ezetimibe only reduced LDL cholesterol by around 18% and total cholesterol by around 12%), we believe that the **product's real potential lies in combination use with statins**.

With regards the mechanism of action of this combination, Zetia, as an acyl coenzyme A cholesterol acyltransferase (ACAT) inhibitor, interferes with the body's ability to absorb dietary cholesterol. Statins (or HMG CoA reductase inhibitors) reduce cholesterol levels by interfering with the body's ability to manufacture cholesterol in the liver. The synergistic effect of such a combination has been displayed in a number of clinical trials.

- In the **Add-On study**, Zetia was shown to reduce LDL ("bad") cholesterol levels by an additional 25% when added to ongoing statin therapy, compared to a 4% reduction seen with the addition of placebo. Another key endpoint in this study was the percentage of patients who reached the National Cholesterol Education Program (NCEP) II target LDL cholesterol goal. Results showed that 72% of patients who were not at goal on their statin, reached goal when Zetia was added (in comparison to 19% of patients with the addition of placebo).
- Four additional Phase III clinical trials showed that Zetia, when **co-administered** with either simvastatin (Zocor), lovastatin (Merck's Mevacor) atorvastatin (Pfizer's Lipitor), or pravastatin (BMS' Pravachol) provided additional reductions in LDL cholesterol levels. Furthermore, Zetia, when co-administered with Lipitor and Zocor, further improved triglyceride and HDL levels.

Such positive results bode well for Zetia. Patients with hypercholesterolemia already receiving a statin often do not reach target LDL cholesterol levels at initial, lower doses. Indeed, recent analysis presented at the American Heart Association suggests that almost 75% of US coronary heart disease patients are not at their LDL goal. However, increasing statin doses can lead to side-effects such as liver toxicity or rhabdomyolysis (witness the withdrawal of Bayer's Baycol / cerivastatin due to its association with fatal cases of rhabdomyolysis at higher doses). Thus, the potential to achieve high-dose statin efficacy with lower statin doses (i.e. when statins are used in combination with Zetia) could well be an attractive treatment option.

In terms of **pricing**, Merck / Schering-Plough have priced Zetia so that combination use with Zocor (10mg) is cheaper than high-dose Zocor (20mg, 40mg and 80mg) monotherapy. Furthermore, labelling for Zetia indicates that when used in combination with Zocor (10mg), it has equal efficacy to Zocor (80mg). Despite this, however, it appears that since launch, the statin of choice for co-administration with Zetia has been Lipitor, reflecting the higher usage of that product in comparison to Zocor.

Reflecting the importance of Zetia to the future success of both Merck and Schering Plough, the product is currently supported by **three distinct sales forces** – one from Merck, one from Schering-Plough and the third from the Merck / SP joint-venture. Overall, it is estimated that some 2400 representatives are currently detailing Zetia.

Zocor / Zetia Combination

Although Merck stands to benefit from the successful launch of Zetia, we believe that the true potential for the product (from Merck's perspective) lies in the development of a once daily combination with the company's leading product, Zocor. If successfully developed, the Zocor line extension product would be entitled to an additional period of market exclusivity. The j-v intends to file the combination product for approval by the end of 2003. With Zocor's US market exclusivity expiring in mid 2006, the partnership should have sufficient time to develop, obtain approval and introduce the combination product well ahead of the entry of generic versions of simvastatin. Such a combination product should have clear clinical benefits over statins as monotherapy (as already suggested by the co-administration studies). However, by the time Zocor / Zetia becomes available, it could be faced by competition from additional combination treatments, such as Pfizer's Lipitor / CP 529,414 or Lipitor / avasimibe combinations.

Life Cycle Management Plans

For the future, we understand that Merck/Schering Plough are also evaluating Zetia's lipid lowering effects when co-administered with fibrates (e.g. Abbott's Tricor / micronised fenofibrate). Furthermore, Zetia is also being investigated in the reduction of C-reactive protein. CRP, marker of inflammation, is considered an emerging risk factor for coronary heart disease. No drugs are currently approved for use in reducing CRP levels.

Aggrastat

Aggrastat (tirofiban) is an injectable platelet fibrinogen receptor (gpIIb/IIIa) antagonist that is indicated for use in combination with heparin to prevent cardiac ischaemic events in patients with acute coronary syndrome (i.e. unstable angina or non-Q-wave myocardial infarction), including those patients who require subsequent procedures such as coronary angioplasty or coronary bypass surgery. Notably, however, Aggrastat has not been approved for use in patients undergoing angioplasty who do not present with acute coronary syndrome. The US NDA for Aggrastat was filed in Q4 1997, and following a priority review by the FDA was subsequently launched in Q2 1998.

This rapid launch strategy reflects the competitive nature of the US anti-thrombotic market. Indeed, only days after the approval of Aggrastat, Cor Therapeutics / Schering-Plough's alternative injectable gpIIb/IIIa antagonist, Integrilin (eptifibatide), was approved for use in both acute coronary syndrome and coronary angioplasty. As a result, Integrilin possesses a broader indication base than both Aggrastat and Eli Lilly's ReoPro (abciximab, the first injectable gpIIb/IIIa antagonist to reach the market). At present, ReoPro is approved for use in patients undergoing coronary angioplasty (the use of ReoPro in acute coronary syndrome is restricted to patients who are scheduled to undergo angioplasty). Nevertheless, ReoPro remains the best-selling product in the gpIIb/IIIa antagonist class.

Merck's marketing effort has focused on the outcome data available from the **PRISM** and **PRISM PLUS** studies of patients with unstable angina. The PRISM study, which had a primary composite endpoint of refractory ischaemia, myocardial infarction or death at two days, resulted in significantly fewer events with tirofiban in comparison to the heparin arm of the study. PRISM PLUS, which randomised patients to either tirofiban, tirofiban plus heparin or heparin alone, had the same composite primary endpoint as PRISM, but after a 7 day period. Although the tirofiban arm was stopped prematurely due to concerns over a higher death rate, the combination of tirofiban and heparin proved to be significantly more effective than heparin alone. Indeed, this potential synergy is being further investigated in the larger scale **A to Z (Aggrastat to Zocor) study**, which also aims to evaluate the potential benefits of using Merck's Zocor in lowering cholesterol following an episode of unstable angina.

In Europe, although Aggrastat has been available in Germany since 1998, launch was delayed in other European countries following queries regarding the PRISM PLUS study. The product's relatively late market entry thus allowed Cor / Schering-Plough's Integrilin to undergo a widespread European roll-out before Aggrastat.

Merck is cognisant of the potential competitive threat from the low molecular weight heparins (LMWH), which provide an alternative treatment option for patients with acute coronary syndrome. In particular, Aventis' LMWH Lovenox (enoxaparin) has performed well since receiving FDA approval for the treatment of patients with acute coronary syndrome. Thus, in what we believe to have been a shrewd move, Merck conducted a trial (**ACUTE II**) to investigate the benefits of combining Aggrastat with Lovenox in patients presenting with unstable angina. Results of this trial indicated that the combination was safe and effective in acute coronary syndrome patients, while the only significant difference was a lower rate of recurrent angina or rehospitalisation for unstable angina in the enoxaparin / tirofiban group.

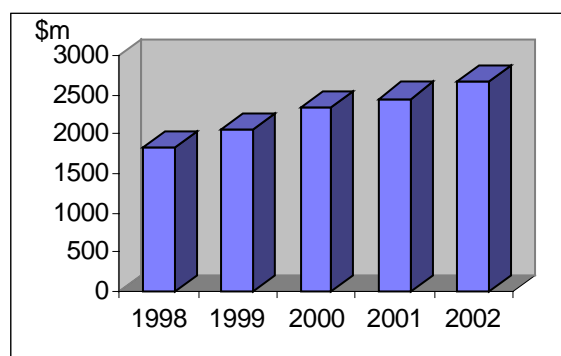
In an attempt to expand the utility of Aggrastat further, Merck initiated the **TARGET** trial, a head-to-head comparison of Aggrastat vs Lilly's ReoPro in angioplasty patients who do not present with acute coronary syndrome. However, results reported in December 2000 showed Merck's product to be less effective in this patient population. Merck must now hope that patients who present with acute coronary syndrome will be initiated on Aggrastat by cardiologists who will then be reluctant to alter treatment to ReoPro when the patient is scheduled for angioplasty.

On a more positive note, data from the **TACTICS** (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy) trial (published in late 2000), designed to investigate early versus delayed intervention, appeared to show that patients with acute coronary syndromes have improved outcomes if treated with an early intervention procedure in addition to treatment with Aggrastat.

In conclusion, Aggrastat can be considered a niche product, which has helped to build Merck's limited hospital cardiovascular franchise, whilst adding support to its dominant primary care franchise. However, its ultimate revenue potential appears to be limited given the level of competition that already exists in the market.

7. Research & Development

Ethical Drug R&D Spend (2002)



7.1 Overview

- In 2002, Merck & Co. spent a total of **\$2677m** on R&D (an increase of 9.0% over the previous year), of which 100% was spent on ethical drug R&D (excluding R&D costs incurred in joint-ventures), representing 12.4% of ethical drug sales. In 2003, total R&D spend is expected to reach \$2.9 - \$3.0bn, re-affirming Merck's commitment to innovative research as the cornerstone of its "Strategy for Growth" (see Section 2.2).
- Merck's stated goal in R&D is "**to introduce innovative, unique-in-class medicines**" in as many new therapeutic areas as possible. However, Merck recognises that this goal cannot always be achieved. Thus a secondary aim is to develop follow-on products to meet new competitors in a timely fashion. The company's overall R&D strategy is specific and focused – Merck concentrates on developing novel therapies for common disease states that are currently inadequately treated.
- At present, many of Merck's R&D programmes are focused on therapy areas where the company already has an **existing franchise** (e.g. anti-infectives). However, in an attempt to broaden its therapeutic portfolio Merck is also committed to expanding its research into key growth areas where it currently has only a minor (e.g. CNS) or no (e.g. diabetes) current involvement.
- One of the most notable features of Merck's R&D strategy is the degree to which the company invests in **post-marketing studies** to expand the use of its marketed products (new indications and line extensions) or to further confirm their safety and effectiveness.
- Historically, a major strength of Merck's R&D effort has been its highly focused and commercially orientated approach. When necessary, Merck has been able to transfer resources to its most promising compounds, leading to their rapid advance through the R&D pipeline. Consequently, within the industry, Merck has long had an enviable reputation for its **R&D productivity**.
- Following a period of exceptional R&D productivity in the late 1990s, Merck's pipeline would currently appear to offer an extremely limited number of products with significant market potential. Hence, Merck has sought to **increase its in-licensing activities** to supplement its internal R&D activities (e.g. access to the novel hypolipidaemic agent Zetia through a joint-venture with Schering-Plough).
- Early stage research work at Merck focuses on the areas of **enzyme inhibitors, peptide chemistry and genomics**. To enhance its enabling technology expertise, Merck acquired the informational genomics company Rosetta Inpharmatics in 2001 for \$620m. For the future, Merck's head of R&D Peter Kim has stated that the company intends to further enhance its activities in the area of genomics, in a bid to cut the industry-wide high failure rate of drugs in development.

7.4 Cardiovasculars

At present, Merck's R&D focus within cardiovasculars is largely directed towards the **life cycle management** (i.e. line and indication extensions) of its key cardiovascular products. For example, Merck is developing a once daily oral product combining **Zocor** with Merck / Schering-Plough's novel hypolipidaemic agent Zetia (ezetimibe). In addition, **Cozaar** has recently been approved for the reduction of stroke in patients with hypertension and the treatment of nephropathy in Type II diabetics, following positive results from two large outcome studies – LIFE and RENAAL respectively.

Merck also has access to Banyu's orally active dual endothelin receptor antagonist **J-104132** which is in Phase IIa development for the treatment of congestive heart failure (CHF). However, we would caution that a number of endothelin receptor antagonists have encountered difficulties in development for this indication e.g. Actelion's Tracleer (bosentan) failed to meet the primary endpoint in the Phase III ENABLE programme, investigating its use in the treatment of severe CHF, while GlaxoSmithKline discontinued the development of enrasentan in CHF following disappointing Phase II results.