

CARDIOVASCULAR (CV) MEDICINES

MARKETED PRODUCTS

Crestor¹ (rosuvastatin calcium) is a member of the class of products known as statins and is used for the treatment of high cholesterol levels and, in the US, to slow the progression of atherosclerosis in patients with high cholesterol as an adjunct to diet.

Seloken/Toprol-XL (metoprolol succinate) is a once daily tablet for 24-hour control of blood pressure and for use in heart failure and angina.

Atacand² (candesartan cilexetil) is an angiotensin II antagonist for the first-line treatment of hypertension and symptomatic heart failure.

Tenormin (atenolol) is a cardioselective beta-blocker for hypertension, angina pectoris and other CV disorders.

Zestril³ (lisinopril dihydrate), an ACE inhibitor, is used for the treatment of a wide range of CV diseases, including hypertension.

Plendil (felodipine) is a calcium antagonist for the treatment of hypertension and angina.

2007 IN BRIEF

- > **Crestor sales up 33% to \$2.8 billion. Over 12 million patients treated and more than 114 million prescriptions written since launch.**
- > **New atherosclerosis indication for Crestor approved in the US. EU prescribing information updated with positive atherosclerosis data.**
- > **Atacand sales up 9% to \$1.3 billion.**
- > **Worldwide (except Japan) collaboration with Bristol-Myers Squibb to develop and commercialise two investigational compounds for the treatment of Type 2 diabetes – saxagliptin and dapagliflozin.**
- > **Generic versions of Toprol-XL now being marketed in the US at all dosage strengths.**
- > **Sales of Toprol-XL in the US down 30%.**
- > **Patent infringement actions filed against seven generic drug manufacturers in the US following abbreviated new drug applications relating to Crestor.**

PERFORMANCE

	2007			2006			2005	2007 compared to 2006		2006 compared to 2005	
	Sales \$m	Growth underlying \$m	exchange effects \$m	Sales \$m	Growth underlying \$m	exchange effects \$m		Growth underlying %	Growth reported %	Growth underlying %	Growth reported %
Crestor	2,796	673	95	2,028	745	15	1,268	33	38	59	60
Seloken/Toprol-XL	1,438	(393)	36	1,795	62	(2)	1,735	(22)	(20)	3	3
Atacand	1,287	99	78	1,110	133	3	974	9	16	14	14
Tenormin	308	(24)	12	320	(24)	(8)	352	(8)	(4)	(7)	(9)
Zestril	295	(30)	18	307	(23)	(2)	332	(10)	(4)	(7)	(8)
Plendil	271	(20)	16	275	(86)	1	360	(7)	(1)	(24)	(24)
Other	291	(14)	22	283	(27)	(1)	311	(5)	2	(9)	(9)
Total	6,686	291	277	6,118	780	6	5,332	5	9	15	15

PIPELINE

Compound	Mechanism	Areas under investigation	Phase			Estimated filing date		
			I	II	III	Europe	US	
NCEs								
AZD6140	ADP receptor antagonist	arterial thrombosis	■	■	■		2H 2009	2H 2009
Saxagliptin	dipeptidyl peptidase-4 (DPP-4) inhibitor	diabetes	■	■	■		2H 2009	2Q 2008
Dapagliflozin	sodium-glucose cotransporter-2 (SGLT2) inhibitor	diabetes	■	■	■		2010	2010
Crestor/ABT-335	statin + fibrate fixed combination	dyslipidaemia	■	■	■			2H 2009
AZD0837	thrombin inhibitor	thrombosis	■	■			2012	2012
AZD4121	cholesterol absorption inhibitor	dyslipidaemia	■	■				
AZD2207	CB1 antagonist	diabetes/obesity	■	■				
AZD1175	CB1 antagonist	diabetes/obesity	■					
AZD1305	anti-arrhythmic	arrhythmias	■					
AZD6370	GLK activator	diabetes	■					
Line extensions								
Atacand	angiotensin II antagonist	diabetic retinopathy	■	■	■		1H 2009	1H 2009
Atacand Plus	angiotensin II antagonist/thiazide diuretic	32/12.5 mg, 32/25 mg for hypertension	■	■	■		2Q 2008	
Crestor	statin	atherosclerosis	■	■	■		Launched	Launched
Crestor	statin	outcomes end stage renal disease	■	■	■		1H 2009	1H 2009
Crestor	statin	outcomes in subjects with elevated CRP	■	■	■		2010	2010
Saxagliptin/metformin FDC	DPP-4 + biguanide FDC	diabetes	■	■	■			
Dapagliflozin/metformin FDC	SGLT2 + biguanide FDC	diabetes	■	■	■			

For discontinued projects see page 30.

¹ Licensed from Shionogi & Co., Ltd.

² Licensed from Takeda Chemical Industries Ltd.

³ Licensed from Merck & Co., Inc..

WE ARE A WORLD LEADER IN CV MEDICINES, BACKED BY OVER 40 YEARS' EXPERIENCE. WE AIM TO BUILD ON OUR STRONG POSITION, FOCUSING ON THE GROWTH AREAS OF DYSLIPIDAEMIA, THROMBOSIS, TYPE 2 DIABETES/OBESITY, ATHEROSCLEROSIS AND ATRIAL FIBRILLATION.

PRODUCTS

Crestor has now been approved in 91 countries and launched in 76, including the US, Canada, Japan and the majority of EU countries. *Crestor* was launched in China in April 2007.

Dyslipidaemia is increasingly recognised as a major health issue. Of those people currently being treated for high cholesterol, only about half reach their cholesterol goal on existing treatments. In multiple clinical studies, *Crestor* has been shown to be highly effective in lowering low-density lipoprotein cholesterol or 'bad cholesterol' (LDL-C), allowing the majority of patients to reach their LDL-C goals with the 10mg usual starting dose. Additionally, *Crestor* produces an increase in high-density lipoprotein cholesterol or 'good cholesterol' (HDL-C), an effect that is observed across the 5, 10, 20 and 40mg doses. At its usual 10mg starting dose, *Crestor* has been shown to reduce LDL-C by up to 52% and raise HDL-C by up to 14%.

Our extensive, long-term global clinical research programme (GALAXY), which began in 2002, includes studies that investigate the effect of *Crestor* on CV risk reduction and patient outcomes. The programme involves over 63,000 patients in over 55 countries.

The GALAXY programme was designed to address important unanswered questions in statin research by investigating links between optimal lipid control, atherosclerosis and CV morbidity and mortality. So far, a number of the studies have been completed and we have seen data from three atherosclerosis studies, ORION, ASTEROID and METEOR. The ORION study examined the potential for *Crestor* to shrink the lipid-rich necrotic core of plaques and so improve their stability, while the ASTEROID study examined the effect of *Crestor* on coronary atherosclerosis. The METEOR data, reported in March 2007, showed that *Crestor* significantly slowed progression of atherosclerosis compared with placebo in people with early signs of carotid artery disease and at low risk of coronary heart disease. In November 2007, the US Food and Drug Administration approved *Crestor* as an adjunct to diet for slowing the progression of atherosclerosis in patients with elevated cholesterol. *Crestor* is the only statin with a broad atherosclerosis indication in the US (irrespective of disease severity

or location and not restricted to patients with coronary heart disease), an important differentiation from other cholesterol-lowering products. In addition, the *Crestor* prescribing information in Europe was updated in July 2007 to incorporate positive atherosclerosis data from the METEOR study. In January 2008, we announced the launch of a new clinical trial for *Crestor*, called SATURN, designed to measure the impact of *Crestor* 40mg and atorvastatin (Lipitor™) 80mg on the progression of atherosclerosis in high-risk patients. The study is expected to enrol more than 1,000 patients across the world and should be completed in 2011.

Data from the CORONA multi-national study in patients with advanced heart failure were presented at the American Heart Association 2007 Scientific Sessions in November 2007. CORONA was a novel study that examined the effect of adding *Crestor* 10mg to optimised treatment on CV mortality and morbidity and overall survival in elderly patients with advanced heart failure who were not candidates for statin therapy. CORONA showed an 8% reduction in the combined primary endpoint of CV death, myocardial infarction or stroke in patients with heart failure taking *Crestor* 10mg, which did not reach statistical significance. This reduction was primarily driven by a decrease in atherosclerotic events, such as stroke and myocardial infarctions. In addition, significantly fewer hospitalisations occurred in patients on *Crestor* compared to placebo, whether due to any cause, cardiovascular causes, or worsening heart failure. *Crestor* 10mg was well-tolerated, with a safety profile similar to placebo in a very high-risk study population. Further clinical trials of *Crestor* as part of the GALAXY programme are continuing and are due to report over the next few years.

Data from two pharmacoepidemiological observational studies investigating the incidence of CV events in over 470,000 patients taking statins (including *Crestor*) in routine clinical practice were presented in October 2007. The results from one study, conducted in The Netherlands, with a median duration of therapy of 11 months suggest that patients taking *Crestor* had significantly fewer CV events compared to patients taking simvastatin and pravastatin. The results from the other study, conducted in the US, showed

that *Crestor* users had a similar incidence of CV events to users of other statins at a median duration of therapy of 100 days. However, amongst patients who were on statin therapy for nine months or longer, the incidence of events was significantly lower in *Crestor* users. These studies have limitations typical of observational research. The large *Crestor* post-marketing surveillance programme in Japan was successfully completed in April 2007, when it was confirmed that the safety of *Crestor* for Japanese patients was in line with other statins.

In December 2007, we filed patent infringement actions against seven generic drug manufacturers in response to receiving notices stating that they had filed abbreviated new drug applications (ANDAs) in the US certifying their intent to market generic copies of *Crestor* before the 2016 expiry of our patent covering the active ingredient in *Crestor*. We did not file patent infringement actions against two other generic drug manufacturers that similarly filed ANDAs seeking approval to market generic copies of *Crestor*. Those ANDAs seek approval to market products only after expiration of the patent covering the active ingredient in 2016. Further information about the ANDAs in respect of *Crestor* is set out in Note 27 to the Financial Statements on page 158. We continue to have full confidence in our intellectual property protecting *Crestor* and will vigorously defend and enforce it.

Atacand continues to be well accepted and competes in the fastest growing sector by value (angiotensin II antagonists – plain and combinations with diuretic) of the global hypertension market. A 32mg dose is available to support the use of *Atacand* in hypertension and congestive heart failure. Launches of the 32mg dosage strength outside the US continued during the year, and this strength is now available in most major markets. The clinical programme (DIRECT) investigating the effect of *Atacand* (up to 32mg dosage) on retinopathy in hypertensive and normotensive diabetic patients continued during 2007.

PIPELINE

Diabetes/obesity

In January 2007, we announced a worldwide (except Japan) collaboration with Bristol-Myers Squibb Company (BMS) to develop and commercialise two investigational compounds discovered by BMS being studied for the treatment of Type 2 diabetes – saxagliptin and dapagliflozin. We will set the development and commercial strategy for the two compounds jointly with BMS.

Saxagliptin is being studied as a once-daily oral anti-diabetic to determine its efficacy and safety profile. Saxagliptin was specifically

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designed to be a selective and durable inhibitor of the DPP-4 enzyme, which regulates hormones that control plasma glucose levels. Phase III clinical trials to evaluate the efficacy and safety of saxagliptin are fully recruited. We plan to file a regulatory application for saxagliptin in the US in the second quarter of 2008. Results from a phase III trial were announced at the American Diabetes Association meeting in June 2007 and demonstrated that saxagliptin, when used as an add-on therapy to metformin, improved glycaemic control in adult patients with Type 2 diabetes, compared with the use of metformin alone, during 24 weeks of treatment.

Dapagliflozin is being studied as a once-daily oral anti-diabetic in the class of sodium-glucose cotransporter 2 (SGLT2) inhibitors. Dapagliflozin is a selective SGLT2 inhibitor, and has the potential to be first in this novel class of anti-diabetics. It is designed to be used both as monotherapy and in combination with other therapies for Type 2 diabetes.

Phase IIa data presented at the 2007 American Diabetes Association meeting demonstrated that administration of dapagliflozin reduced fasting serum glucose in patients with Type 2 diabetes when administered for 14 days alone or concomitantly with metformin.

In addition to saxagliptin and dapagliflozin, we have compounds in the area of diabetes and obesity in the cannabinoid receptor inhibitor class, as well as glucose kinase activating compounds in early patient testing.

Atherosclerosis/dyslipidaemia

In August 2007, we confirmed that the fixed-dose combination treatment of Abbott's next generation fenofibrate (ABT-335) and *Crestor* will progress into phase III development. The single pill would target all three major blood lipids: LDL-C 'bad cholesterol', HDL-C 'good cholesterol' and triglycerides.

In April 2007, we terminated our licensing and collaboration agreement with AtheroGenics, Inc. for AGI-1067. AGI-1067, an investigational anti-atherosclerotic agent, was studied in the ARISE phase III clinical outcomes trial involving more than 6,000 patients with coronary artery disease, but the trial failed to meet its primary endpoint.

Thrombosis

AZD6140 is the first reversible, oral, adenosine diphosphate (ADP) receptor antagonist. AZD6140 selectively and reversibly binds to the platelet receptor, in contrast to the irreversible binding seen with thienopyridines. The selective and reversible binding of AZD6140 means that platelet function recovers

as drug plasma levels decline. AZD6140 is being developed to reduce the risk of thrombotic events in patients diagnosed with acute coronary syndromes (ACS). AZD6140 is currently being studied in the phase III PLATO clinical trial. This is a head-to-head outcomes study to determine if AZD6140 is superior to clopidogrel for reducing the risk of thrombotic events in patients with ACS. It is being conducted in over 40 countries at up to 1,000 investigational centres and will include approximately 18,000 ACS patients.

In anti-coagulation, our principal project is AZD0837, an oral, direct thrombin inhibitor in late phase II testing. An extended release formulation is being developed, giving the possibility to use once-daily dosing without significant peak-trough variability, in other words reduced variability in anti-coagulation effect throughout the dosing interval.

Atrial fibrillation

Our lead compound is AZD1305, an atrial repolarisation-delaying agent, which has progressed into phase I testing in man.

PERFORMANCE 2007

Reported performance

Reported CV sales rose by 9% from \$6,118 million in 2006 to \$6,686 million in 2007. Continued strong growth from *Crestor* more than offset the significant declines in *Seloken/Toprol-XL*.

Underlying performance

Excluding exchange effects, CV sales grew by 5%. *Crestor* sales increased by 33% to \$2,796 million. In the US, *Crestor* sales for the full year were \$1,424 million, a 24% increase over 2006. Total prescriptions in the US statin market increased 8% for the year; *Crestor* prescriptions were up 22%. *Crestor* share of total prescriptions in the US was 8.6% in December 2007, marginally down from the 8.7% recorded in December 2006. Sales outside the US for the full year increased 45% to \$1,372 million, nearly half the total worldwide sales for the product. Sales were up 26% in Western Europe with good growth in France and Italy. Sales in Canada increased 43%. The launch in Japan continues to progress well, with *Crestor* achieving an 8.8% volume share in November 2007.

Global sales of *Seloken/Toprol-XL* fell by 22% to \$1,438 million. US sales of the *Toprol-XL* product range, which includes sales of the authorised generic were down 30% for the full year, as the full range of dosage strengths were subject to generic competition from August 2007. Generic products accounted for 85% of dispensed prescriptions in the fourth quarter and the *Toprol-XL* product

range declined by 69% in that period compared with 2006. Sales of *Seloken* in other markets were up 5% for the full year as a result of growth in Emerging Markets.

Atacand sales in the US were unchanged for the full year whilst sales in other markets increased 12%.

Continued small declines were seen in *Zestril* (down 10% to \$295 million) and *Plendil* (down 7% to \$271 million), with general global falls compensated by increases in discrete markets.

PERFORMANCE 2006

Reported performance

CV sales were up by 15% on a reported basis, rising from \$5,332 million in 2005 to \$6,118 million in 2006. The strong performance of *Crestor* was the principal driver of growth.

Underlying performance

Excluding exchange effects, CV sales grew by 15%. Annual sales for *Crestor* exceeded \$2 billion for the first time in 2006 and, since launch in early 2003, more than 70 million prescriptions have been written. *Crestor* sales in the US were up 57% to \$1,148 million for the year. New prescriptions for statins in the US were up 18%; *Crestor* new prescriptions were up 58%. *Crestor* new prescription market share in December 2006 was 9.6%. In other markets *Crestor* sales increased by 61% on good growth in Europe (up 56%) and in Asia Pacific following launch in Australia and Japan in the second half of 2006.

Sales of *Toprol-XL* in the US were up 7% for the full year to \$1,382 million. Total prescriptions in the US increased by 10% versus 2005. The November 2006 launch of Sandoz's generic 25mg metoprolol succinate product in the US was followed by an announcement that we had entered into a supply and distribution agreement with Par Pharmaceutical Companies, Inc. to distribute an authorised generic version of the same 25mg dosage strength in the US market. As a consequence, adjustments were taken in respect of pipeline inventory in the marketplace with the effect that sales are now being recognised as prescriptions are written. Sales of *Seloken* in other markets were down 7% for the full year to \$413 million.

Atacand sales in the US were up 12% to \$260 million with new prescriptions up 7%. In other markets, *Atacand* sales were up 14% to \$850 million.

Plendil sales were down 24% as a result of generic competition in the US market, where *Plendil* sales declined by 71% to \$24 million.