

# Cardiovascular

The list of top 50 CV products to emerge from “the Aughts” looks set for a shakeup entering “the Tens.” **Marc Iskowitz** examines threats and opportunities expected from generic Lipitor and emerging CETP inhibitors, as well as market dynamics within the anti-platelet and anti-hypertensive segments

**O**ver the last decade, improved methods of prevention and treatment have helped lower heart disease and stroke deaths. Reducing the toll from these epidemics has a commercial upside, as well. Many of the cardiovascular products featured in *MM&M*'s top 50 chart, at right, have reaped reward by addressing unmet medical need while also capitalizing during narrowing patent windows, aggressively pursuing new indications and leveraging marketing and advertising.

Megabrands like Lipitor (#1, US) and Plavix (#2, US) have propelled the overall CV market to a new high. Total sales for the top 50, as measured by wholesale acquisition costs (the price pharmacies pay distributors), surged \$4.8 billion to \$62 billion during the 12 months from December 2008 to November 2009, according to Wolters Kluwer Pharma Solutions. That's an 8.4% increase over the previous 12-month period.

To maintain their position, the top brands have raised DTC and professional advertising spend 1.4% to about \$650 million, October 2008-September 2009 figures from SDI show. While the long-term fight against CV disease promises to keep this category one of pharma's most lucrative segments, the list of threats facing existing brands is long, namely generic exposure and a robust pipeline.

## Lipid management

Statins—the drugs designed to lower LDL, or “bad,” cholesterol—have been the dominant product group within CV, and analysts and business reporters have been gripped by a single question: how will the category shake out once Lipitor goes off patent? During the

**The year 2012, when Diovan will start giving way to generics, will bring a weakening of Novartis' hold on the hypertension category, says Sanford Bernstein analyst Tim Andersen**

12-month period that ended last September, Pfizer ramped up total ad support for its statin by 61.5% to \$211 million.

The marketing push, which comes amid the drug's final years of patent exclusivity, is an indicator of how much is at stake. Lipitor, the best-selling Rx drug in the world, begins facing generic exposure in 2011. After that, AstraZeneca appears best-positioned to grab share with its statin Crestor (#5, US).

Last year AstraZeneca applied for approval to broaden Crestor's label to reduce the risk of CV events among patients with normal cholesterol levels and elevated C-reactive protein (CRP). Being able to market the drug to this patient group could help AZ add to Crestor's sales, which reached \$2.9 billion last year, a 44.1% surge. In December, an FDA advisory panel voted overwhelmingly to allow the new indication.

Yet Sanford Bernstein analyst Tim Andersen, MD, says any gains from such an indication are going to be very slow: “Translating the CRP data into real-world usage will be a challenge.”

Impediments, namely generic statins, may also keep Crestor's sales from going stratospheric. Zocor lost exclusivity a few years ago, and generics and managed care firms pounced, driving simvastatin (#3, US) sales to \$5.1 billion for the 12 months ending last November, a 36.7% rise.

Pravastatin (#12, US) is also gaining, with prescriptions and sales increasing 31% and 28%, respectively. These products—sold on the cheap by big drug chains—have already affected Lipitor's sales, which dropped 4.1% during that period.

Come 2011, a generic could play spoiler again. “Crestor is the drug to watch with label expansion, etc.,” says Andersen. “But the investment community is underestimating the negative impact that generic Lipitor will have on Crestor once generics launch. Just like Zocor hurt Lipitor, Lipitor will hurt Crestor, but not as bad.”

## CETP-inhibitor reprise

Indeed, the push to convert Lipitor 'scripts to generic may limit overall revenue in this segment. And long after patent expiry exacts its pound of flesh, two experimental products—GlaxoSmithKline's darapladib and Merck's anacetrapib—could further alter the landscape.

The Phase-III CETP inhibitors, both of which are designed to



**TOP 50 CARDIOVASCULAR PRODUCTS, 2009**

Category leaders, ranked by US sales, and their media spend for the 12 months ending Nov. 30 (for sales/TRx) and Sept. 30 (for media)

Rank	Product	Manufacturer	US sales dollars (millions)*	% change vs. prior 12 mos.	TRx count (millions)*	TRx % change vs. prior 12 mos.	US media spend dollars (thousands)**	Media spend % change vs. prior 12 mos.
1	<b>Lipitor</b>	Pfizer	\$7,219.0	-4.1%	51.7	-11%	\$211,259	61.5%
2	<b>Plavix</b>	BMS/Sanofi-Aventis	\$5,431.8	15.8%	28.4	5%	\$149,592	21.2%
3	<b>Simvastatin</b>	Generic	\$5,054.1	36.7%	82.3	28%	0	N/A
4	<b>Lovenox</b>	Sanofi-Aventis	\$3,001.7	7.6%	1.5	9%	\$1,006	-18.5%
5	<b>Crestor</b>	AstraZeneca	\$2,964.3	44.1%	21.4	25%	\$123,124	28.8%
6	<b>Diovan</b>	Novartis	\$1,672.4	7.4%	16.7	-3%	\$1,573	-15.6%
7	<b>Tricor</b>	Abbott Labs	\$1,582.6	2.7%	12.0	-5%	\$191	98.9%
8	<b>Vytorin</b>	MSP	\$1,579.8	-22.3%	11.7	-32%	\$8,640	-88.7%
9	<b>Diovan HCT</b>	Novartis	\$1,454.0	5.8%	14.0	-5%	0	N/A
10	<b>Amlodipine Besylate</b>	Generic	\$1,432.1	21.7%	49.9	18%	0	N/A
11	<b>Zetia</b>	MSP	\$1,406.7	-9.7%	10.5	-20%	\$39,977	3.5%
12	<b>Pravastatin Sodium</b>	Generic	\$1,164.9	28.0%	20.6	31%	0	N/A
13	<b>Lisinopril</b>	Generic	\$1,146.6	3.8%	84.9	9%	0	N/A
14	<b>Cozaar</b>	Merck	\$1,087.4	6.0%	90.9	-4%	0	N/A
15	<b>Niaspan</b>	Abbott Labs	\$1,079.5	13.8%	6.3	11%	\$18,608	143260.5%
16	<b>Carvedilol</b>	Generic	\$906.7	19.4%	17.4	27%	0	N/A
17	<b>Metoprolol Succinate</b>	Generic	\$780.5	-12.2%	28.7	-27%	\$51	80.0%
18	<b>Lovaza</b>	GlaxoSmithKline	\$732.9	49.5%	4.7	36%	\$8,848	316.5%
19	<b>Hyzaar</b>	Merck	\$702.3	9.2%	6.2	-9%	0	N/A
20	<b>Amlodipine Besylate-Benzazepril</b>	Generic	\$681.9	-3.8%	11.6	-6%	0	N/A
21	<b>Lovastatin</b>	Generic	\$636.5	-1.5%	16.7	-2%	0	N/A
22	<b>Benicar HCT</b>	Daiichi-Sankyo	\$632.1	11.6%	6.9	2%	0	N/A
23	<b>Benicar</b>	Daiichi-Sankyo	\$613.3	19.5%	7.9	7%	\$403	-44.7%
24	<b>Toprol XL</b>	AstraZeneca/Par	\$531.4	52.1%	7.9	45%	0	N/A
25	<b>Avapro</b>	BMS/Sanofi-Aventis	\$485.1	4.4%	5.3	-8%	0	N/A
26	<b>Atenolol</b>	Generic	\$452.6	-2.9%	41.8	-5%	0	N/A
27	<b>Sensipar</b>	Amgen	\$426.5	8.0%	0.6	-5%	\$400	10.2%
28	<b>Caduet</b>	Pfizer	\$423.2	-11.3%	2.6	-17%	\$83,433	4.1%
29	<b>Lotrel</b>	Novartis	\$413.4	-6.3%	2.8	-19%	0	N/A
30	<b>Heparin Sodium</b>	Generic	\$413.0	113.3%	0.1	0%	\$11	72.9%
31	<b>Metoprolol Tartrate</b>	Generic	\$409.0	-1.2%	38.3	22%	0	N/A
32	<b>Lisinopril-HCTZ</b>	Generic	\$406.5	17.6%	26.6	15%	0	N/A
33	<b>Avalide</b>	BMS/Sanofi-Aventis	\$395.2	4.0%	3.9	-91%	0	N/A
34	<b>Aggrenox</b>	Boehringer Ingelheim	\$389.3	9.3%	1.8	-2%	\$124	N/A
35	<b>Angiomax</b>	The Medicines Co.	\$385.5	10.2%	N/A	N/A	0	N/A
36	<b>Coreg CR</b>	GlaxoSmithKline	\$347.4	5.7%	2.3	-6%	0	N/A
37	<b>Arixtra</b>	GlaxoSmithKline	\$340.0	46.4%	0.1	20%	\$79	N/A
38	<b>Integrilin</b>	Schering-Plough	\$332.0	-5.8%	N/A	N/A	0	N/A
39	<b>Warfarin Sodium</b>	Generic	\$324.5	5.8%	25.9	4%	0	N/A
40	<b>Welchol</b>	Daiichi-Sankyo	\$307.7	21.7%	1.6	14%	\$2,008	N/A
41	<b>Ramipril</b>	Generic	\$295.2	8.9%	9.9	N/A	0	N/A
42	<b>Micardis</b>	Boehringer Ingelheim	\$281.0	24.2%	2.6	1%	\$453	-67.2%
43	<b>Coumadin</b>	Generic	\$269.4	0.1%	2.8	-16%	0	N/A
44	<b>Enalapril Maleate</b>	Generic	\$252.1	-1.4%	13.5	-4%	0	N/A
45	<b>Micardis HCT</b>	Boehringer Ingelheim	\$251.3	17.4%	2.3	-2%	0	N/A
46	<b>Cardene I.V.</b>	EKR Therapeutics	\$248.7	30.0%	N/A	N/A	0	N/A
47	<b>Exforge</b>	Novartis	\$247.2	64.3%	2.3	49%	\$269	-92.8%
48	<b>Thrombin-JMI</b>	Generic	\$241.3	-13.8%	0.0	-8%	0	N/A
49	<b>Nifedipine ER</b>	Generic	\$209.9	-3.7%	5.0	-1%	0	N/A
50	<b>Revatio</b>	Pfizer	\$209.0	22.9%	0.1	8%	\$210	66.8%

\* Integrated wholesale acquisition cost (WAC) sales and TRx between 12/08-11/09 inclusive.

\*\* DTC/journal spend between 10/08 and 9/09 inclusive. Sources: Sales/TRx, Wolters Kluwer Pharma Solutions; media spend, SDI. TRx count includes retail only.

**On the CV beat**

**Niaspan**



Abbott Laboratories' Niaspan saw NRx rise 30% in the weeks following the release of data from clinical trial ARBITER 6-HALTS, which suggested HDL-raising is a positive strategy for reducing atherosclerosis. Abbott has hiked Niaspan ad spend sharply over the past year—143% according to

October 2008-September 2009 figures from SDI—yet the extended-release niacin will remain a “niche drug,” predicts Sanford Bernstein analyst Tim Andersen

**Zetia**



Merck/Schering-Plough has increased media support for Zetia 3.5% to \$39.9 million (during October 2008-September 2009), prior to patent expiry in 2016. Still, Zetia and its cousin Vytorin have been gradually losing sales since unflattering data from the ENHANCE trial were

released in 2007. “Despite the negative data [Zetia] is probably a drug that is doing what it is supposed to,” says Andersen. “That will ultimately be shown in the IMPROVE-IT trial, or not”

**Crestor**



AstraZeneca's move to capitalize on the 2007 METEOR data in its advertising (to wit, the 2008 campaign “Us Against Athero”) was textbook marketing. Now the company is applying for another indication based on the 2008 JUPITER clinical trial results. Revised labeling could come this year, but “gains in the ‘normal cholesterol and elevated [C-reactive Protein]’ population are going to be

very slow,” says Andersen. “Translating the CRP data into real-world usage will be a challenge”

**Plavix**



The impending US patent cliff for Plavix, the world's second-best-selling drug behind Lipitor, portends a sales implosion for co-marketers Bristol-Myers Squibb and Sanofi-Aventis. Both Plavix and Lovenox, another megablockbuster anticoagulant nearing the end of its patent

life, have seen reduced media spend. Two experimental anti-platelet drugs on the horizon, meanwhile, could become replacements for Coumadin, notes Ben Weintraub, PhD, director of research at Wolters Kluwer *inThought*

**Lipitor**



What will replace megablockbuster Lipitor when the world's best-selling pharmaceutical begins facing patent expiry in 2011? The one to watch in this category is AstraZeneca's Crestor, which has been expanding its label in a bid to capture sales. But generic Lipitor could limit growth. And remember CETP inhibitors? Two analogues of Pfizer's failed compound torcetrapib are nearing approval to raise

HDL cholesterol and could pose another impediment for Crestor, says Weintraub

raise HDL or “good” cholesterol, are analogues of torcetrapib, the compound Pfizer had at one time hailed as a Lipitor successor before suddenly halting development in 2006 due to safety reasons.

“It's time for people to get over the torcetrapib failure and start to get excited about HDL-raising again,” says Ben Weintraub, PhD, director of research, Wolters Kluwer *inThought*. “Talking to cardiologists, there's a lot of hope that the problems with torcetrapib were not class-specific. There's some nice studies...to show [the newer products are] not falling into the same trap.”

The anticoagulant segment is another one bracing for change. For starters, there's generic competition to Bristol-Myers Squibb/Sanofi-Aventis' Plavix and Sanofi-Aventis' Lovenox (#4, US)—projected to arrive in 2011 and 2010, respectively. (In Europe, copcat versions of Plavix are already available.)

Potential game-changers also include the anticipated approval of two new oral blood thinners moving through the late-stage pipeline—Xarelto, from Johnson & Johnson/Bayer, and Pradaxa, from Boehringer Ingelheim. Both Phase-III candidates are once-daily, oral and don't require coagulation monitoring.

**Replacing warfarin**

As such, the newer products could replace Coumadin (warfarin, #43/#39, US), a generic drug which “is essentially free but is used by a lot of patients,” says Weintraub.

Without the need for monitoring, the two products could provide a cost-neutral way for doctors to avoid warfarin's well-documented adversities. Warfarin is commonly used in the setting of venous thromboembolism (VTE), as well as for stroke prevention in patients with atrial fibrillation (aFib)—areas in which the two experimental therapies are being tested.

Plavix is set to go off patent before their possible approval for acute coronary syndrome (ACS), Andersen points out. Assuming they work in ACS, which is unclear at this point, Lovenox presents more of a “direct target,” although it may hold its own, he predicts.

Turning to antihypertensives, Novartis' Diovan franchise stands as the 800-lb. guerilla, with a combined \$3.2 billion in US sales but is set to face generic competition in 2012. The franchise may not fall completely off the cliff, though, says Mark Perlotto, managing director of healthcare communications agency Adair Greene McCann, which launched the blood-pressure med Micardis (#42, US) a decade ago.

**High blood pressure**

Hypertension drugs, he says, have a second life in brand extension, as “there is a lot more variability in hypertension response among patients.” To wit: Boehringer Ingelheim's Micardis franchise and other brands, such as Merck's Cozaar and Hyzaar (#14, #19, US), are strong performers despite the presence of generics like amlodipine besylate, Perlotto points out.

Andersen takes a less optimistic view of the blood-pressure segment. “There will be no market leader,” he says. Diovan will be overtaken by a host of small brands, including, to a lesser degree, Novartis' own Tekturna. ■

*This is the first in a series of five bi-monthly features examining different therapeutic categories, culminating in the December Pipeline Report. The next installment will be April's focus on vaccines*