

Cardiovascular

The patent cliffs for the two biggest cardiovascular products are due to arrive this year and next, paving the way for generics. But don't count brands out in this category just yet. New drugs may spur a generic-to-brand switch the likes of which haven't been seen in a decade. **Marc Iskowitz** reports

The stage is set for sales erosion and a wave of generic switching among cholesterol and antiplatelet products. Pfizer's potent lipid-lowering drug Lipitor (atorvastatin) is losing patent protection in November. Bristol-Myers Squibb/Sanofi-Aventis' blood thinner Plavix (clopidogrel) will lose exclusivity several months later. But the pendulum could swing back to brands.

"You know, Zocor (simvastatin) did expire [in June 2006], and the world didn't come to an end," recalls Tony Butler, PhD, managing director and senior pharma analyst for Barclays Capital. "The world can still change to brands, even in a generic atorvastatin/generic simvastatin world."

Aren't there fewer players developing new cardiovascular drugs nowadays, what with Pfizer exiting CV research a few years back, and isn't the FDA less likely to approve a drug based on a surrogate endpoint? Yes, but some big innovator firms remain committed to the space, and what's emerging from the pipeline looks promising.

In the meantime, generics are making their presence felt. For the 12 months ending October 31, 2010, total category sales rose 7.1% to \$65.7 billion, from \$61.3 billion during the prior 12-month period, according to wholesale acquisition cost sales data from Wolters Kluwer Pharma Solutions. The December 2008-November 2009 growth rate was 8.4%. Slower growth could be due to big brands seeing cheaper competition this past year, such as Cozaar (#18, US) and Hyzaar (#33, US)—the Merck blood pressure pills which lost exclusivity in April. In the anti-thrombotic space, US sales of Sanofi-Aventis' Lovenox (#5, US) dipped 47% in the quarter that Sandoz launched a generic copy, the company said.

Back to brands, Butler believes the most exciting opportunity lies in factor Xa inhibitors, a class of drugs that competes with blood thinner warfarin. Boehringer Ingelheim's Pradaxa, approved last year, and Johnson & Johnson/Bayer's Xarelto, which could see approval this year, along with BMS/Pfizer's phase III agent

apixaban, are oral and require no coagulation monitoring, so they stand a good chance of minimizing doctors' use of warfarin. "I believe you will see a generic-to-brand switch, and this will be the first time [such] switches have occurred since Claritin," he says, adding that the warfarin-replacement market could reach \$15 billion.

Further out on the horizon, Merck's thrombin receptor antagonist vorapaxar has a different mechanism of action and more selectivity than clopidogrel and Eli Lilly/Daiichi Sankyo's Effient and, in theory, could be used in combination with them or with AstraZeneca's investigational antiplatelet agent Brilinta, for what Butler calls "an Effient effect without Effient bleeding." But in January Merck halted one of two phase III vorapaxar trials and narrowed the other, likely due to safety, and has yet to update its regulatory projection.

In addition, there are still questions being pursued in the cholesterol market, both in primary prevention (people without a history of heart disease) and secondary prevention (those who have hypertension, diabetes, etc.). In patients with hypercholesterolemia, can more aggressive lowering of LDL, or "bad" cholesterol, reduce death and heart attack by more than 30%, the current standard? Merck is trying to find out in its IMPROVE-IT trial of Vytorin vs. simvastatin alone, and Vytorin (#11, US) could get a boost if the idea pans out.

AstraZeneca's Crestor (#4, US), another high-potency statin, faces increased risk from generic atorvastatin, but a recently secured indication in patients without clinically evident heart disease could spur usage (whether managed care officials agree is another matter). Other drugs in big phase III trials include Merck's anacetrapib and Roche's dalcetrapib, both in the CETP inhibition class of drugs that raise HDL, or "good" cholesterol, as well as Merck's Tredaptive, which combines extended-release niacin with a flush inhibitor to boost HDL.

So, who'll be the big winner in the post-Lipitor/Plavix expiry period? "I don't know about a big winner per se," says Butler. "It may be a clinical research organization." ■

The next installment of MM&M's bi-monthly series examining different therapeutic categories will be April's focus on metabolic products



TOP 50 CARDIOVASCULAR PRODUCTS, 2010

Category leaders, ranked by US sales, and their media spend for the 12 months ending October 31 (for sales/TRx) and August 31 (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	Lipitor	Pfizer	\$6,887.7	-4.8%	45.2	-13.2%	\$298,065	33.6%
2	Simvastatin	Generic	\$6,282.6	27.7%	92.3	14.4%	0	N/A
3	Plavix	BMS/Sanofi-Aventis	\$6,021.4	12.5%	28.2	-0.1%	\$141,119	-6.0%
4	Crestor	AstraZeneca	\$3,693.9	27.9%	23.9	14.0%	\$120,090	1.8%
5	Lovenox	Sanofi-Aventis	\$2,942.9	-1.3%	1.3	-7.3%	\$79	-92.2%
6	Diovan	Novartis	\$1,830.7	10.5%	16.5	-0.8%	\$13	-99.2%
7	Diovan HCT	Novartis	\$1,522.4	5.4%	13.2	-5.4%	0	N/A
8	Amlodipine Besylate	Generic	\$1,430.2	13.2%	56.0	14.0%	0	N/A
9	TriCor	Abbott Labs	\$1,375.6	-13.2%	9.5	-21.8%	0	-100.0%
10	Pravastatin	Generic	\$1,363.3	24.6%	23.7	18.0%	0	N/A
11	Vytorin	MSP	\$1,351.7	-15.1%	9.0	-24.4%	\$23,724	277.6%
12	Zetia	MSP	\$1,329.6	-5.3%	9.0	-15.0%	\$32,616	-5.2%
13	Lisinopril	Generic	\$1,253.1	10.1%	90.0	7.2%	0	N/A
14	Niaspan	Abbott Labs	\$1,207.5	12.6%	6.7	8.1%	\$19,872	14.5%
15	Carvedilol	Generic	\$1,135.2	28.3%	19.6	14.7%	0	N/A
16	Metoprolol succinate	Generic	\$870.7	21.6%	5.3	15.8%	\$71,495	693.0%
17	Lovaza	GlaxoSmithKline	\$780.5	-12.2%	28.7	-27%	\$51	80.0%
18	Cozaar	Merck	\$715.9	-33.4%	4.7	-48.4%	0	N/A
19	Benicar	Daiichi-Sankyo	\$684.7	13.6%	7.4	-5.6%	\$12	-97.6%
20	Lovastatin	Generic	\$634.1	-1.1%	16.0	-4.0%	0	N/A
21	Benicar HCT	Daiichi-Sankyo	\$623.0	-0.6%	6.2	-9.3%	\$12	-97.3%
22	Amlodipine Besylate-Benezepril	Generic	\$614.4	-9.7%	10.2	-11.9%	\$35	N/A
23	TriLipix	Abbott Labs	\$491.9	190.1%	4.1	163.1%	\$67,735	87.3%
24	Avapro	BMS/Sanofi-Aventis	\$464.5	-3.9%	4.5	-14.0%	0	N/A
25	Angiomax	The Medicines Co.	\$459.3	20.2%	N/A	N/A	0	N/A
26	Lisinopril-HCTZ	Generic	\$456.7	15.2%	28.6	9.3%	0	N/A
27	Atenolol	Generic	\$437.4	-3.2%	38.9	-6.7%	0	N/A
28	Arixtra	GlaxoSmithKline	\$432.4	30.8%	N/A	N/A	0	-100.0%
29	Metoprolol tartrate	Generic	\$427.7	5.5%	37.8	0.1%	\$12	N/A
30	Heparin sodium	Generic	\$423.4	3.4%	N/A	N/A	\$22	104.9%
31	Aggrenox	Boehringer Ingelheim	\$421.5	9.6%	1.7	-5.9%	\$168	62.5%
32	Lotrel	Novartis	\$390.9	-5.5%	2.4	-17.7%	0	N/A
33	Hyzaar	Merck	\$388.9	-44.2%	3.1	-50.5%	0	N/A
34	Avalide	BMS/Sanofi-Aventis	\$375.4	-4.7%	3.3	-15.2%	0	N/A
35	Welchol	Daiichi-Sankyo	\$362.7	19.3%	1.8	13.2	0	N/A
36	Caduet	Pfizer	\$352.2	-17.6%	2.0	-24.6%	\$10,619	-86.0%
37	Micardis	Boehringer Ingelheim	\$350.8	27.8%	2.6	3.4%	\$7,580	>999.9%
38	Warfarin sodium	Generic	\$337.0	5.0%	26.6	3.4%	0	N/A
39	Toprol XL	AstraZeneca/Par	\$314.5	-40.4%	4.0	-49.3%	\$443	-97.2%
40	Coreg CR	GlaxoSmithKline	\$305.5	-11.9%	2.0	-14.5%	0	N/A
41	Integrilin	Merck	\$303.4	-9.1%	N/A	N/A	0	N/A
42	Exforge	Novartis	\$291.0	20.7%	2.5	10.4%	\$576	47.2%
43	Diltiazem 24HR ER	Generic	\$287.6	82.6%	3.7	63.5%	0	N/A
44	Fragmin	Eisai	\$278.3	39.0%	N/A	N/A	0	-100.0%
45	Micardis HCT	Boehringer Ingelheim	\$274.8	10.4%	2.3	-1.5%	0	N/A
46	Ramipril	Generic	\$272.1	-5.1%	9.4	-4.4%	0	N/A
47	Enalapril maleate	Generic	\$254.7	2.0%	12.8	-4.9%	0	N/A
48	Activase	Genentech	\$243.6	22.1%	N/A	N/A	0	-100.0%
49	Bystolic	Forest	\$241.9	76.2%	3.8	67.4%	\$7,653	21.8%
50	Gemfibrozil	Generic	\$230.8	25.0%	6.2	-2.6%	0	N/A

* Integrated wholesale acquisition cost (WAC) sales and TRx between 11/09-10/10 inclusive.

** DTC/journal spend between 9/10-8/10 and 9/09 inclusive. Sources: Sales/TRx, Wolters Kluwer Pharma Solutions; media spend, SDI & Kantar Media. TRx count includes retail only.