Cardiovascular

So much for "best in class." Despite having the brightest data set of all the oral anticoagulants, the newest one is off to a rocky start. What's behind the Factor Xa fail? A confluence of factors, from sales strategy to market access. DTC advertising and medical education are under way, but it may take more to revive this launch. **Noah Pines** reports

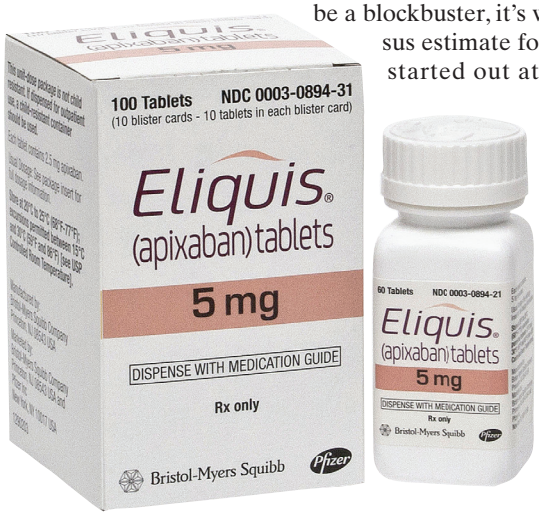
Mention a primary care sales force in a pharmaceutical company boardroom today and you're likely to elicit a lot of frowns and scowls, if not a spear thrown in your general direction. With specialty medicine, biotech and rare diseases on fire, everyone is seeking to emulate Gilead Sciences, Biogen Idec and Celgene.

Yet, if you're going to build a multi-billion-dollar cardiovascular franchise, effectively capturing the hearts and minds of the PCP is still critical. And those CV marketers who don't engage the PCP as fervently as in years past may elicit a lot of frowns and scowls—and possibly a spear—from disappointed investors.

Which brings us to the case of Pfizer and Bristol-Myers Squibb's Eliquis (apixaban), the third-in-class Factor X oral anticoagulant. The drug was expected to eventually dominate what could be a $10-billion class.

"We expected a lot more out of Eliquis in terms of sales," notes Leon Henderson, an internist and senior analyst at *in*Thought, part of Symphony Health Solutions. "While it has strong backing from the cardiologists, there is some evidence that its under-performance is attributable to its being under-marketed to internists."

That's just one of the questions swirling around what's been an extremely sluggish launch. While the drug is still expected to be a blockbuster, it's way off the consensus estimate for 2013 sales, which started out at $400 million and was reduced, as of press time, to $129 million.



And even that may be a stretch. BMS reported $41 million in Eliquis sales during the third quarter, of which $27 million was from the US, far below analyst expectations when Eliquis was approved by the FDA for stroke prevention in patients with atrial fibrillation (SPAF) in December 2012 and launched in the US in early 2013.

Drugmaker efforts to improve performance have included deploying a DTC campaign and increasing peer-to-peer med-ed activities—basically paying physicians to lecture other docs about the full data set. "We are the only agent with superiority claims vs. warfarin in the three key outcomes of stroke and embolism, major bleeding and also mortality," said BMS CEO Lamberto Andreotti on a second-quarter call with analysts.

"The other two new agents cannot make the same triple-superiority claim," he said, referring to the two previously approved factor drugs, Boehringer Ingelheim's Pradaxa (dabigatran) and Johnson & Johnson/Bayer's Xarelto (rivaroxaban).

Yet differentiation through data has yet to prevail, perhaps because the company has not put sufficient marketing muscle behind PCP efforts, despite good initial uptake in cardiology. Since cardiologists may be more difficult to see, PCPs are the ones who are driving the Factor Xa anticoagulant business. They have little time to fight with insurers and thus they may be more likely to cave when access becomes a challenge, especially when warfarin is available cheaply.

Another factor is market access. The drug has over 80% of lives covered in the commercial space, BMS said, and over 75% of lives covered in the Medicare space. However, that coverage has primarily been in a non-preferred status.

Eliquis has slightly higher rejection rates than Xarelto in both commercial (9% vs. 6%) and Medicare (15% vs. 12%) channels, data from Symphony Health Solutions show. And Eliquis's rejection rate from commercial payers has actually increased since launch, from 7% to 9%. Those rates are similar between cardiologists and other specialties.

As to why Eliquis 'scripts are being bounced more frequently, the reasons for that relate specifically to restricting utilization. Symphony's analysis of Medicare rejection rates show the top four reasons have been need for prior authorization (43%), product not covered (21%), premature refill (13%) and product not on formulary (11%).

"The launch did not go as expected for a product that had supe-

TOP 50 CARDIOVASCULAR PRODUCTS, 2013

Category leaders, ranked by US sales, and their media spend for the 12 months ending Oct. 31 (for sales/TRx) and Sept. 30 (for media)

Rank	Product	Manufacturer	US sales $ (millions)	Vs. prior 12 mos.	TRx (millions)	Vs. prior 12 mos.	US DTC media $ (000s)	Vs. prior 12 mos.	US journal media $ (000s)	Vs. prior 12 mos.
1	**Crestor**	AstraZeneca	$5,341.2	6.9%	23.6	-8.2%	$76,066.5	47.0%	$622.5	-41.0%
2	**Diovan**	Novartis	$2,164.4	5.5%	13.0	-9.0%	$5,701.3	58.0%	$0.0	N/A
3	**Zetia**	MSP	$1,672.5	14.4%	7.7	-3.4%	$1,014.8	-94.0%	$52.7	N/A
4	**Enoxaparin sodium**	Generic	$1,477.5	-12.8%	2.9	5.7%	$0.0	N/A	$60.6	-31.0%
5	**Lovaza**	GlaxoSmithKline	$1,084.4	-0.2%	4.8	-10.3%	$5,018.3	-80.0%	$1,397.6	50.0%
6	**Niaspan**	AbbVie	$1,041.2	-7.2%	4.1	-24.2%	$314.2	-48.0%	$960.6	-46.0%
7	**Fenofibrate**	Generic	$1,021.3	>100.0%	13.2	75.0%	$0.0	N/A	$220.4	N/A
8	**Metoprolol Succinate**	Generic	$945.8	-7.4%	37.0	4.1%	$0.0	N/A	$0.0	N/A
9	**Vytorin**	MSP	$885.4	-10.1%	3.6	-24.6%	$0.0	N/A	$0.0	N/A
10	**Pradaxa**	Boehringer Ingelheim	$858.6	-1.3%	2.7	-11.6%	$23,605.2	-78.0%	$3,538.8	-17.0%
11	**Xarelto**	Johnson & Johnson	$847.9	>100.0%	3.1	>100.0%	$81,803.0	>100.0%	$14,732.7	27.0%
12	**Benicar**	Daiichi-Sankyo	$830.5	7.7%	5.0	-7.1%	$0.9	N/A	$0.0	N/A
13	**Atorvastatin calcium**	Generic	$740.5	-71.9%	63.6	67.0%	$0.0	N/A	$0.0	-100.0%
14	**Benicar HCT**	Daiichi-Sankyo	$683.7	4.2%	3.9	-9.6%	$0.0	N/A	$0.0	N/A
15	**Bystolic**	Forest	$671.6	29.2%	6.8	8.9%	$0.0	-100.0%	$0.0	N/A
16	**Valsartan HCTZ**	Generic	$615.1	>100.0%	7.9	>100.0%	$0.0	N/A	$319.0	N/A
17	**Welchol**	Daiichi-Sankyo	$563.7	17.3%	1.8	-0.8%	$11.5	-95.0%	$0.0	N/A
18	**Angiomax**	The Medicines Co.	$468.0	4.7%	N/A	N/A	$0.0	N/A	$0.0	N/A
19	**Aggrenox**	Boehringer Ingelheim	$460.4	-8.9%	1.4	-12.0%	$0.0	N/A	$0.0	N/A
20	**Activase**	Genentech	$453.7	34.7%	0.0	51.5%	$0.0	N/A	$0.0	-100.0%
21	**Lipitor**	Pfizer	$449.0	-85.1%	2.0	-86.3%	$1.3	-100.0%	$0.0	-100.0%
22	**TriLipix**	AbbVie	$414.7	-25.8%	2.1	-32.1%	$0.0	-100.0%	$0.0	N/A
23	**Effient**	Daiichi-Sankyo/Lilly	$407.0	16.7%	1.4	0.9%	$0.0	N/A	$2,186.5	3.0%
24	**Exforge**	Novartis	$394.9	1.0%	2.0	-10.3%	$3,648.0	N/A	$0.0	N/A
25	**Clopidogrel**	Generic	$378.2	>100.0%	24.8	>100.0%	$0.0	-100.0%	$0.0	-100.0%
26	**Lovenox**	Sanofi-Aventis	$366.7	-38.3%	0.1	-53.8%	$0.0	N/A	$0.0	N/A
27	**Azor**	Daiichi-Sankyo	$288.4	11.4%	1.5	-4.8%	$0.0	N/A	$0.0	N/A
28	**Micardis**	Boehringer Ingelheim	$274.8	-0.5%	1.5	-16.2%	$0.0	-100.0%	$0.0	N/A
29	**Diovan HCT**	Novartis	$269.3	-83.1%	1.5	-84.0%	$0.0	N/A	$0.0	N/A
30	**Amlodipine Bes.-Benaz.**	Generic	$268.4	-27.5%	8.5	-9.2%	$0.0	N/A	$0.0	N/A
31	**Diltiazem HCl**	Generic	$257.4	12.9%	6.4	5.4%	$0.0	N/A	$0.0	N/A
32	**Coreg CR**	GlaxoSmithKline	$236.8	-10.6%	1.0	-21.2%	$0.0	N/A	$0.0	N/A
33	**Pravastatin**	Generic	$230.7	67.8%	30.4	6.2%	$0.0	N/A	$0.0	N/A
34	**Toprol XL**	AstraZeneca/Par	$226.4	44.4%	3.4	-6.2%	$18.2	N/A	$0.0	N/A
35	**Micardis HCT**	Boehringer Ingelheim	$216.6	-2.5%	1.2	-18.6%	$0.0	N/A	$0.0	N/A
36	**TriCor**	AbbVie	$211.8	-83.9%	1.1	-83.0%	$0.0	N/A	$0.0	N/A
37	**Fondaparinux Sod**	Generic	$207.9	-8.5%	0.2	-9.9%	$0.0	N/A	$0.0	N/A
38	**Simvastatin**	Generic	$184.4	-19.5%	77.8	-11.4%	$0.0	N/A	$0.0	N/A
39	**Cathflo Activase**	Genentech	$181.8	-5.8%	0.0	12.5%	$0.0	N/A	$0.0	N/A
40	**Integrilin**	Merck	$177.0	-13.3%	0.0	-75.0%	$0.0	N/A	$0.0	N/A
41	**Heparin sodium**	Generic	$170.7	-5.5%	0.7	2.2%	$0.0	N/A	$0.0	N/A
42	**Clonidine**	Generic	$168.0	-8.5%	1.1	2.9%	$0.0	N/A	$16.0	N/A
43	**Nifedipine ER**	Generic	$158.2	12.8%	4.9	11.2%	$0.0	N/A	$0.0	N/A
44	**Lisinopril**	Generic	$153.6	-15.0%	93.3	3.4%	$0.0	N/A	$33.1	N/A
45	**Losartan potassium**	Generic	$145.2	-29.0%	31.8	24.8%	$0.0	N/A	$0.0	N/A
46	**Amlodipine Bes/Atorva**	Generic	$141.0	-18.8%	0.8	5.1%	$0.0	N/A	$0.0	N/**A**
47	**Tribenzor**	Daiichi-Sankyo	$141.0	25.3%	0.8	7.8%	$0.0	N/A	$0.0	N/A
48	**Exforge HCT**	Novartis	$139.0	16.9%	0.8	2.9%	$0.0	N/A	$0.0	N/A
49	**Livalo**	Kowa	$137.5	24.3%	0.9	9.4%	$7,701.8	-78.0%	$1,770.4	-37.0%
50	**Plavix**	BMS/Sanofi-Aventis	$131.8	-96.8%	0.5	-96.7%	$0.0	-100.0%	$0.0	N/A

Sources: Sales/TRx, IMS Health; DTC media spend, Nielsen; journals, Kantar Media.

CLINICAL CORNER

A big cardiovascular pipeline question is whether new American Heart Association-American College of Cardiology (AHA/ACC) guidelines will help or hurt companies developing LDL-cholesterol therapies, especially the anticipated new class of anti-PCSK9 monoclonal antibodies.

The answer may rest on the extent to which the guidelines broaden usage of statins, as it has been suggested that they would.

This past November, controversy erupted as the ACC–AHA task force issued updated guidelines for the treatment of high cholesterol levels. In contrast to the well-accepted Adult Treatment Panel III (ATP3) report in 2002, the new guidelines have drawn criticism over certain recommendations about which patients should be considered at-risk. The upshot, however, is the endorsement of more widespread statin utilization in populations deemed to be at risk for atherosclerotic cardiovascular disease.

Dr. Leon Henderson

"Statins do a great job at reducing cardiovascular risk, but they are still imperfect," says Dr. Leon Henderson, medical consultant and senior principal with *in*Thought, part of Symphony Health Solutions. "If more people enter the market by virtue of these guidelines, more people will have the opportunity to be refractory at some point."

He pegs the percentage of statin-intolerant patients at about 7%. ISI Group's Odysseas Kostas estimates about 10% of people won't take statins because of complaints.

Henderson concurs with other physicians that the new AHA-ACC guidelines are likely to boost the usage of statins, albeit not as dramatically as other estimates. "A doubling of statin usage is highly unlikely. Our company expects a 5% increase," he says.

He also thinks the guidelines bode well for anti-PCSK9's, which are being looked at as potentially advancing the standard of care in cholesterol management. There are three such assets in development.

The furthest along and highest-profile candidate is Sanofi/Regeneron's alirocumab (also known as SAR236553 and REGN727), which announced favorable top-line Phase III results in October, with additional data readouts expected in 2014. Next is Amgen's evolocumab (AMG 145), which is looking at monthly dosing as part of its late-stage clinical development pathway, which could give it a convenience edge.

Regeneron and Sanofi have been testing alirocumab dosed once every two weeks, but will be evaluating it for use every four weeks in subsequent studies. Bringing up the rear in the development of this class are anti-PCSK9 biologic assets from Pfizer, Novartis and Roche.

Henderson anticipates that it will be a data-driven field, but that dosing interval differences will be weighed by physicians and patients since these biologics all are parenterally administered. He is also encouraged by the FDA's announcement that outcomes studies will not be required for initial marketing approval. "That means they will be here a couple of years earlier."

rior data compared to the competition; demand and access could have been better," John Whang, COO and president of consultancy Reimbursement Intelligence, told *MM&M* by e-mail.

To improve access, Whang, who is also a board-certified cardiologist, suggests the companies leverage the AVERROES study with, and target populations more clearly to, payers. He also advises that they better support patient cost share, and demonstrate net process-of-care benefits over Coumadin clinics.

Some still see reason for optimism. "With renewed vigor, the sponsors have been re-focusing on the rank-and-file docs, and we see the gap closing," says *in*Thought's Henderson.

Indeed, according to a November note from Bloomberg analyst Sam Fazelli, US prescription growth for Eliquis has been on a "strong trajectory" since early September, after both companies increased marketing efforts to promote the drug to a wider prescriber base. "Importantly, the 40% gain in weekly prescription volumes during the past seven weeks has narrowed the gap vs. the launch of Xarelto," he wrote.

The slow launch has dampened recovery plans for both marketing partners. Eliquis was seen as the sign of a new beginning for Pfizer following the devastating financial crater that was left by the patent expiry of Lipitor. The drug was also expected to fill a hole in the BMS balance sheet that was left by the LOE on antiplatelet drug Plavix.

Their setback could work to the advantage of the two oral anticoagulant incumbents, Pradaxa and Xarelto. According to Henderson, "There are some data that J&J has done a great job of approaching the PCP."

On the other hand, the Eliquis situation may or may not foster opportunity for a potential new Factor X entrant in Phase III trials, Daiichi Sankyo's edoxaban. Although Bernstein Research Global Pharmaceuticals analyst Tim Anderson considers its recent Phase III data presentations at the American Heart Association to be "lackluster," the agent offers more convenient once-daily dosing (while Eliquis is dosed BID).

"Edoxaban is not likely to set the world on fire, but it should nonetheless be an approvable new entrant into the category," notes Anderson. "And, as Xarelto's resilience in the setting of Eliquis' launch has shown, once-daily dosing does appear to have commercial value."

Dr. Anderson posits two potential commercial pathways for Daiichi Sankyo, either a "go it alone," or one where it partners with a cardiovascular market incumbent hungry for new products, such as Merck or AstraZeneca.

ISI Group's Mark Schoenebaum, meanwhile, added this point to the consideration mix: "In the long run, [the] key driver for the class includes availability of reversal (antidote) agents."

Does the Eliquis experience suggest that pharma's pendulum has swung too much toward specialists? As drugmakers have shifted toward specialty drugs, and sized their field forces accordingly, the big companies no longer have armies of PCP sales reps able to blanket the country's internists on a moment's notice with a sales message. That whole model is a thing of the past. But the small sales force adept at getting to specialists doesn't work when launching a drug for anticoagulation.

Henderson sums up the lesson learned: "When you are third to market...you have to be better. This is a case where data did not win—and hopefully it will at some point." ■