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Vantage Point – As Eliquis limps on Xarelto dominates oral blood thinners

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A speedy launch for Eliquis was probably always too much to ask, considering that it was the third novel, oral anti-coagulant to reach the market. However, the tiny sales reported by marketing partners Bristol-Myers Squibb and Pfizer so far this year appear to have surprised sellside analysts, many of whom had pinned huge expectations on the product.

Consensus for Eliquis sales next year has dropped 60% in the last 12 months, *EvaluatePharma* data show, and currently stands at $491m. Over the same period, expectations for Johnson & Johnson and Bayer's Xarelto have surged – consensus for sales in 2014 has jumped by 81% and 60% in the companies' respective territories, to $1bn and $1.4bn. The Eliquis launch is still early but the ultimate potential of this product is now less certain, as it appears that Xarelto's broader label and dosing advantage might have been underestimated (see tables).

Missed expectations

With three novel, oral anti-coagulants reaching the market at roughly the same time – as well as Eliquis and Xarelto, Boehringer Ingelheim launched Pradaxa – differentiation was always going to be important to grab share in the biggest target market, stroke prevention in patients with nonvalvular atrial f brillation (SPAF).

Both Eliquis and Pradaxa showed superiority over warfarin in preventing stroke, but only the Bristol-Myers pill managed to reduce major bleeding over warfarin and improve mortality. In both Europe and the US these superiority claims over warfarin have been reflected on the Eliquis label and many analysts assumed this would give the product an edge over the competitors.

On approval of Eliquis in the US at the end of 2012, Goldman Sachs analysts wrote that this differentiation would drive penetration and reimbursement, adding that they viewed consensus for global sales of $350m in 2013 as a "low hurdle". Cowen analysts were even more effusive: "We believe there is no compelling reason to prescribe any other anticoagulant for SPAF," they told their clients.

In reality, Eliquis has limped from the blocks. Consensus for 2013 currently stands at $129m, but even this much reduced figure looks unlikely to be hit. Second-quarter sales came in at $12m; consensus was $43m.

In its first full year on the market after being approved for stroke prevention, Pradaxa sold $875m; Xarelto sold $582m, globally.

Taking time

Bristol-Myers and Pfizer were not expecting an easy ride and executives cautioned as much at the time of the approval, warning investors to expect a slow rollout. Despite huge expectations and prophesies of seismic shifts in practice, the launches of all of these products have happened slower than many anticipated, with reimbursement and entrenched use of warfarin throwing up bigger barriers than were foreseen.

It has also taken time for physicians to embrace these drugs, given the big step change in practise they represent, says Dr Ralph Sacco, chairman of neurology at the University of

Miami.

"They offer tremendous benefit over warfarin – they have less bleeding risk, they are easier to use, they have less drug and food interactions. But it takes time for this to penetrate down, particularly to the community practitioner," he says.

Despite all this many analysts were still expecting Eliquis to stop Xarelto in its tracks. But prescription data suggests that the impact has been negligible and as such the consensus view of the market for these oral thinners has shifted dramatically this year, with numbers for Xarelto climbing back up and Eliquis falling, producing the picture in the table below.

Changing outlook for the oral anti-coagulants

Product	Company	Current 2018 sales forecast ($m)	% change over last 12 months	Current 2014 sales forecast ($m)	% change over last 12 months	% change in 2014 forecast since launch	First launch in major market
Xarelto	Bayer	2,667	54%	1,353	60%	110%	Sep 2008 (Europe)
Eliquis	Bristol-Myers Squibb	2,631	-37%	491	-60%	-68%	Sep 2011 (US)
Xarelto	Johnson & Johnson	1,839	50%	1,005	81%	-11%	Jul 2011 (US)
Lixiana	Daiichi Sankyo	850	65%	94	-17%	-22%	Jul 2011 (Japan)

The big gap in this picture is Boehringer Ingelheim's Pradaxa, which reached the main markets first. The company being privately owned, consensus sales forecasts are not available; Boehringer reported global sales of $1.43bn last year.

US prescription data indicate that Pradaxa lost market share on the arrival of Xarelto in July 2011 and continues to do so, while Xarelto demand is still climbing strongly. Eliquis was only launched in March, and has so far captured only 1.1% of the market, according to data Bayer presented at an investor conference this week; Xarelto is on 19.3% to Pradaxa's 15.4%, the company said.

In part, this will be thanks to Xarelto's broad label, the widest of all three blood thinners with seven approved indications – Pradaxa and Eliquis are only approved in stroke prevention in the US.

The J&J/Bayer pill is also approved to treat deep vein thrombosis and pulmonary embolisms, and to prevent deep vein thrombosis in patients undergoing knee or hip replacement surgery. On top of this Xarelto has generated some positive data in acute coronary syndromes, a severely ill patient population in which Eliquis failed and Boehringer declined to test Pradaxa in phase III.

European regulators allowed marketing in this setting earlier this year and although the US has so far declined to grant approval, evidence of utility in a very hard-to-treat population can only have helped the drug's reputation (*FDA's no means no for new blood thinners in acute coronary syndrome, March 5, 2013*).

Eliquis is due to hear on approval in the albeit smaller pre-surgery setting in the US in May next year – it has already sold for this use in Europe – and this could help bump up demand.

Once vs twice

Dosing is likely to be another factor favouring Xarelto. While both Eliquis and Pradaxa pills need to be taken twice a day in stroke prevention, Xarelto is once daily. Tim Race, pharma analyst at Deutsche Bank, reckons this could be providing an edge.

"These patients are on many other drugs and once daily fits in best. Also, doctors don't trust patients to take their pills, so is [Eliquis] really better in the real world if you miss a dose?" he says.

Bayer is convinced that dosing is playing a major part in Xarelto's success. "Physician surveys have shown that they use Xarelto over other agents because of its breadth of indications at launch and once daily dosing," Dr Kemal Mal k, head of development and chief medical officer, said at Bayer's presentation yesterday.

Dr Sacco, who was involved in one of the pivotal trials testing Eliquis, agrees that Xarelto's

schedule can be an advantage.

"Once a day often improves compliance." But whether any of these drugs is truly better is "the million dollar question", he adds, as there have been no head-to-heads, and comparing trials results is fraught with the usual caveats.

"It's really hard to choose between them. Ultimately it comes down to what the physician is most comfortable using," he says.

Inertia

This stance will naturally favour an incumbent, and helps explain Eliquis's struggles to get off the ground, despite being perceived as the safest. As such, it is too early write off the drug as an also-ran, although if it still does have market-leading potential it seems this will longer than expected to fulfil.

And there is another cloud on the horizon for Eliquis, in the shape of a fourth oral contender – Lixiana or edoxaban from Daiichi Sankyo. Like Eliquis and Xarelto this is a Factor Xa inhibitor – Pradaxa is a thrombin inhibitor – and is also being tested as a once-a-day medicine.

Phase III data released earlier this year, in patients with deep vein or lung blood clots, found the project non-inferior to warfarin at preventing the recurrence of clots and superior to warfarin at preventing bleeding. Superiority on both measures would have been a huge win for the Japanese company, but results in the all-important stroke prevention indication will be the real measure of edoxaban. Those data are l kely to emerge at the AHA conference in November (*ESC – Daiichi joins the US-EU blood-thinning race with positive Lixiana data, September 2, 2013*).

Of course, a strong showing in stroke prevention will mark once-a-day edoxaban as a strong competitor to all of the anti-coagulants. Although Daiichi still has to get the drug to market – the FDA did not give Xarelto or Eliquis an easy ride – and then battle in an even more crowded market place.

And Bayer and J&J will not let their lead go without a fight – the German company set out plans yesterday to recruit another 30,000 patients in trials in additional clotting settings and a wider atrial f brillation population, to broaden the label further.

It is undoubtedly early days for Eliquis, and Bristol-Myers and Pfizer have laid out plans for a big marketing push to reinvigorate the launch. But its third-to-market handicap and twice-a-day dosing disadvantage, which were brushed off by the companies and bullish analysts before launch, will take time to overcome.

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