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Payer demands threaten rosy PCSK9 forecasts

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The $10bn opportunity forecast for the PCSK9 class of cholesterol-lowering drugs depends heavily on pharma companies' ability to attract patients unable to achieve goals on statins. But a huge obstacle stands in their way: the well-recognised knowledge that statins are underused.

This novel class has shown impressive potency, lowering low-density lipoprotein (LDL) cholesterol in numerous phase III trials, offering a new alternative for 20 million people not now reaching lipid targets on statins. But with these drugs expected to cost over $8,000 a year, payers will demand clear evidence that patients are intolerant to statins or uncontrolled even at the highest dose before authorising PCSK9 use.

Many patients, but undertreated

The PSCK9s include Amgen's evolocumab and Sanofi and Regeneron Pharmaceuticals' alirocumab, and are the next hope for patients who need an agent more powerful than statins like Pfizer's off-patent Lipitor to lower their LDL.

The biggest population of potential PCSK9 users, estimated at more than 18 million in the US and Europe by Morgan Stanley, are patients at high risk of cardiovascular complications; factors include diabetes, pre-existing cardiovascular disease, and LDL levels that have remained elevated despite treatment with statins. This population could be worth €6.5bn ($8.4bn), according to Morgan Stanley.

Another view, from a survey of cardiologists at Leerink, suggested that 11% of patients are statin-intolerant, with another 21% not achieving LDL goals – although 42% of this latter group are not taking a high-intensity statin as recommended by US guidelines (*New US cholesterol guidelines reinforce the importance of outcomes data, November 13, 2013*).

An analysis of US government data published in the Annals of Family Medicine earlier this year estimated that 9 million Americans with diabetes older than 40 were not taking statins, along with 5.6 million with coronary artery disease.

Payers almost certainly know that treatment with statins is suboptimal, and even cardiologists themselves recognise that some of the answer to preventing cardiovascular problems lies in the exam room and not necessarily in new agents.

Speaking at the European Society of Cardiology scientific meeting earlier this month, Christie Ballantyne, a Baylor University professor of medicine, pointed to data from the US Department of Veterans Affairs healthcare system suggesting that a million patients were candidates for high-intensity statins but just 22% were taking them, and another 30% were not taking a statin at all.

"The key question is why do patients not take a statin?" Dr Ballantyne said in a presentation at the ESC. "You get the greatest benefit if you're taking a statin – you increase the dose, you get more benefit. If you're taking 10mg of rosuvastatin versus 40mg, there's some incremental difference, but that's not as much as zero vs 10.

"The main thing is they have to take it and comply with it."

PCSK9 sales forecast ($m)							
Product	**Company**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**
Evolocumab	Amgen/Astellas	45	254	551	891	1,203	1,537
Alirocumab	Sanofi/Regeneron	15	219	497	786	1,045	1,324
Bococizumab	Pfizer	-	-	111	231	371	567
Total		**60**	**473**	**1,159**	**1,908**	**2,619**	**3,428**
Source: EvaluatePharma							

In the highest-risk patients, the US guidelines recommend high-intensity statin treatment, such as 80mg of Lipitor or 40mg of Crestor. High-risk patients include those with diagnosed atherosclerotic cardiovascular disease younger than 75, LDL levels of more than 190mg/dl or diabetics with elevated LDL and a 10-year risk of complications of over 7.5%.

Payers confronted with a choice of relatively inexpensive pills – most of the statins are now off-patent – or the costly biologicals will want to see signs that the statin route was exhausted before authorising a PCSK9.

More than just sore

If LDL is uncontrolled at that maximum dosage this should be apparent on lab tests, and the move to the more expensive biological should be clear. But of those who cannot tolerate this maximum dosage, the question of how to prove it arises. The “addressable population” of statin intolerants, according to Morgan Stanley, is 2.7 million in the US and Europe, worth on the order of €1.9bn ($2.5bn).

Payers are likely to say, “if you want to use this drug … show us evidence that you have tried hard with compliance and tried hard with a maximum dosage,” said Ian Graham, cardiovascular medicine professor at Trinity College in Dublin. “Just because somebody says they’re sore, I don’t think that’s going to work.”

“Everybody knows about serious myositis – that’s obvious. But for most of the aches and pains, there is no test,” Dr Graham told *EP Vantage*. To test patients’ tolerance, “the best you can do is withdraw it two or three times and reinstitute it, and if they get the pain back every time you have to believe it.”

When asking to trade a $1-a-day off-patent drug for one that costs 30 times more, payers will not go easily. If the cheaper drug is not used effectively, as with the case of statins, payers have a ready-made reason to say no.

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