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Outcomes Claim May Help Amgen Make Case For PCSK9 Inhibitor Repatha

By Emily Hayes

LABELING FOR REDUCTION OF CARDIOVASCULAR RISK may help a bit with payers, but the "twin problem" of pricing and lack of patient adherence is likely to continue to present hurdles for reimbursement.

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Amgen Inc.'s injectable PCSK9 antibody *Repatha* (evolocumab) has secured the long-sought labeling claim for reducing the risk of cardiovascular events in patients needing greater lowering of LDL cholesterol, but the real-world impact in terms of prescribing and payment remains to be seen.

The company announced on Dec.1 that the US FDA expanded labeling for Repatha to include a claim for preventing heart attacks, strokes and coronary revascularizations in adults with established cardiovascular disease.

The FDA also approved Repatha for use as an adjunct to diet, alone or in combination with other lipid-lowering therapies, such as statins, for the treatment of adults with primary hyperlipidemia to reduce LDL cholesterol. The agency had held off on approving Repatha and **Sanofi/Regeneron Pharmaceuticals Inc.**'scompeting PCSK9 inhibitor *Praluent* (alirocumab) for this broader patient population, pending outcomes data. *(Also see "US advisers endorse PCSK9 Praluent, but limited population" - Scrip, 10 Jun, 2015.)*

Repatha was originally approved in August 2015 for use in high-risk patients not achieving goals with "maximally tolerated" available therapies (statins and other lipid lowering therapies) and did not have a claim for CV risk reduction (*see box below*).

Amgen says that following the label change, its focus remains on high-risk cardiovascular patients.

The label change was supported by results from the FOURIER outcomes study, which demonstrated a significant reduction in the risk of heart attack (27%), stroke (21%) and coronary revascularization (22%) with Repatha. There was also a 20% significant reduction in the secondary endpoint related to major adverse cardiovascular events in the study. *(Also see "Is Amgen's FOURIER Enough For Physicians, Payers To Expand Repatha Use?" - Scrip, 17 Mar, 2017.)*

The label change was supported by results from the FOURIER outcomes study, which demonstrated a significant reduction in the risk of heart attack (27%), stroke (21%) and coronary revascularization (22%) with Repatha.

However, the reduction for the primary composite endpoint was lower than some expected, at 15%, and there was no significant mortality benefit in the study. Although mortality benefits have not been seen in high intensity LDL lowering trials against moderate statins, the lack of an impact prompted the Institute for Clinical and Economic Review (ICER) to lower its value-based pricing benchmark for Repatha. *(Also see "Amgen Faces New ICER Roadblock To Repatha Reimbursement" - Scrip, 15 Jun, 2017.)*

The label change has been expected and analysts see the language as clean. In a Dec. 1 note, Mizuho Securities analyst Salim Sayed pointed out that FDA removed

Repatha's US FDA Labeling: Comparison Of Indications And Usage	
As Of Aug. 27, 2015	**As Of Dec. 1, 2017**
Indicated as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of low density lipoprotein cholesterol. Also indicated for use with other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia who require additional lowering of LDL-C. Limitations of Use: The effect of Repatha on cardiovascular morbidity and mortality has not been determined.	Indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease. Also approved for use as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce LDL-C and as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia who require additional lowering of LDL-C.

language regarding patients being on a maximally tolerated statin, as the FOURIER study tested Repatha with an "optimized stable lipid-lowering therapy," ideally including a high intensity statin but at least a moderate intensity statin, with or without ezetimibe (**Merck & Co. Inc.**'s *Zetia*).

"While reflective of the trial (69.3% of patients in FOURIER on high-intensity statin, 30.4% on moderate-intensity statin), we believe this language was not exactly expected by Street, is marginally above expectations, and bodes well for the continued increased uptake of Repatha (and the PCSK9 class), especially in high-risk patients who require additional LDL-lowering but may not already be on max-tolerated statin," Sayed said.

Roger Longman, president and CEO of the reimbursement intelligence company Real Endpoints, commented that the new label is marginally but not dramatically better.

The change in language regarding statins may help a little bit as some health plans have been insisting on the "letter of the law" in terms of requiring that patients have had a maximally tolerated statin prior to getting a PCSK9 inhibitor. This can significantly increase the burden for potential prescribers in that they need to prove a patient has been adherent to a maximally tolerated statin over a period of time, Longman said.

New labeling could, at least temporarily, give Repatha an edge over Praluent, which is still approved for use in high-risk patients not meeting goals on a maximally approved statin, and does not yet have a claim for reduction of cardiovascular risk. Results from the ODYSSEY CV outcomes study of Praluent are due early in 2018.

Sales of Repatha started to outpace Praluent in the fourth quarter of 2016. *(Also see "PCSK9 Sales Still Slow, But May Get Boost From Label, Guideline Changes" - Scrip, 4 Aug, 2017.)* Amgen reported $89m worldwide for Repatha in the third quarter of this year, while Sanofi/Regeneron reported €42m ($49m) during that period. *(Also see "Keeping An Eye On Regeneron: What's Next To Drive Growth" - Scrip, 8 Nov, 2017.)* and *(Also see "Amgen Focuses On Pipeline As Mature Products Face Declining Demand" - Scrip, 26 Oct, 2017.)*.

The CV risk reduction claim also may help boost acceptance with prescribers and payers, although the data from the FOURIER outcomes study supporting the filing have been known for some time and have not had a big impact on sales.

Pricing of PCSK9 inhibitors has proven very controversial. Praluent and Repatha both carry an annual list price of about $14,500. And both have faced challenges breaking into the market due to restrictions on utilization, even for patients who meet the high-risk parameters of labeling.

Many critical cost-effectiveness studies have been published. Some researchers have concluded that relative to adding Zetia on top of statins, the PCSK9 inhibitors would be cost-effective if their list price was cut by 71% to $4,215 annually or less.

A key issue for many plans is they don't see much more adherence to a PCSK9 inhibitor than for a statin, so there is the "twin problem" of price and adherence, Longman explained.

Amgen funded its own study that found $9,669 annually is cost-effective. *(Also see "The Price Is Right: Amgen Defends Repatha At $9,669 Against More Critics" - Scrip, 23 Aug, 2017.)* The company has also offered value-based pricing deals to plans, guaranteeing a refund in the case a patient has a heart attack or stroke while on Repatha.

The annual net price nowadays in the US for PCSK9 inhibitors is in the $8,000 to $9,000 annual range, Longman commented.

Following a label change, access may be slightly better but plans will still put significant hurdles in the way of prescribing Repatha until the price comes down to a level equivalent to new branded small molecule cardiovascular drugs, such as **Novartis AG**'s heart failure *Entresto*, and until adherence can be demonstrated, Longman maintained.

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"If somebody can solve the adherence problem and solve the price problem, that would be a game changer," Longman said.

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