

# Alirocumab's Price Reduction

## Implications of a Paradigm Shift Toward Cost-Effective Pricing

**O**n March 10, 2018, results were presented of the ODYSSEY Outcomes trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) for alirocumab, a monoclonal antibody that inhibits PCSK9 (proprotein convertase subtilisin/kexin type 9), showing that alirocumab reduced major adverse cardiovascular events among patients with a recent acute coronary syndrome. Coinciding with the presentation, alirocumab's manufacturers, Sanofi and Regeneron, announced price reductions of thousands of dollars annually, meeting the price suggested by the Institute for Clinical and Economic Review's (ICER) revised cost-effectiveness analysis (CEA). This landmark decision illustrates both the potential and limitations of using CEA to inform medication pricing.

Manufacturers generally set prices to maximize profit. At a minimum, drug prices must offset manufacturing costs, which are higher for biologics like PCSK9 inhibitors than small-molecule drugs like statins. Manufacturers also likely set higher prices when there are fewer competing alternatives. Payers have few tools to mitigate manufacturer pricing power except to restrict access, even if some patients likely to benefit will not receive therapy. This generates all-around frustration: patients and clinicians unable to access medications, insurers faced with spiraling drug costs, and manufacturers confronted by suboptimal adoption of effective therapies. The initial experience of alirocumab seemed to follow this path.

Alirocumab and another PCSK9 inhibitor, evolocumab, were initially approved by the Food and Drug Administration in 2015 based on studies demonstrating significant reductions in low-density lipoprotein cholesterol. Both drugs were priced at >\$14 000 annually.<sup>1</sup> However, these high prices failed to meet conventional cost-effectiveness thresholds. Widespread PCSK9 inhibitor adoption also raised enormous budgetary implications: treating the 10 million potentially eligible US patients for 5 years would cost \$600 billion, 38% more than the entire cost of all prescription drugs in 2015.<sup>1</sup>

As expected, payers imposed restrictive prior authorization criteria, leading to more than half of prescriptions being rejected.<sup>2</sup> When prescriptions were authorized, payers imposed substantial cost-sharing requirements such that one-third of patients approved to receive PCSK9 inhibitors abandoned their prescription at the pharmacy.<sup>2</sup> Despite the March 2017 publication of the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) showing that evolocumab reduced cardiovascular events among patients with established cardiovascular disease, utilization management criteria seem to have been minimally relaxed, and PCSK9 inhibitor adoption did not improve.

In anticipation of the public presentation of ODYSSEY Outcomes, Sanofi and Regeneron shared the trial results with ICER, a private United States-based group that conducts CEAs. ICER concluded that to meet a value-based

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price benchmark range of \$100 000 to \$150 000 per quality-adjusted life year (QALY), alirocumab's price should be "\$2,300-\$3,400 per year if used to treat all patients who meet trial eligibility criteria, and \$4,500-\$8,000 per year if used to treat only higher-risk (primary prevention) patients with low-density lipoprotein cholesterol  $\geq$ 100 mg/dL despite intensive statin therapy."<sup>3</sup> Surprising the medical community, Sanofi and Regeneron promised to lower the price of alirocumab to within ICER's benchmark. On May 1, Express Scripts, a pharmacy benefit manager covering 25 million patients, announced a negotiated price for alirocumab "on the low end" of the \$4500 to \$8000 annual range through higher rebates in exchange for streamlining prior authorization requirements.

Although these actions provide a model for manufacturer-payer cooperation with CEA serving as the intermediary to promote optimal value, they raise several questions.

First, if CEA forms the basis of pricing decisions, what should the threshold be? Thresholds vary between \$50 000 and \$150 000 per QALY, with the World Health Organization recommending an upper threshold  $\approx$ 3times a nation's gross domestic product per capita; thus,  $\approx$ \$150 000 per QALY in the United States. Different thresholds can lead to dramatically different recommendations. For example, 1 CEA of evolocumab after the FOURIER trial used a threshold of \$150 000 per QALY and suggested a cost-effective price of \$6780,<sup>4</sup> whereas another CEA used a threshold of \$100 000 per QALY and suggested \$4215.<sup>5</sup> The \$2500 price difference raises questions about underlying assumptions of benefit and even the potential influence of funding, because one was independent whereas the other was supported by the manufacturer.

Second, what organization should conduct CEAs? Outside the United States, national health technology assessment bodies, such as the National Institute for Health and Care Excellence in the United Kingdom, evaluate medical products and advise coverage. A government body ideally would also play this role in the United States with transparency about the benchmarks for cost-effectiveness, underlying assumptions, analytic perspective(s), and data reviewed. In the United States' fragmented health technology assessment landscape, ICER has stepped into this void. ICER is transparent about its methods and allows public comments, both of which are important, because many assumptions go into a CEA.

Third, how should payers respond to this pricing change? For alirocumab, in exchange for cheaper prices, Sanofi and Regeneron are requiring relaxing of prior authorization criteria. But prior authorization requirements should not disappear given the large budgetary impact. Alirocumab's high costs and millions of candidate patients mean that increasing its use over

the long term, even at cost-effective prices, will cause population premiums to rise. Therefore, payers have a responsibility to ensure PCSK9 inhibitor use preferentially among those patients most likely to benefit. Recent studies indicate that 40% of patients prescribed PCSK9 inhibitors did not have cardiovascular disease (an entry criterion for the randomized controlled trials) and half were not taking a statin,<sup>2</sup> suggesting that prior authorization may have a role.

Fourth, can we expect other manufacturers to take the same actions, dropping drug prices to those established by CEAs? Manufacturers of new Food and Drug Administration–approved specialty drugs may be most likely, but may lack an incentive unless there are multiple competing drugs for payers to use as leverage in negotiations; evolocumab and alirocumab offer alternatives as PCSK9 inhibitors.

The experience with PCSK9 inhibitors is not likely to be an isolated one. Several cardiovascular drug candidates currently in phase III clinical trials could also be candidates for QALY-based benchmarks, such as canakinumab, a monoclonal antibody currently approved for rare autoinflammatory diseases that reduced cardiovascular outcomes in a randomized controlled trial. If it receives Food and Drug Administration approval for this indication, high costs could impede adoption; the manufacturer may learn from alirocumab's path by integrating CEA into initial pricing decisions. Payers may even start expecting prices aligned with CEA. However, if CEA-based pricing is increasingly accepted, some manufacturers could conceivably raise prices for new drugs toward the \$150 000 per QALY benchmark. Such an unintended consequence of using QALY benchmarks to manage higher-cost medications deserves monitoring.

Unaddressed is the merit of basing CEAs on the results of a single randomized controlled trial (ODYSSEY Outcomes). The trial's results have not yet been published in the peer-reviewed literature, preventing scientific and statistical peer review. Before payers agree to broad coverage, the data should be published and shared for independent evaluation to ensure their robustness. Outcome benefits would ideally be replicated in another trial or at least through real-world data evaluations. Value should be periodically reassessed, and prices should be iteratively adjusted: if reductions in cardiovascular events are more modest in subsequent studies, prices should be lowered.

The implications for patients with established cardiovascular disease are obvious: alirocumab will become somewhat easier for their physicians to prescribe. Patient out-of-pocket costs will only be reduced if the list price is decreased or if rebates are passed on to consumers; however, costs may still be prohibitive for some patients. Ultimately, greater access and use could improve cardiovascular outcomes for certain patients,

whereas greater use of CEA could improve outcomes for our health system.

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### Disclosures

None.

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