Alirocumab for Treatment of High Cholesterol: Effectiveness and Value

Preliminary New Evidence Update

March 10, 2018

Based on the results of the ODYSSEY Outcomes trial, ICER has calculated two updated value-based price benchmarks, net of rebates and discounts, for alirocumab in patients with a recent acute coronary event: $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 higher-risk patients with LDL cholesterol ≥100 mg/dL despite intensive statin therapy

NOTE: ICER is issuing this preliminary update to help inform new pricing and coverage negotiations between manufacturers and payers. We plan to issue a final New Evidence Update for alirocumab by May 3, 2018, following the methodology and procedures defined on our website. ICER previously assessed the cost-effectiveness of alirocumab and evolocumab shortly after these drugs were first granted regulatory approval in the US in 2015, and performed a new evidence update for evolocumab in September, 2017 following the release of outcomes data from the FOURIER trial.

	CVD Policy Model Group
Jeffrey A. Tice, MD Professor of Medicine University of California San Francisco **Daniel A. Ollendorf, PhD** Chief Scientific Officer Institute for Clinical and Economic Review **Rick Chapman, PhD, MS** Director of Health Economics Institute for Clinical and Economic Review **David M. Rind, MD, MSc** Chief Medical Officer Institute for Clinical and Economic Review **Steven D. Pearson, MD, MSc** President Institute for Clinical and Economic Review	**Dhruv S. Kazi, MD, MSc, MS** Associate Professor Department of Medicine (Cardiology), Department of Epidemiology and Biostatistics, Center for Vulnerable Populations, and Center for Healthcare Value, University of California San Francisco **Pamela G. Coxson, PhD** Mathematics Specialist Department of Medicine, University of California San Francisco **Joanne Penko, MS, MPH** Research Analyst Center for Vulnerable Populations, Department of Medicine, University of California San Francisco **Kirsten Bibbins-Domingo, MD, PhD, MAS** Professor Department of Medicine, Department of Epidemiology and Biostatistics, and Center for Vulnerable Populations, University of California San Francisco *The role of the CVD Policy Model Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the CVD Policy Model Group.*

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports, developed in partnership with research groups at academic institutions, include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

Background

ICER's Preliminary New Evidence Update for alirocumab (Praluent®, Regeneron/Sanofi) is based on results from the ODYSSEY outcomes trial presented at the American College of Cardiology's 2018 Scientific Session. Under ICER's established protocols for accepting in-confidence data, an agreement with Regeneron and Sanofi allowed ICER to evaluate the new evidence and, working with a team of academic faculty from the University of California, San Francisco, to update its cost-effectiveness analyses and associated value-based price benchmarks for this drug. ICER's value-based price benchmarks suggest a price range that aligns fairly with the added benefits of new treatment options for patients and the health care system.

Given these new outcomes data confirming a mortality benefit for alirocumab, ICER is issuing this preliminary update to help inform new pricing and coverage negotiations between manufacturers and payers. We plan to issue a final New Evidence Update for alirocumab by May 3, 2018, following the methodology and procedures defined on our website. ICER previously assessed the cost-effectiveness of alirocumab and evolocumab (Repatha®, Amgen) shortly after these drugs were first granted regulatory approval in the US in 2015, and performed a new evidence update for evolocumab in September 2017 following the release of outcomes data from the FOURIER trial.

Summary of Clinical Trial Results

The ODYSSEY Outcomes trial was a multi-site randomized controlled trial testing alirocumab versus placebo in patients with the following eligibility criteria: 1) age ≥ 40 years; 2) hospitalization for acute coronary syndrome with myocardial infarction (MI) or unstable angina 1-12 months prior to randomization; 3) a run-in period of 2-16 weeks of high-intensity or maximally tolerated dose of atorvastatin or rosuvastatin; and 4) following the run-in period, at least one of the following lipid entry criteria: low-density lipoprotein cholesterol (LDL-C) ≥70 mg/dL (1.8 mmol/L), non-high-density lipoprotein cholesterol (Non-HDL-C) ≥100 mg/dL (2.6 mmol/L), or Apolipoprotein B ≥80 mg/dL.

In the ODYSSEY Outcomes Trial, the primary outcome was a composite of coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), ischemic stroke (fatal and non-fatal), and hospitalization for unstable angina. The incidence of the primary outcome was lower in the alirocumab arm of the trial (hazard ratio (HR) 0.85, 95% CI 0.78-0.93)). There was a non-significant reduction in CHD death (HR 0.92) and cardiovascular disease death (HR 0.88) and a nominally significant reduction in all-cause mortality (HR 0.85, 95% CI (0.73-0.98)). In the subgroup of patients with a high LDL-C level (≥100 mg/dL) on maximally tolerated statin therapy, the HR for all-cause mortality was 0.71 and for CV mortality was 0.69. There were statistically significant reductions in the HR for the primary outcome and key secondary mortality outcomes for patients in the high LDL-C group (Table 1), as well as an improvement in clinical benefit over time in a landmark analysis (Table 2).

Table 1. Subgroup Analysis by Baseline LDL-C Level in ODYSSEY Outcomes Trial

Outcome	Entire Cohort HR (95% CI)	LDL-C ≥100 mg/dL HR (95% CI)
Primary outcome: CHD death, non-fatal MI, ischemic stroke, unstable angina	0.85 (0.78-0.93)	0.76 (0.65-0.87)
CHD death	0.92 (0.76-1.11)	0.72 (0.53-0.98)
CVD death	0.88 (0.74-1.05)	0.69 (0.52-0.92)
All-cause death	0.85(0.73-0.98)	0.71 (0.56-0.90)

CHD: coronary heart disease, CVD: cardiovascular disease, HR: hazard ratio, LDL-C: Low density lipoprotein cholesterol, MI: myocardial infarction

Table 2. Post-hoc Landmark Analysis for Entire Cohort and LDL-C ≥100 mg/dL in ODYSSEY Outcomes Trial

Outcome	Follow-up Period	Entire Cohort	LDL-C ≥100 mg/dL HR (95% CI)
Primary outcome: CHD death, non-fatal MI, ischemic stroke, unstable angina	0-12 months	0.94 (0.83-1.08)	0.81 (0.66-1.01)
	>12 months	0.77 (0.69-0.87)	0.71 (0.58-0.87)
All-cause death	0-12 months	1.01 (0.77-1.32)	0.79 (0.51-1.22)
	>12 months	0.79 (0.66-0.94)	0.67 (0.50-0.89)

CI: confidence interval, CVD: cardiovascular disease, HR: hazard ratio, LDL-C: Low density lipoprotein cholesterol, MI: myocardial infarction, NR: not reported

Summary of Updated Cost-Effectiveness Analysis Results

We updated our estimates of the long-term cost-effectiveness of alirocumab based on data from the ODYSSEY Outcomes trial as described above. This analysis was conducted in partnership with an independent research group at the University of California, San Francisco led by Dr. Kirsten Bibbins-Domingo and Dr. Dhruv Kazi. The team used the Cardiovascular Disease (CVD) Policy Model, an established simulation model of cardiovascular disease in the U.S. population that systematically combines data from vital statistics, epidemiologic studies, clinical trials, and registries. Structurally, the approach was similar to that previously described in ICER's final report on PCSK9 inhibitors developed as part of deliberations held by the New England Comparative Effectiveness Public Advisory Council in October 2015, which was subsequently published in the peer-reviewed literature. As before, the analyses adopted a health system perspective and assessed costs and outcomes over a lifetime horizon. Cost-effectiveness was presented in terms of cost per additional quality-adjusted life year (QALY) gained for treatment with alirocumab + statin compared with statin alone among patients who meet the inclusion criteria of the ODYSSEY Outcomes Trial. We ran the CVD Policy Model under two different scenario assumptions. In the first, we applied the observed reduction in major coronary heart disease (CHD) events and stroke as observed in the trial to CHD and stroke events in the model. Given the marked reduction in all-cause mortality observed in the trial – which may be partly due to incorrect adjudication of CV deaths as non-CV deaths in the trial – we performed a scenario analysis that applied the reduction in all-cause mortality from the trial (which was larger than the reduction in major CHD events above) to CHD events including CHD deaths in the model.

Because the reduction in all-cause mortality from alirocumab varies inversely with the "competing" risk of dying of non-CV causes, cost-effectiveness of the agent depends on patient selection. The drug would be most cost-effective in patients at high risk of CV events (e.g., patients with a baseline LDL-C ≥100mg/dL despite intense statin therapy) who have a low risk of non-CV death (e.g., from terminal cancer). We therefore believe that it is reasonable to view the two analyses described above – with varying degrees of impact on CHD and hence all-cause mortality in the population – as ends of the spectrum of what may be the real-world effectiveness of alirocumab based on the ODYSSEY Outcomes trial results. We have calculated willingness-to-pay threshold prices for alirocumab under both scenarios needed to meet thresholds of $50,000, $100,000, and $150,000 per QALY. As can be seen, the price range – net of discounts or rebates provided to the payer – needed for alirocumab to meet the ICER value-based price benchmark range of $100,000 to $150,000 per QALY is approximately $2,300 to $3,400 if the drug is used to treat all patients. This represents a 77%-84% discount from the list (wholesale acquisition cost (WAC)) price for alirocumab of $14,560. When the drug is used only for the patient cohort with LDL-C ≥100mg/dL despite intensive statin therapy, the cost-effectiveness improves. Under the two scenarios described above, the ICER value-based price benchmark is $4,500-$8,000 given the uncertainty in

the characteristics of the patient population that would ultimately be treated and the real-world, long-term effectiveness of the drug. This price range represents a 45%-70% discount from the WAC price. Among patients with a recent acute coronary syndrome and an LDL-C ≥100mg/dL, the upper half of the value-based price range would apply to patients whose CV and non-CV risk resembles that of the trial population. If treated patients reflect the more general secondary CV prevention population – putting them at increased risk of death from non-CV causes and therefore making them less likely to benefit from cholesterol-lowering, the lower half of the range would be applicable.

Table 3. Value-Based Price Benchmarks, Based on Patient Population and Mortality Assumptions

	Incremental Cost Effectiveness Ratio ($/QALY)	Annual Price to Achieve $50,000 /QALY	Annual Price to Achieve $100,000 /QALY	Annual Price to Achieve $150,000 /QALY	Value-Based Price Benchmark Range
Assumes observed reduction in major CHD events					
All eligible patients	$314,999	$1,171	$2,306	$3,441	**$2,306-$3,441**
Only patients with LDL-C ≥ 100 mg/dL	$164,006	$2,234	$4,460	$6,578	**$4,460-$6,578**
Assumes observed reduction in major CHD events and all-cause mortality					
Only patients with LDL-C ≥ 100 mg/dL	$135,137	$2,673	$5,324	$7,975	**$5,324-$7,975**

CHD: coronary heart disease, LDL-C: Low density lipoprotein cholesterol, MI: myocardial infarction, QALY: quality-adjusted life year

Potential Budget Impact

ICER will include a potential budget impact analysis as part of its final evidence update report. For this preliminary report we note only that estimates of the eligible population that are likely to be considered for PCSK9 inhibitor treatment have been contentious. Data on the secondary CVD prevention population in the United States suggest that approximately 300,000 to 400,000 patients each year have an acute coronary event and also have LDL-C ≥ 100 mg/dL. Not all of these patients are likely to be considered good candidates for PCSK9 inhibitor treatment by their clinicians, but even at the low end of this range, and at a price at the lower end of the updated value-based price benchmark for alirocumab, the budget impact may be substantial. Policymakers will need to continue to evaluate strategies to ensure affordable access to alirocumab.

Comment

The new evidence from the ODYSSEY Outcomes trial does not alter ICER's cost-effectiveness assessment for another PCSK9 inhibitor, evolocumab. In September 2017, after assessing new data from the FOURIER outcomes trial, ICER announced that the value-based price benchmark for a year's treatment with evolocumab would change to a range from approximately $1,700 to $2,200. The primary reason that this price range is lower than the updated range calculated for alirocumab is that, although the FOURIER trial showed that evolocumab combined with statin therapy is effective in reducing the incidence of cardiovascular events such as MI and stroke, the evidence did not demonstrate a statistically-significant reduction in CV or all-cause mortality, nor a trend toward improved clinical benefit in patients with higher LDL C levels.