PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks

Summary of Public Comment Received on Initial Draft Report and ICER Response

The Institute for Clinical and Economic Review (ICER) values the opportunity to receive and respond to public comment on its work products by interested stakeholders. The initial draft CEPAC report on PCSK9 inhibitors for high cholesterol (posted on September 8, 2015) received comments from 10 stakeholder groups. Below is a summary of the major comments received, organized by topic, as well as responses from the ICER team and its research collaborators, including any major changes made to the report.

Evidence Review Sources

- The systematic review[1] used as a major source for our own evidence assessment was criticized, as its meta-analyses of data on cardiovascular events were based on clinical trials not adequately powered to detect differences in these events. We agree with this assessment, but also feel that we have described these limitations in detail throughout the report.

Populations of Interest

- We received comments suggesting that the prevalence of FH and its associated cardiovascular risks are greater than described in our report. The prevalence of FH in our modeling is consistent with the widely cited estimate of 1 in 500 for the U.S. population but we now acknowledge the variation in estimates in the Executive Summary. The cardiovascular risk in our model is approximately threefold higher than the average population risk, which is consistent with that described in a study published after statin use became widespread.[2] There is considerable uncertainty regarding the true prevalence of FH in the U.S., as recent studies have suggested higher prevalence rates.[2,3] Modeling a larger FH population is unlikely to impact the cost-effectiveness estimates in this report, although budget impact would obviously increase with population size. Higher estimates of FH prevalence resulting from use of a lower LDL threshold as some have suggested (e.g., >190 mg/dL) would result in a lower-risk population than we modeled and would increase the resulting cost per QALY gained.

- Several stakeholders also requested additional transparency on the populations identified in the model of incremental cost per outcomes achieved. We have added two tables to Appendix 7 (Tables 3 and 4) that provide a more comprehensive list of model input parameters as well as a demographic and clinical profile of each population evaluated.

- Mention also was made that use of a 20-year time horizon rather than a lifetime horizon, as well as a focus only on patients age 35-74, ignores the benefits that would accrue to older patients, who experience a disproportionate number of CVD events. Despite our remaining concerns regarding the serious limitations of data on the effects of treatment in patients over age 75, we have revised the base case economic model to extend the time horizon to lifetime, which captures the costs and benefits realized in patients as they age beyond 75. The cost-effectiveness of PCSK9 inhibitors now ranges between $275,000 and $300,000 per QALY gained for each subpopulation. The drug prices to achieve cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY gained have also increased (to $3,166, $5,404, and $7,735 respectively). The value-based price benchmark of $2,177 has not changed, however, as it is based on a cost growth target for health-system impact alone.

- Several stakeholders commented that PCSK9 inhibitors are not currently indicated for use in patients who are statin-intolerant. The current indications focus on patients who require additional LDL-lowering while on a maximally-tolerated dose of statins. For those individuals who cannot tolerate statins, the maximally-tolerated dose may be no statin. We include this analysis in order to inform the likely impact in this population subgroup.

Cardiovascular Event Risk

- Several stakeholders felt that the CVD Policy Model systematically underestimates cardiovascular event risk in patients with pre-existing cardiovascular disease (CVD). We respectfully disagree. The CVD Policy Model is calibrated to reproduce the numbers of MI events and total CVD deaths in the U.S. in any given year. Below we also compare annual rates of nonfatal MI, nonfatal stroke, and cardiovascular death among CVD patients in the model to rates seen across that range of high-intensity treatment arms included in the Cholesterol Treatment Trialists (CTT) meta-analysis:[4]

Event Type	CVD Policy Model	CTT high-intensity statin trials
	Annual rate (%)	
Nonfatal MI	1.0	1.0 – 1.3
Nonfatal stroke	1.0	0.6
Cardiovascular death	1.0	0.7

- Mention was also made of underestimation of risk in the FH population. Older studies cited event rates 8-20 times higher among FH patients compared to matched non-FH peers, but none of these studies were conducted in the statin era, and these excess risks have not been

observed by any study conducted in the statin era. As noted above, a recent Dutch study noted an approximate threefold greater risk,[2] which is consistent with the rates generated by the CVD Policy Model.

- The earliest age of therapy initiation in the model is 35, which may have underestimated risk in FH patients diagnosed as children or adolescents, who would have had essentially lifetime exposure to elevated LDL levels. We acknowledge this limitation in the report, but note again that our estimates of threefold higher risk in the adult population is similar to recently-reported estimates.[2] In addition, PCSK9 inhibitors are indicated for treatment of adults only.

Budget Impact Analysis

- ICER's assumed uptake percentages (75% in FH and 25% in CVD by 5 years) were criticized as unreasonably optimistic, given lower rates of uptake observed with statins and other cardiovascular agents. As described in the report, these uptake levels reflect our estimate of utilization that is "umanaged" – without consideration of potential policies to limit utilization that might be instituted by provider groups or payers. In addition, the report's Figure 7 allows the reader to evaluate the potential budget impact across a range of uptake assumptions and drug prices.

- The annual budget threshold of $904 million was also criticized as an arbitrary "cap" that is exclusively focused on drug cost and not on the net clinical benefit to patients. As described in the report, this threshold is intended to serve as a policy trigger to stimulate efforts to address utilization, pricing, and payment mechanisms to improve overall health system value.

- Finally, the 5-year budget impact horizon was felt to be too short to accurately reflect the long-term benefits of preventive therapies. Our analysis of cost-effectiveness reflects the long-term perspective on value to patients, and this analysis captures long-term benefits of preventive treatment with PCSK9 inhibitors based on a critical assumption that favors treatment value: that the LDL lowering seen with treatment translates into reductions in cardiovascular outcomes. The 5-year horizon we have adopted for short-term budget impact stretches as far as feasible to capture potential cost-offsets of preventive treatment while providing important perspective on the impact of net cost growth on health system affordability.

Other Concerns

- An error was noted in the estimation of the percent reduction in LDL with ezetimibe in patients currently on statin therapy. The original estimate (13.9%) has been replaced with a revised estimate (23.6%), and the model results have been adjusted accordingly.

- A request was made to consider non-adherence to PSCK9 inhibitors in our analysis, given their delivery by self-injection. There are no available data to measure adherence as of yet, nor is

there information comparing the possible *benefits* of biweekly or monthly treatment vs. daily oral therapy.

- Mention was made that treatment-related adverse events are under-reported in clinical trials, and that comparisons involving real-world data and the FDA's Adverse Events Reporting System (AERS) would be more complete. We are not aware of any such real-world comparisons, nor of any reports to the AERS system at this time.

- The cost-effectiveness estimates for ezetimibe were compared to prior published evaluations by several stakeholders and found to be substantially higher. However, all of the other evaluations cited were conducted in non-US settings, using annual drug cost estimates that are roughly one-quarter the current wholesale acquisition cost in the US, focused on higher risk populations (e.g., baseline LDL-C levels from 95 – 155 mg/dL vs. >70 in our analysis), and were conducted prior to the availability of data on ezetimibe's effects on cardiovascular events as documented in the IMPROVE-IT trial.[5]

References:

1. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. Ann Intern Med 2015;doi:10.7326/M14-2957.

2. Huigen R, Kindt I, Defesche JC, et al. Cardiovascular risk in relation to functionality of sequence variants in the gene coding for the low-density lipoprotein receptor: a study among 29,365 individuals tested for 64 specific low-density lipoprotein-receptor variants. Eur Heart J 2012;33:2325-30.

3. Wiegman A, et al. Familial hypercholesterolemia in children and adolescents: gaining decades of life by optimizing detection and treatments. Eur Heart J 2015;doi:10.1093/eurheartj/ehv157.

4. Baigen C, Blackwell L, Emberson J, et al, for the Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010; 376(9753):1670-81.

5. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372(25):2387-97.