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Dear Dr. Pearson:

Amgen is a science-based company committed to developing and delivering innovative medicines that make a difference in patients' lives. We welcome the opportunity to provide comments in response to the CEPAC/ICER request for public comments on the PCSK9 inhibitor (PSCK9i) report.

Executive Summary and Background

PCSK9i's are a significant advance in an area of enormous unmet need in lowering LDL-C, a major risk factor for cardiovascular disease (CVD). CVD remains the number one cause of premature mortality and morbidity worldwide, and causes one out of every three deaths in the United States. A fatal CV event shortens a person's life by an average of 17 years.[1,2] The annual direct and indirect cost of CVD in the US is expected to grow to approximately $600 billion in 2015.[3] PCSK9i's offer unprecedented ability to lower LDL-C and studies to determine PCSK9i's effect on CV morbidity and mortality are ongoing.

Amgen supports having a robust and balanced dialogue about the value of PCSK9i's. Such a dialogue should be based on realistic assessments of these new medicines, using well-tested and transparent methodology. Value-based discussions should keep the interests of patients at the center of the analysis. In doing so, these assessments should take a broad societal perspective related to the costs and benefits of healthcare interventions. Amgen disagrees with the methodology, conclusions, and lack of transparency of the ICER report, and does not believe that voting on questions is appropriate before these deficiencies are addressed.

Specifically, Amgen believes that ICER's assumptions and methodology have the following significant errors and deficiencies:

1. The ICER report for PCSK9i's performs a cost-effectiveness evaluation that models extensive product uptake by a population at lower risk than the FDA label and real-world adoption would suggest. An appropriately calibrated model could confirm PCSK9i cost-effectiveness within ACC/AHA thresholds for value.
2. ICER uses assumptions to assess budget impact (mislabeled as "health system value") that are not based on evidence, and which overstate the population size likely to receive PCSK9i's. For perspective, ICER estimates that PCSK9i use alone will grow to over one third of the entire US expenditure on all medications.
3. The newly proposed ICER method confuses the concept of "value" with an indiscriminant form of budget-based rationing. In defining a budget-based benchmark price, ICER has redefined value by capping price and spending on aggregated and individual medicines and limiting their growth. ICER's budget-based price benchmark is based on short-term costs (a maximum of five years) and does not include important long-term aspects of value such as assumptions around improving patient survival and avoidance of event-related deterioration in quality of life.

In summary, the ICER report underestimates CV risk in cost-effectiveness and budget impact models, overestimates the population size likely to receive PCSK9i's, overestimates drug uptake, and invents a new method for assessing "value" by employing arbitrary budget caps, which inevitably results in a low estimate of value.

Detailed Discussion of Issues 1-3

1) The ICER cost-effectiveness model systematically underestimates CV risk, and is not directly applicable to the population most likely to receive PCSK9i's

The model used by ICER was intended to model CV risk in the entire US population (age 35-74) and was not designed for a high-risk population without extensive modification. In cost-effectiveness analysis, correct estimation of the magnitude of the risk (events) to be avoided is among the most critical inputs. Lack of transparency prevents replication of ICER's assumptions and results; however, tables in the ICER report suggest that it has modeled PCSK9i's in a lower-risk population, compared with the population that is defined in the FDA label and the population that Amgen has modeled in its cost-effectiveness analysis.

Table 17 of the ICER report shows that 201.6 million patient-years of treatment would be required to prevent 2.2 million major CV events over a 20 year period, or roughly 1% event avoidance per year of treatment. The American Heart Association's (AHA) 2015 Statistics cite the incidence of cardiac events in a population of patients with clinical atherosclerotic cardiovascular disease (ASCVD) as approximately 8% per year or 40% over 5 years.[4] If the CV event rate reduction seen with PCSK9i's approaches that seen in the recently published Navarese meta-analysis[5], this would imply 4% event avoidance per year, four times higher than what ICER assumes.

Further, when one compares the ICER-predicted risk with the risk seen in the active treatment arms of randomized clinical trials (RCTs) for statins in secondary prevention patients[6,7,8,9,10,11], the CV event rates seen in the RCTs were between 2 to 7 times higher than the ICER model events rates for the secondary prevention population. For example, the A to Z trial reports that the total major adverse cardiac event rate is 4 times higher than the event rate predicted by the ICER model. These published sources of event rates suggest that the ICER estimates for cost-effectiveness could vastly improve using evidence-based risk rate estimates.

ICER should also make transparent and justify the effect of other modeling assumptions which may currently bias the model against the benefits of LDL-C lowering, such as modeling LDL-C as a categorical variable instead of using a more appropriate continuous variable approach, or the effect of ignoring patients with baseline age 75 and over, now one the fastest growing segments of the American population. More than half of all cardiac events occur in patients aged 75 and over.[12]

Amgen has worked with clinical and economic experts to develop a cost-effectiveness model aligned with a model used by the National Institute for Clinical Excellence (NICE), a prominent health technology assessment (HTA) organization. This model assumes use in the familial hypercholesterolemia (FH) and clinical ASCVD populations, in line with the FDA label, and uses event rates that are calibrated accordingly. The model has been validated to appropriately predict the CV event rates seen in clinical trials and real world data and produces cost-per-QALY estimates that are significantly lower (*e.g.* PCSK9i's are cost-effective at current prices) than those produced by ICER. This model is currently undergoing peer review prior to publication and has been submitted to several national HTAs worldwide. We believe an appropriately calibrated CV Policy Model would confirm PCSK9i cost-effectiveness ratios of $150,000 or below, which is the ACC/AHA recommended threshold for value.[13]

2) The ICER model overestimates the population size that is likely to be treated with PCSK9i's

Referring again to ICER's cost-effectiveness modeling, the estimate of 201.6 million patient years of treatment over 20 years equates to an average of 10 million patients per year. Assuming the price used by ICER of $14,600, the average national expenditure for PCSK9i's in the US would be $146 billion dollars per year for every year out to 20 years. For perspective, $146 billion dollars is over a third of the entire US expenditure on all medications.[14] Such estimates garner headlines, but they do not encourage a balanced discussion about value or result in patient-centered decision-making.

The ICER analysis assumes a worst case scenario where there is no utilization management. Since such controls are common for biologics, this starting place is disconnected from the reality of the US health care system. The uptake of PCSK9i's will also be attenuated by the injectable route of administration, patient cost-sharing, expected adherence rates, and the typical uptake curve for new biologics. Further, renewed interest in statin optimization and the label requirement for maximally tolerated statins will also limit the eligible population. All of these factors must be taken into account when seeking to offer an accurate estimate of a new class of medicine's impact on drug cost, particularly when it may influence decision-making that impacts patient care.

We urge ICER to consider the history of statin uptake, the most relevant analog. In the first five years on the market, statins achieved 9% uptake.[15] After more than 10 years on the market, statin uptake in patients with high risk was ~23-30%, depending on the definition of high-risk.[16,17] Financial analysts confirm a balanced longer-term uptake of PCSK9i's (15% in ASCVD to 25% in FH).[18] All of these data sources taken together suggest a much lower uptake for PCSK9i's than ICER's 5-year uptake assumptions of 25% in the clinical ASCVD population and 75% in the FH population.

The rate of ezetimibe use is also instructive. Ezetimibe is a second-line therapy that reduces LDL-C, is indicated for a broader population then PCSK9i's, and now has CV outcomes results. The ICER model estimates average annual sales of ezetimibe equivalent to $24 billion per year over the next 20 years. This is in stark contrast to the 2014 annual sales of $1.8 billion. In fact, if the ICER model estimates are correct, ezetimibe sales should be higher than the peak sales of all statins combined.

In short, it is highly unlikely that the PCSK9i class will grow to the enormous expense predicted by ICER. The starting place for a balanced dialogue on value should take past experience into account and not begin with unrealistic worst case scenarios.

3) The ICER warning threshold for a drug's budget impact is not a meaningful method for assessing health system value and could undermine important health system priorities. Any value framework should consider long-term costs and include all patient-relevant aspects of value.

Critical US health system priorities include: 1) Addressing unmet medical needs that impact large populations, 2) Ensuring that the biopharmaceutical industry is productive and brings important innovative medicines to patients, 3) Encouraging health systems to invest more in interventions that work and less in those that don't across the entire healthcare sector, and 4) Ensuring that long-term value drives health system planning and investment.

Unfortunately, the new method proposed by ICER could undermine all four priorities as follows:

- **Significant Burden of Illness in Large Populations:** The new method penalizes medicines that address unmet needs in large populations of patients, the very conditions that degrade population health and increase health care costs.
- **Productivity:** The new method penalizes biopharmaceuticals for increased productivity: ICER-recommended growth and spending were determined by dividing permissible medicine spending growth by the average number of drugs approved.
- **Sector-wide, efficient resource allocation:** The new method discourages the efficient allocation of resources, only placing caps and growth limits on biopharmaceuticals and not on other aspects of the healthcare system. Budget caps have been repeatedly shown in research to reduce efficient healthcare delivery, diminishing patient access and outcomes.[19,20,21,22]
- **Long-term focus:** A five year budget focus is especially inappropriate to value treatment for chronic, long term illness.

The concept that value is determined by rationing the budget for individual new products has not been widely subjected to public input or review by health economists or policy-makers. The ICER budget impact method (mislabeled as "health system value")

proposes that drug growth and spending should be independently capped at no more than GDP growth + 1%. The negative effect of this artificial growth cap is compounded by other simplifying assumptions that create additional disincentives for drug development in the most important diseases that should be a national priority. ICER's model applies the same $900 million threshold for all new medicines regardless of the size of the population being treated by the medicine, and is not linked to the clinical importance or effect size of the particular medicine. Clearly, a disease such as CVD with large populations of sufferers is going to require far more treatment resources than less common diseases.

This system of allocation and rationing assures that many more budgetary warnings will be issued than are warranted, which could impact patient access to these important medicines for the patients in greatest need. For the PCSK9i's in particular, the ICER budget impact model projects that the sales of PSCK9i's in the five years after introduction will be more than $100 billion dollars. If ICER had assumed more realistic estimates of product uptake, and taken the larger impact of CV disease into account when allocating growth, it is unlikely that the incremental expense of PCSK9i's would have warranted any warnings. Artificially unaffordable estimates are the inevitable result of overestimations of drug uptake together with an arbitrarily low budget and no allowance for disease prevalence or broader aspects of long term value.

Finally, a five year estimate of a drug's costs and direct cost offsets is a payer finance metric, not a value metric. Short-term budget impact ignores some non-financial but critical aspects of value, such as the improved survival and avoidance of event-based deterioration of quality of life and productivity. The ICER "health system value" methodology is not a good metric for value because it ignores much of what patients and society consider value and focuses on the short-term financial interests of insurers.

Recommendations

Amgen recommends that the following changes be made to the final report before voting on questions is appropriate.

The event risk of the modeled population should be revised to be consistent with the known risk among high risk patients for whom the PSCK9i's are intended

For patients with clinical ASCVD, estimates of the risk of events range from 10% to 28% in the control arms of various clinical trials that studied such patients [23,24,25,26,27,28] and in patients with FH, the age-adjusted risk has been estimated to be 8-20 times greater than in patients without FH.[29,30] The ICER model should be calibrated to ensure consistency with events seen in clinical trials and ensure that the event rates apply to the appropriate high-risk patients. The methods and assumptions of these calibrations and other model parameters should be made transparent.

The estimates of the treated population should be revised to reflect a realistic scenario

The treated population should be revised to align with the current FDA approved label, *i.e.* "as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic CVD, who require additional lowering of LDL-C." Utilization rates should be revised to reflect historical data for agents for similar diseases and include estimates of the effects of likely utilization management policies that are in place for many biologics. Statin and ezetimibe uptake patterns are a reasonable starting place, even though they may still overstate uptake because they have outcomes evidence, and utilization controls for PCSK9i's will presumably be more restrictive. Finally, assessments of lifetime drug cost should take into account rates of compliance based on analogs and include estimates of likely discounts.

Eliminate the arbitrary budget cap and the associated "value based price"

The budget cap is arbitrary and creates perverse incentives to develop new treatments that affect small rather than large numbers of patients irrespective of the unmet medical need. Pricing healthcare based on a drug expenditure cap rather than value leads to inefficient rationing of healthcare resources, and could undermine important health system priorities. ICER's "value based price" ignores the most important aspects of value and focuses primarily on short term financial costs. Any representation of value should include all societal and patient-relevant aspects of value such as event related mortality and deterioration of quality of life) and should consider long term costs and benefits of medicines.

Conclusion

A balanced and scientifically robust dialogue on value is a vital part of maintaining a focus on patient care, and making good choices in our dynamic health care system. Such dialogue must begin with estimates that are as accurate as possible using appropriate historical analogues and plausible, real-world assumptions. Equally important is publically available and transparent methodology and results, which ideally are peer-reviewed prior to introducing it publically as a potential platform for payer decision-making that could impact patient care. ICER's report on the value of PCSK9i's does not begin with these essential prerequisites, and therefore is an unsuitable starting point for a meaningful discussion until these deficiencies are remedied.

Amgen is committed to responsible pricing for our products, and an ongoing dialogue with patients, providers, payers, policymakers and regulators to finding ways to promote innovation, and alleviating the financial and societal burden of some of the world's most serious diseases. We look forward to a balanced, science-based dialogue about the value of PCSK9i's.

Sincerely,
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