Amgen Response to ICER Rheumatoid Arthritis Draft Evidence Report

Amgen is a science-based company committed to developing and delivering innovative medicines. As part of our mission is to serve patients, we appreciate the opportunity to comment on the ICER Draft Report "Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value" in patients with rheumatoid arthritis (RA) who have inadequate response to conventional disease modifying anti-rheumatic drugs (cDMARDs).

The ICER model fails to incorporate evidence from over 20 years of real-world use of targeted immune modulators (TIMs). The main premise of the ICER model is to estimate the value of TIMs, in patients who have had an inadequate response to cDMARD therapy in real-world practice. As the result of flawed assumptions and methodologic issues, the ICER model overestimates the treatment effect of continued cDMARD therapy in a way that belies the severity of the disease and contradicts years of observational evidence cataloging the devastation of long-term, uncontrolled RA.[1,2] To correct this, ICER should adjust treatment effect (eg, Health Assessment Questionnaire [HAQ] scores) using observational data to account for disease progression on cDMARDs. Methodologically, ICER should adopt a patient-level modelling approach and use improved methods to estimate long-term utility to account for patient characteristics and treatment variability.

To produce a meaningful and clinically relevant model, Amgen strongly recommends that ICER correct the flawed assumptions and methodologic issues associated with the current model. The following changes would more appropriately model the effect of TIMs in a population whose disease is inadequately controlled with cDMARDs:

1. Incorporate evidence that best represents the long-term clinical and patient outcomes from over 20 years of real-world use
   a. Evaluate the trajectory of HAQ scores appropriately for cDMARDs
   b. Incorporate treatment sequences with multiple changes that reflect clinical practice
2. Use the disease appropriate individual patient-level simulation model to address patient differences and uncertainty in the base case
   a. Account for RA population variability
   b. Adjust treatment discontinuation rates
3. Estimate utilities based on the mixture model approach

Incorporate evidence that best represents the long-term clinical and patient outcomes from over 20 years of real-world use

The benefits of cDMARDs are overestimated when clinical trial data are extrapolated over a lifetime horizon without accounting for the disease progression that occurs in patients whose RA is inadequately controlled with cDMARDs.[3-5]

The ICER model assumes that patients with moderate-to-severe RA achieve a consistent lifetime benefit on cDMARDs. As noted in ICER Table 8 reporting the network meta-analysis (NMA) derived populations, only 27% of inadequate cDMARD responders achieve an ACR 20 in the "second-chance" clinical trial setting. This low response is compounded further by the discontinuation of these therapies in real-world situations with about half the patients treated with methotrexate discontinuing therapy within 12 months.[6] Thus, the evidence does not justify

the ICER assumption that these patients would achieve a consistent lifetime benefit on cDMARDs.

Instead of relying on clinical trial data, the ICER model should account for long-term outcomes and disability in patients with RA by using observational data.

Evaluate the trajectory of HAQ scores appropriately for cDMARDs

The ICER model uses fixed HAQ scores over time after cDMARD treatment. This demonstrates one serious limitation of using short-term data to assess the value of TIMs relative to cDMARDs.

Real-world observational studies suggest that HAQ outcomes vary by treatment and that HAQ scores deteriorate with long-term cDMARD therapy.[7,8] As HAQ scores are used to derive utility outcomes, the assumption that HAQ scores do not change in the ICER model leads to an overestimation of the utilities, quality-adjusted life years (QALYs), and overall value of cDMARD therapy.

ICER should adjust HAQ scores for long-term cDMARD therapy based on real-world data.

Incorporate treatment sequences with multiple changes that reflect clinical practice

The treatment sequences implemented in the ICER economic model do not reflect those used in clinical practice and consequently could mislead payers on the true cost effectiveness of TIMs utilization, leading to patient access concerns.

Insights gained from physicians, patients, and patient groups affirm that "it is not uncommon for patients to cycle through various therapies before finding a treatment option to which they both respond to and tolerate" (ICER report p17). Given that many treatment changes occur in the course of RA patient management, the ICER model should better account for the number of lifetime drug sequences and switches that can occur as well as the challenges of evaluating individual therapies.

ICER should examine US RA registries like CORRONA, RISE, or National Data Bank to identify the most common sequences of TIMs used in clinical practice. Data from these sources also provide real-world estimates of drug discontinuation due to switching agents or stopping therapy because of lack of response or intolerance.

ICER should include additional sequences of TIMs (ie, at least 2 TNF inhibitors plus one of each of the other classes) rather than converting to cDMARD palliative therapy following the failure of three TIMs (ICER report p71).

Use the disease appropriate individual patient-level simulation model to address patient differences and uncertainty in the base case

Account for RA population variability

The ICER economic model uses a rigid cohort approach that inappropriately assumes a homogeneous RA population (ICER report p86). This model is severely limited by not accounting for future outcomes influenced by patient history or individual patient characteristics.

The ICER base case analysis should include the following important factors: treatment history, the effects of patient characteristics on utilities, and treatment discontinuation rates. For example, the probability of a patient switching to the next TIM must depend on the number of previous

TIMs the patient failed. In addition, lifetime QALYs are larger for younger patients because they have more potential life years; comorbid conditions such as cardiovascular disease and diabetes degrade HAQ scores.[7] It is not possible to include such assumptions with the cohort model currently used by ICER.

Adjust treatment discontinuation rates

The ICER base case analysis does not adjust discontinuation rates based on patient response (ICER report p70). The reasoning is flawed as patients with lower response levels have higher rates of treatment discontinuation.[9] Furthermore, the ICER base case analysis assumes that patients only discontinue treatment due to adverse events. In reality, patients stop treatment for many reasons, including lack of adequate clinical response, so only using adverse events to estimate discontinuation overestimates time on treatment. The model should incorporate treatment discontinuation from "all cause" and estimate the probability of discontinuation due to an adverse event or other reason.

A patient-level simulation model is common in RA analyses due to patient heterogeneity, the variability in treatment sequences, and uncertainty in treatment effects and duration.[9,10] ICER should use a patient-level simulation model to capture the patient complexity and the variability and uncertainty associated with treatment in clinical practice.

Estimate utilities based on the mixture model approach

The ICER model does not appropriately degrade HAQ scores in patients whose RA is inadequately controlled with cDMARD therapy.

In most RA models, including the ICER economic model, the utility estimation is the central predictor of QALY outcomes. The HAQ score is the primary variable in the RA utility algorithm and is used to estimate hospitalizations, mortality, and costs. As HAQ scores are only available in a few clinical trials, the ICER model calculates HAQ scores using ACR scores and modified Total Sharp Scores (mTSS) sourced from short-term clinical trials. The ACR scores and mTSS are inputted into various equations to estimate the long-term HAQ scores and QALY outcomes.

Without direct clinical trial estimates of HAQ scores, it is important to use the best available method to estimate utilities. The HAQ-utility algorithm used in the ICER model is out of date and does not properly predict the distribution of utility scores.[11] A recently published algorithm based on the mixture model to translate HAQ scores to patient utility has better predictive accuracy than previous algorithms.[12-14]

Given that different algorithms convert HAQ score to different utility values, possibly leading to different QALY and cost-effectiveness results,[15] we recommend that ICER use the mixture model algorithm,[12-14] which we believe is the best performing algorithm for estimating utilities.

Concluding remarks

The ICER RA Draft Report fails to fully capture the value of TIMs by using an outdated, one-size-fits-all economic model that relies too heavily on short-term controlled clinical trial data that fail to capture real-world patient-specific impacts. This approach greatly underestimates the disability (that can take years to develop) associated with untreated or undertreated RA. The ICER model overestimates the effectiveness of cDMARDs on maintaining good disease control, uses treatment sequences that fail to reflect clinical practice, does not acknowledge individual

patient differences in its simulation, and uses fixed HAQ scores that do not adequately account for observed degradation of patient functioning over time. As a result of these flawed assumptions and extrapolations, the ICER model leads to an overstated cost per QALY for cDMARDs and an undervaluation of TIMs.

When evaluating TIMs, ICER has a responsibility to incorporate the totality of evidence, costs, and patient/societal perspective in a highly transparent and credible manner. As currently presented, the ICER analysis fails to reinforce the importance of preserving patient treatment choice across all RA treatments based on individual patient needs, specific disease characteristics, clinical expertise, and patient preference. When patients with moderate-to-severe RA lack access to effective and well-tolerated treatments, they experience lifelong disability.

ICER should correct the flawed assumptions and methodologic issues highlighted above to produce a meaningful and clinically relevant patient-centric model.

References

1. Pincus T, Callahan LF. What is the natural history of rheumatoid arthritis? *Rheum Dis Clin North Am.* 1993;19(1):123-151.
2. Gordon P, West J, Jones H, Gibson T. A 10 year prospective followup of patients with rheumatoid arthritis 1986-96. *J Rheumatol.* 2001;28(11):2409-2415.
3. Bologna C, Viu P, Picot MC, Jorgensen C, Sany J. Long-term follow-up of 453 rheumatoid arthritis patients treated with methotrexate: an open, retrospective, observational study. *Br J Rheumatol.* 1997;36(5):535-540.
4. Krause D, Gabriel B, Herborn G, Braun J, Rau R. Radiologic damage at baseline predicts patient-related outcomes 18 years after the initiation of methotrexate therapy in patients with severe rheumatoid arthritis. *Clin Exp Rheumatol.* 2015;33(5):611-616.
5. Combe B, Logeart I, Belkacemi MC, et al. Comparison of the long-term outcome for patients with rheumatoid arthritis with persistent moderate disease activity or disease remission during the first year after diagnosis: data from the ESPOIR cohort. *Ann Rheum Dis.* 2015;74(4):724-729.
6. Curtis JR, Zhang J, Xie F, et al. Use of oral and subcutaneous methotrexate in rheumatoid arthritis patients in the United States. *Arthritis Care Res (Hoboken).* 2014;66(11):1604-1611.
7. Michaud K, Wallenstein G, Wolfe F. Treatment and nontreatment predictors of health assessment questionnaire disability progression in rheumatoid arthritis: a longitudinal study of 18,485 patients. *Arthritis Care Res (Hoboken).* 2011;63(3):366-372.
8. Wolfe F, Michaud K. The loss of health status in rheumatoid arthritis and the effect of biologic therapy: a longitudinal observational study. *Arthritis Res Ther.* 2010;12(2):R35.
9. Stevenson M, Archer R, Tosh J, et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. *Health Technol Assess.* 2016;20(35):1-610.
10. Tosh J, Brennan A, Wailoo A, Bansback N. The Sheffield rheumatoid arthritis health economic model. *Rheumatology (Oxford).* 2011;50 Suppl 4:iv26-31.
11. Wailoo AJ, Bansback N, Brennan A, Michaud K, Nixon RM, Wolfe F. Biologic drugs for rheumatoid arthritis in the Medicare program: a cost-effectiveness analysis. *Arthritis Rheum.* 2008;58(4):939-946.

12. Hernandez Alava M, Wailoo A, Wolfe F, Michaud K. A comparison of direct and indirect methods for the estimation of health utilities from clinical outcomes. *Med Decis Making.* 2014;34(7):919-930.
13. Hernandez Alava M, Wailoo A, Wolfe F, Michaud K. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. *Rheumatology (Oxford).* 2013;52(5):944-950.
14. Hernandez Alava M, Wailoo AJ, Ara R. Tails from the peak district: adjusted limited dependent variable mixture models of EQ-5D questionnaire health state utility values. *Value Health.* 2012;15(3):550-561.
15. Pennington B, Davis S. Mapping from the Health Assessment Questionnaire to the EQ-5D: the impact of different algorithms on cost-effectiveness results. *Value Health.* 2014;17(8):762-771.