NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

# Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value

## *Summary of Public Comments 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. There were 15 sets of stakeholder comments submitted in response to the initial draft New England CEPAC report on treatment options for plaque psoriasis that was posted on September 29, 2016. Below is a summary of the major comments received as well as responses from the ICER team and its research collaborators, including any major changes made to the report.

We also received a number of comments asking for language clarification and/or corrections in our draft report. While not summarized in detail here, we have adjudicated each stated concern and revised our report and analyses accordingly.

**Overarching Concerns**

- The review was criticized for not including the full range of psoriasis impacts on patients including quality of life, mortality, or the impact of disease management on related health conditions. Many comments pointed out that psoriasis is a heterogeneous disease. Others pointed out that psoriasis causes psychological distress (e.g., depression, anxiety). In the revised reports, we have attempted to express the heterogeneity of patient populations and severity of psoriasis burden, review the available evidence on the disease burden, and describe the limitations of the current evidence base in addressing these concerns. ICER's process includes formal outreach to patient groups and advocacy organizations for input, beginning with the scoping process and continuing through report generation and the public meeting. For this topic, we have benefited from specific patient input on the limitations of trial outcomes as well as other benefits and disadvantages of new treatment options. We have updated the report to clarify these considerations where possible.

- The review was criticized for not appreciating challenges faced by racial and ethnic minority patients with psoriasis, in particular African American and Hispanic patients. Comments pointed out that African Americans and Hispanics are subject to more misdiagnosis, delayed diagnosis, non-treatment, and more severe disease. In several places throughout the report, we note the particular challenges faced by African American and Hispanic patients. In the Comparative Value Discussion section, we mention that more severe disease suffered by minority patients might not be captured estimates of the impact of psoriasis on quality of life. We hope our report will add further weight to calls for new evidence that can elucidate the treatment regimens that are appropriate for all patients.

- Several comments pointed out that there is limited availability of long-term effectiveness and safety data for some drugs, and that drugs for which these data are available should be preferentially rated. Because the primary outcome for virtually all trials was assessed at the end of a relatively brief induction period (i.e., 10-16 weeks), much of our review of the evidence focused on this timeframe. Assessments of durability of response and longer-term harms are further complicated by crossover, and variable timepoints at which outcomes are measured across trials and agents. However, the revised report also acknowledges targeted immunomodulators for which there are longer-term comparative and safety data (e.g., data from the CLEAR trial of secukinumab and ustekinumab that are now available at 52 weeks).[1]

- Comments mentioned forthcoming guidelines from the American Academy of Dermatology and the National Psoriasis Foundation that focuses on combination therapy. The revised report makes mention of these anticipated guidelines and the potential for combination therapy (e.g., targeted immunomodulators together with topicals or methotrexate). The focus of the present review was on the substantial evidence base for monotherapy. We recognize that more data on the most effective treatment strategies are likely to emerge over time. However, patients, clinicians, payers, and other stakeholders also need to make decisions now, based on the bulk of the currently-available evidence.

- Several comments mentioned that the report took an overly rigid approach to medication dosing, when in actual practice dosing may vary. We agree that there may be dosing variability, but the regimens evaluated in the available evidence generally used the FDA-approved dosing. In addition, in studies that have examined variability of dosing over time, the proportion of patients receiving higher-than-approved dosing was roughly counterbalanced by patients receiving lower-than-approved dosing.[2] The issue of non-standard dosing is discussed in the Other Aspects of Treatment section and the Comparative Value Limitations section.

**Comparative Clinical Effectiveness**

- Comments requested clarification of the methods, included trials, and our approach to accounting for between-trial heterogeneity in the network meta-analysis. The revised report provides more detail about the network meta-analysis in the body of the report and in Appendix G, which clarifies our approach. In addition, we have further explained that the base-case network meta-analysis used best-practice methods to adjust for the response in the placebo or comparator arm in order to account for between-trial heterogeneity and control for potential known and unknown confounders.

We received several requests to remove the LIBERATE trial from our network meta-analysis, as the etanercept arm did not receive FDA-approved dosing. In fact, the network meta-analysis did not include the etanercept arm because etanercept was underdosed and the etanercept-apremilast comparison was underpowered. In the final report, we have clarified the use of only the apremilast and placebo arms from LIBERATE, and omitted outcomes for head-to-head comparisons of these agents.

**Comparative Value**

- The model was criticized for not including of adverse events and route of administration. The model included upper respiratory tract infections and pneumonia to explore the potential impact of adverse events on value. Similar to previous economic analyses, we found that serious adverse events play only a small role in the overall value of targeted agents because adverse events are relatively rare and generally similar across agents. Regarding route of administration, the model assumed the first dose of the injectable drugs were given in the clinic. For infliximab, the model included the costs of intravenous infusion and for the patient to miss a full day's work (i.e., in sensitivity analyses incorporating productivity). We have clarified these methods in the final report.

- Some comments noted an inconsistency between the conclusions of the economic model and real-world use of some agents (e.g., very low use of infliximab despite it being rated a good value). While we acknowledge that there may be exogenous factors affecting use of infliximab and other agents, the results of the model are consistent with findings from other models as well as with our conclusions from the clinical evidence, including a higher rate of discontinuation from infliximab due to neutralizing antibody development and other possible safety concerns.

- The model was criticized for not including loss-of-productivity costs. This was to be consistent with previous ICER evaluations and to reflect the healthcare payer perspective. We did examine productivity costs in a scenario analysis to examine the effect of improvement in psoriasis on absenteeism and presenteeism (diminished disease-related productivity while someone is at work).

- We also received criticism for not including the true cost of actual second line therapy, instead using average costs for all second line therapy. Unfortunately, we identified no RCTs of targeted immunomodulator use as a second line agent after first immunomodulator use. We have expanded our discussion of this decision and how it was modeled in the Comparative Value Limitations and Discussion section.

- The model was criticized for using wholesale acquisition costs (WAC) instead of an approximation of the average sale price (ASP), not clearly specifying the date of the WAC, and not accounting for drug rebates. We have modified, expanded, and clarified our discussion of all these criticisms in the Economic Inputs section and in the Comparative Value Limitations and Discussion section, and have also used a new source of data to estimate real-world discounting and rebating practices for our base case analyses.

- The modeling section of the report was criticized for not including sufficient detail or a lack of clarity in places. Specific comments referred to hospitalization costs, infusion costs, discontinuation rates, dosing of ustekinumab, and not including the effects of psoriatic arthritis. For each of these points, we have verified, modified, and/or clarified the description of the model and discuss our approach, including limitations, in the Comparative Value Limitations and Discussion section.

**Voting Questions**

- Stakeholders requested that the voting questions be posed in a consistent way, that we evaluate each pairwise comparison among all 8 targeted immunomodulators, and that we delete a direct voting question comparing apremilast directly to etanercept. In response to input and as a result of other changes to the report, we have extensively revised the voting questions to focus attention on areas where direct evidence is more prominent as well as policy-relevant items regarding newer vs. more established agents.

**References**

1. Blauvelt A, Reich K, Tsai TF, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. *J Am Acad Dermatol.* 2016.
2. Feldman SR, Zhao Y, Navaratnam P, Friedman HS, Lu J, Tran MH. Patterns of medication utilization and costs associated with the use of etanercept, adalimumab, and ustekinumab in the management of moderate-to-severe psoriasis. *J Manag Care Spec Pharm.* 2015;21(3):201-209.